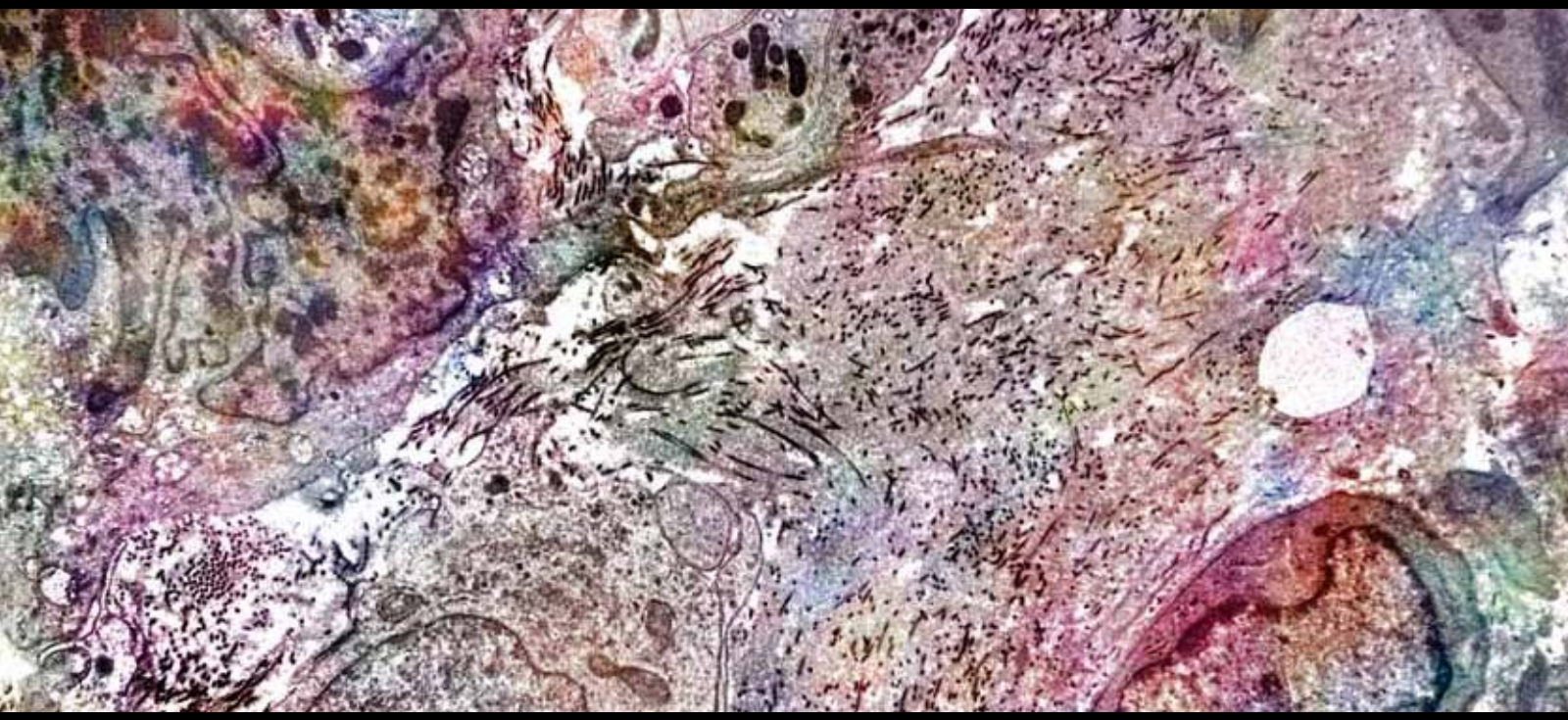
International Journal of Surgical Oncology

Spine Metastasis

Guest Editors: Alessandro Gasbarrini, Rudolf Beisse, Charles Fisher, and Laurence Rhines



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Editorial Board

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Editorial

Spine Metastasis

Alessandro Gasbarrini,[1] Rudolf Beisse,[2] Charles Fisher,[3] and Laurence Rhines[4]

[1] *Depatment of Oncologic and Degenerative Spine Surgery, Rizzoli Orthopaedic Institute, 40136 Bologna, Italy*
[2] *Spine Center Munich, Orthopedic Hospital München-Harlaching, Grünwalderstr aße 51, 81547, Munich, Germany*
[3] *Division of Orthopaedic Spine Surgery, Department of Orthopaedics, The University of British Columbia, Vancouver, BC, Canada V6T 1Z4*
[4] *Department of Neurosurgery, The University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA*

Correspondence should be addressed to Alessandro Gasbarrini, alessandro.gasbarrini@ior.it

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Up to 70% of patients with cancer will develop spine metastasis. Clinical presentations vary, but pain, instability, and neurologic deficit alone or in combination are usually manifested. General management options include analgesia or more comprehensive palliative care pathways, hormonal or chemotherapy, radiation therapy, and surgery. Metastatic patients are unique compared to patients in other domains of health care. For the most part, these patients cannot be cured and are on a palliative trail of uncertain duration and quality of life. Decisions around care in this patient population must be shared with the patient, loved ones, and a multidisciplinary team knowledgeable in the spectrum of interventions available and the evidence on which they are founded.

Because of the multitude of issues involved in these patients' treatment decision making is difficult and controversial and must be individualized. Several scoring systems or classifications have been developed over the past 2 decades to help guide physicians in making the right treatment choices for their patients. Although no one classification is comprehensive enough or has gone through exhaustive psychometric analysis, they do help guide physicians in determining some treatment options. Often they are based on life expectancy, general health or imaging parameters and not on the primary clinical outcome of interest—health-related quality of life (HRQOL). Although HRQOL has broad and varying definitions depending on what aspect you are focussing on, treatment of patients with spine metastases should be directed to improving generic HRQOL or a specific aspect of it, such as pain. Recently there has been a growth in HRQOL research in patients with spine metastases and this has helped direct treatment.

Another area of rapid growth has been in technology in both the radiation and surgical domains. Stereotactic radiosurgery, percutaneous vertebral augmentation, and minimally invasive surgery have added to the physician and surgeon's armamentarium. Where they stand in comparison to more conventional forms of treatment has not been clearly determined, but their impact on HRQOL has certainly been positive. The real challenge now lies in the development of a new paradigm in the management of spine metastases as new technology has expanded indications and provided potentially more options to improve HRQOL.

In this special issue, we have invited seven papers that provide the most up-to-date and comprehensive information about the management of patients with spine metastases. Essential background has been provided by G. Maccauro and colleagues with a detailed and clear paper on physiopathology of spine metastasis, underlining the aspects related to epidemiology, pathogenesis, and prognosis. An exhaustive reference list guides the reader to a deeper knowledge on the issue.

L. M. Shah and K. L. Salzman have described the state of the art of imaging in spinal metastatic disease, underlining the role of new technology and innovation through CT, MRI and nuclear medicine such as FDG-PET/CT. Imaging actually plays a fundamental role in not only diagnosis but also treatment planning and is part of the multidisciplinary approach to the issue.

Metastatic tumors of the spine can be either intradural or extradural. Intramedullary spinal cord metastases are even rarer than bone spine malignancies. Optimal management is difficult to identify due to the variety of clinical situations and the lack of controlled studies. O. Kalita and colleagues show a review of the literature on this topic.

W. A. Hall and colleagues wrote an evidence-based review on stereotactic body radiosurgery that is emerging as an effective and safe treatment modality for spinal tumors, both primary and metastatic. C. A. Molina, P. S. Rose and J. H. Schwab report about the minimally invasive spine surgery (MISS). The first of them has performed a systematic review of the actual role of the procedure in the setting of spine metastases management. P. S. Rose and colleagues describe the surgical techniques used and possible combination with other procedures to gain the best possible result. J. H. Schwab deals with outcome evaluation in patients affected by spine metastases and treated with MISS. Good preliminary results reported are in favour of these techniques, but authors also underline the need for a multidisciplinary approach and a careful evaluation of the surgical indication.

In conclusion a global, contextualized, multidisciplinary approach to spinal metastases is essential if optimal HRQOL is to be achieved [1]. Furthermore, we must encourage and evaluate new technology so as to expand the options for this challenging and very deserving patient population.

Alessandro Gasbarrini
Rudolf Beisse
Charles Fisher
Laurence Rhines

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Review Article

Physiopathology of Spine Metastasis

Giulio Maccauro,[1] Maria Silvia Spinelli,[1] Sigismondo Mauro,[2] Carlo Perisano,[1] Calogero Graci,[1] and Michele Attilio Rosa[2]

[1] *Department of Orthopaedics and Traumatology, Agostino Gemelli Hospital, Catholic University, L.go F. Vito, 1-00168 Rome, Italy*
[2] *Department of Orthopaedics, Messina University, Via Consolare Valeria, 1-98122 Messina, Italy*

Correspondence should be addressed to Giulio Maccauro, giuliomac@tiscali.it

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The metastasis is the spread of cancer from one part of the body to another. Two-thirds of patients with cancer will develop bone metastasis. Breast, prostate and lung cancer are responsible for more than 80% of cases of metastatic bone disease. The spine is the most common site of bone metastasis. A spinal metastasis may cause pain, instability and neurological injuries. The diffusion through Batson venous system is the principal process of spinal metastasis, but the dissemination is possible also through arterial and lymphatic system or by contiguity. Once cancer cells have invaded the bone, they produce growth factors that stimulate osteoblastic or osteolytic activity resulting in bone remodeling with release of other growth factors that lead to a vicious cycle of bone destruction and growth of local tumour.

1. Introduction

The metastasis is the spread of cancer from one part, where it started (called its primary site) of the body to another. A tumour formed by cells that have spread is called a "metastatic tumour" or a "metastasis." The metastatic tumour contains cells that are like those in the original (primary) tumour [1]. When cells break away from a cancerous tumour, they can travel to other areas of the body through the bloodstream or lymph system. From there, they can end up in any organ or tissue. Many of the cancer cells that break off from the original tumour die without causing any problems. Some, however, settle in a new area. There, they begin to grow and form new tumours. Sometimes metastatic tumours are found by tests that are done when the primary cancer is first diagnosed. In other cases, the metastasis is found first, causing the doctor to look for the place that the cancer started [2, 3].

2. Epidemiology

Approximately two-thirds of patients with cancer will develop bone metastasis [4]. Of the estimated 569,490 people who will die of cancer in 2010, almost all will have metastasis to some part of the body. It is estimated that about 350,000 people die with bone metastasis each year in the United States [5]. Sometimes bone metastasis is not clinically visible and their demonstration occurs during autopsy; therefore, the real incidence of bone metastasis is not possible to report [6]. Bone metastasis is actually much more common than primary bone cancers [2, 7] because the incidence is 25/1 and they are the neoplastic lesions more seen by orthopedist [8, 9]. Bones are the most common place for metastasis after lung and liver [2, 3, 10]. Primary tumors that most often leads to bone metastasis are in the order of incidence: prostate, breast, kidney, lung, and thyroid cancer [6]. The incidence of skeletal metastasis from autopsy studies is of 73% (range of 47–85%) in the breast cancer, 68% (range of 33–85%) in the prostate cancer, 42% (range of 28–60%) in the thyroid cancer, 36% (range of 30–55%) in the lung cancer, 35% (range of 33–40%) in the kidney cancer, 6% (range of of 5–7%) in the esophageal cancer, 5% (range of 3–11%) in the gastrointestinal tract cancers, 11% (range of 8–13%) in the rectal cancer [11]. Given the high prevalence of breast, prostate, and lung cancer, they are responsible for more than 80% of cases of metastatic bone disease [12].

According to Roodman GD, up to 70% of patients with breast cancer or prostate cancer, and 15 to 30% of patients with lung, colon, bladder, or kidney cancer develop bone metastasis [13]. Breast cancer is the most common malignant tumour and the main cause of bone metastasis in women [14]. About 70% of people who die from breast cancer will have radiological evidence of skeletal metastasis before their death and in 40% of cases the bone is the first metastatic site [11]; the estrogen receptors [11], the sialoprotein [15], the parathyroid-related peptide (PTHrP) [16], and 69 gene signature correlated with fibroblasts growth factors [17] are predictive markers of bone recurrence [12]. While prostate and lung metastasis are those that occur more in men [14]. The primary tumor cannot be determined in 9% of cases of spinal metastases [18].

3. Locations of Spine Metastasis

Metastasis can occur in any bone in the body but is most often found in bones near the center of the body. The spine is the most common site of bone metastasis [2, 12]. It is estimated that over the 10% of patients with cancer will develop a symptomatic spinal metastasis [19, 20]. Algra et al. suggest that the initial anatomic location of metastases within vertebrae is in the posterior portion of the body. Analysis of CT scans shows that the body is involved before the pedicles, although destruction of the pedicles is the most common finding on plain films. Destruction of the pedicles occurs only in combination with the involvement of the vertebral body [21]. Other common sites are the hip bone (pelvis), upper leg bone (femur), upper arm bone (humerus), ribs, and the skull [2, 14]. Studies showed that the thoracic spine is the region more involved with metastasis [22], while others studies highlighted how the lumbar spine is more involved [23, 24]. The cervical spine is the least involved (10%) [14]. More than 50% of patients with spinal metastasis have multiple levels involved, and 10 to 38% of patients have multiple, noncontiguous segments involved [14]. The lung and breast cancers metastasize preferably in the thoracic region because the venous drainage of the breast through the azygos communicates with the plexus of Batson in the thoracic region [21, 23, 25], while lung cancer drains through the pulmonary veins in the left heart and from there is distributed in the generalized manner in the skeletal; prostate cancer metastasizes usually to the lumbar-sacral spine and pelvis, because it drains through the pelvic plexus in the lumbar region [25]. Colon and rectal tumors usually metastasize through the portal system in the liver and lung, and only late in skeletal [14].

4. Symptoms of Bones and Spine Metastasis

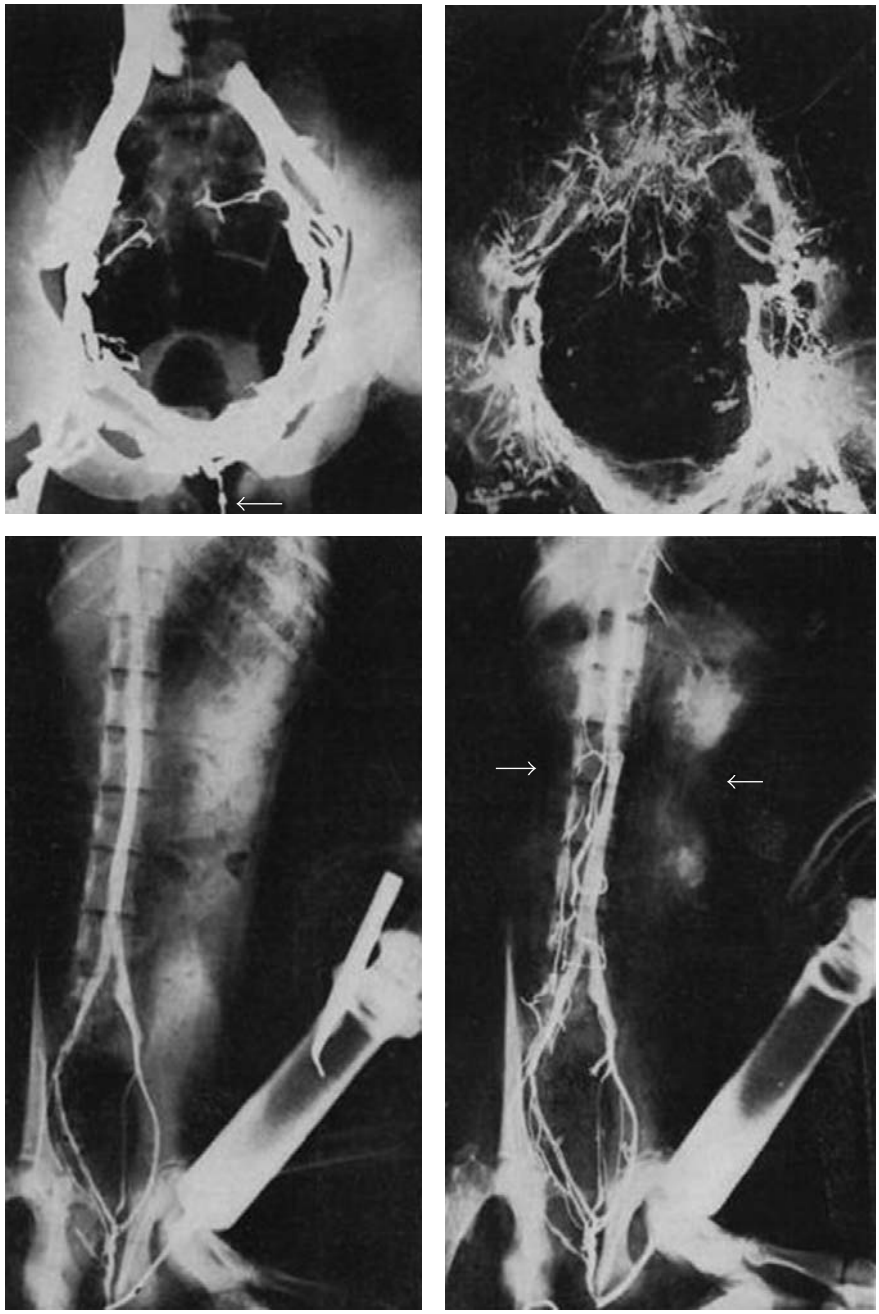
Bone metastasis is one of the most frequent causes of pain in people with cancer. When a cancer spreads to the bone, it can make the bones weaker and even cause them to break without an injury [2, 7]. As the cancer cells damage the bones, calcium is released into the blood. This can lead to problems from high blood calcium levels. Bone metastasis can also cause other problems that can limit your ability to keep up your usual activities and lifestyle [2]. A spinal metastasis may cause pain, instability, neurological injuries with loss of control urinary and rectal sphincter up to paraplegia. However, 60% of all bone metastasis [26] and 36% of vertebral lesions [27] are asymptomatic and discovered occasionally. Symptomatic spinal cord involvement occurs in 18 000 patients per year [18]. Brihaye et al. analyzed 1477 cases concluded that 16.5% of spinal metastases with epidural involvement came from the breast cancer, 15.6% from the lung cancer, 9.2% from prostate cancer, and 6.5% from kidney cancer; they also analyzed 1585 cases of symptomatic epidural metastases and reported that 70.3% had involvement of thoracic and thoracolumbar region, 21.6% of the lumbar and sacral region, and 8.1% of the cervical and cervical-thoraco region, concluding that although the lumbar region is more involved, the majority of patients with neurological dysfunction have thoracic lesions [28].

5. Prognosis

Once cancer has spread to the bones or to other sites in the body, it is rarely able to be cured, but often it can still be treated to shrink, stop, or slow its growth. Even if cure is no longer possible, treating the cancer may be able to help you live longer and feel better [2]. The diagnosis of metastasis changes the patients' prognosis; according to data from the ACS, the survival rate at five years in nonmetastatic carcinomas treated from 1996 to 2002 was of 100% in prostate cancer, 97% in the thyroid cancer, 89% in the breast cancer, 66% in the kidney cancer, and 16% in the lung cancer; in the same period, in the metastatic tumors at presentation, the five-year survival rate was of 56% in thyroid cancer, 33% in prostate cancer, 26% in breast cancer, 10% in renal cancer, and 2% in lung cancer [29].

6. Method of Dissemination

The cancer can metastasize in the bone through different ways of propagation: the most frequent is the hematogenous way, the intravenous one for lesions of the spinal column, and the arterial one for lesions that at the beginning are proximal (shoulder and pelvis) and then distal (elbow and knee). Less frequent lesions are those ones by contiguity and even less frequent are those ones for lymphatic spread (whose role is not well defined) [6, 14]. The diffusion through the venous system is the principal process of spinal metastasis. In 1940, Batson (Figure 1) demonstrated by injecting contrast into the vein of the penis in males and into the veins of the breast in women that the contrast and so the tumor cells spread in the blood into the spinal veins as a result of venous reflux that occurred after an increase of intrathoracic pressure and/or intra-abdominal as for a Valsalva maneuver [30]. It was an explanation of the possibility of the diffusion of breast cancer in the column that is drained mainly by the azygos vein which communicates with the paravertebral venous plexus of Batson in the thoracic region and prostate cancer that is drained from the venous plexus which communicates with the pelvic plexus of Batson at the lumbar [31]. This hypothesis was confirmed by the study of Coman and DeLong, who



(a) (b)

Figure 1: Batson venous plexus, from Batson O.V., "The function of the vertebral veins and their role in the spread of metastases," *Ann Surg.* 1940 July; 112 (1): 138–149.

noted that lumbar spinal tumor metastasis appeared in 70% of the animals, injecting cancer cells into the femoral vein of rats, when an external abdominal pressure was carried out [23, 32]. The venous plexus of Batson is a system of veins located in the epidural space between the spinal column bone and the dura mater, with no valves that control the flow of blood, so that each increase of pressure in the system of the vena cava results in an increased flow level of the plexus. It is connected to the portal and caval system that in normal conditions deviate 5–10% of blood in the vertebral venous system and with the latter [14, 23, 30, 33, 34]. Cancer cells may metastasize through the blood system and into the vertebral body directly through the nutrient arteries as in the case of lung cancer [14, 35]. Arguello et al. showed that the injection of a variety of tumor cells into the systems arterial circulation of mice resulted in a syndrome of tumor colonization of the vertebra followed by a spinal cord compression [36]. The direct diffusion of prostate cancer at the lumbar

spine and the direct diffusion of the breast and lung ones at the thoracic spine are other methods of spreading [14].

7. Mechanism of Localization of Metastases in Bone

The development of a bone metastasis is not a simple process of transport, arrest, and growth of cancer cells in these spaces. Before moving to the bone marrow and taking root and growing in its spaces, neoplastic cells have to follow a long route [37]. They must first spread through the primary site at the expense of the preexisting cells and stroma then detach from it by the reduction of adhesion molecules and the opening of the epithelial basal lamina, afterwards reach the blood vessels and penetrate into them by degradation of their basal lamina and endothelium, then migrate with the bloodstream and escape the surveillance of the immune cells, reach the bone marrow sinusoids, stop and grow there [38, 39]. These processes mainly occur through the activity of proteinases, such as the metalloproteinases, the serine, cysteine, and aspartic proteinases [40–53], stromelysin [54], uPA [55, 56]. These proteinases destroy the epithelial basal lamina and the surrounding tissue by degradation of type IV collagen, laminin, proteoglycans, and other proteins but also uncover hidden biologic activities and reduce cell-to-cell adhesion by interfering with adhesion receptors in the cell membrane [47, 57]. Tumour-host interactions are mediated by a number of cell surface adhesion molecules which belong to the four superfamilies of integrins, cadherins, immunoglobulins, and selectins. The acquisition of invasive and diffusive properties by cancer cells are clearly connected with changes in these molecules, especially a fall in the expression of E-cadherin and a rise in that of CD44 [58]. The expression of adhesion molecules such as integrins αIIbβ3 and αLβ2, or PECAM-1, ICAM-1 and N-CAM, plays a relevant role in the interaction of cancer cells with the endothelium and matrix [59–61]. Preferential localization in skeletal segments which contain red bone marrow (vertebral bodies, ribs, iliac bones, the sternum, the femoral head, the epiphysis of long bones) can be explained by the fact that the rich vascularity allows cancer cells to be transported to this level and reduced blood flow velocity [62], together with the formation of vortices and/or microthrombi, promotes the adhesion and immobilization of the tumour cells on the endothelial ones. Another theory suggests that neoplastic cells migrate to and localize in a preferential target tissue because that is where they find the most fertile "soil" in which to grow, because the bone and bone marrow cells contain and express a variety of growth factors, cytokines, enzymes, and hormone-like substances which, together with similar factors produced by cancer cells, can make the bone microenvironment (the "soil") suitable for cellular implantation (the "seeding") and development [39, 63–66]. MMPs, BSP, and OPN play a key role in the implantation of neoplastic cells in bone marrow by degrading the extracellular matrix modifying cell-cell and cell-matrix contacts and interactions regulation of attachment and chemotactic migration of endothelial cells, and the promotion of angiogenesis [40, 49, 57, 67, 68]. After their localization in bone marrow spaces, their growth to clinically manifest metastases depends on a number of promoting or inhibiting conditions, primarily on interaction with surrounding bone and bone marrow cells, through the increased expression of adhesion molecules, the availability of space, degree of vascularity, and type of bone remodelling. The development of a metastasis obviously depends on the proliferation of neoplastic cells, but other processes are critical in this connection, primarily neo-angiogenesis [69].

8. Pathogenesis

The bone tissue undergoes a continuous process of resorption by the action of osteoclasts, and remodelling, through the action of osteoblasts. In normal individuals, this process is balanced. In cancer cells, this balance is lost and lytic, thickener, or mixed lesions are created [12, 13]. The osteolytic lesions are caused by stimulation of osteoclastic activity accompanied by reduced osteoblastic activity not by direct effects of tumour cells on the bone [70, 71]. The osteoblastic lesions are expression of an increased bone formation around the tumour cells associated with a disequilibrium of the osteolytic activity and with an altered turnover of the bone [71]. Once cancer cells have invaded the bone, they produce growth factors that directly stimulate osteoclastic activity and/or osteoblastic activity resulting in bone remodelling and further release of growth factors that lead to a vicious cycle of bone destruction and growth of local tumour [13, 71, 72].

9. Osteolytic Metastasis Pathogenesis

Tumour cells produce IL-1-6-8-11, PgE2, TGFα, TGFβ, EGF, VEGF, TNF, CSF-1, GM-CSF, and M-CSF, which can directly or indirectly stimulate osteoclastic activity and then bone resorption [5, 12, 13, 72, 73]. Proteolytic enzymes, as acid phosphatase, acid hydrolase, alkaline phosphatise [74], metalloproteinase MMP-2, MMP-9, and K cathepsin seemed to be involved in the early phase of bone metastasis formation degrading bone basal membrane, facilitating tumoral diffusion and bone matrix cytokine release and stimulating tumour cell proliferation [75]. Tumour cells may increase bone resorption also stimulating the tumour-linked immune response with release of osteoclastic activating factors [76]. PTHrP produced by breast cancer cells plays a key role in bone resorption stimulating osteoclastic activity [77, 78]; it is more present in metastatic breast cancer (92%) than in not metastatic ones (50%) [79]. PTHrP and IL 1-6-11 induce osteoclastic bone resorption stimulating osteoblasts and stromal cells to produce the receptor activator of nuclear factor-kB (RANK) ligand; this factor links to its receptor on the osteoclastic precursors inducing their proliferation and differentiation (Figure 2) [76]. The bone damage consequently obtained facilitates the growth factors release causing tumour cells proliferation, as TGFβ, IGFs, FGFs, PDGF, BMPs, which stimulates PTHrP production and then osteolysis [12, 80]. So a vicious circle is present (Figure 3): osteolysis and growth factors release stimulate tumour cells proliferation and then metastatic cells growth [72, 80]. Usually OPG production by osteoblasts neutralizes

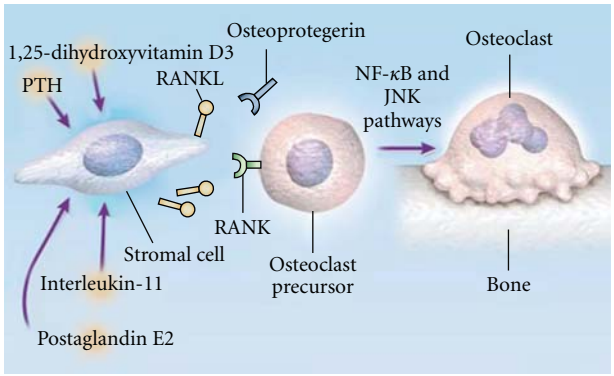


Figure 2: Receptor Activator of Nuclear Factor *k* B Ligand (RANK) and Osteoclast Formation, from Roodman G. D., "Mechanisms of bone metastasis," *N Engl J Med.*, 15; 350 (16): 1655–64, Apr 2004.

RANK ligand locking osteclastic stimulation, but it has been demonstrated that OPG release is reduced in MCF-7 estrogen-dependent breast cancer cell line stimulating also osteoclastic activity [81]. Also IL-6 expressed in prostate and breast cancer cells stimulates osteoclasts cells strengthening the effects of PTHrP onto osteoclasts [82, 83].

10. Osteoblastic Metastasis Pathogenesis

Bone blastic metastasis is usually present in prostate cancer. Growth factors as TFGβ, PDGF, BMPs, IGFs, FGFs, and l'uPA (which stimulates TGFβ release) have been isolated in prostate cancer cells and stimulate osteoblastic differentiation and they have a role in growing and survival tumour cells itself [70, 74, 84, 85]. It has been demonstrated that endothelin 1 level is elevated in bone metastatic prostate tumours than in nonmetastatic ones [86]. It stimulates osteoblastic activity and inhibits the osteoclastic one [87], increases cancer cells proliferation, and stimulates the other growth factors mitogen effects [88]; its production is reduced by androgens and is increased in the androgen-resistant diseases [89]; it is important because usually prostate cancer develops androgene resistance. ET-1 antagonists reduce either osteoblastic bone metastatic growth or tumour growth [90]. Also PTHrP and its receptor have been found in bone metastases and in primary prostate cancer, and it has been demonstrated that prostate tumour cells are able to directly express a form of RANK ligand, which directly induces bone resorption [91], revealing that osteolytic activity is present in prostate cancer [92]. Bone degradation products have been found in urine leading to the hypothesis that in prostate cancer there is at the beginning an osteolytic activity followed by high osteoblastic one [93]. Another study demonstrated that the insertion of PC-3 tumour cells in SCID mice tibia caused osteolytic lesions due to RANK ligand, while other cell lines caused osteoblastic ones, so authors reported that osteoclastic activity is not a prerequisite for osteoblastic lesions [94]. Further study is necessary for this [13]. Moreover, in prostate cancer Wnt induces osteoblastic activity, that in the early phase may be balanced by DKK1 Wnt agonist (an osteoblastic differentiate inhibitor), leading to lythic

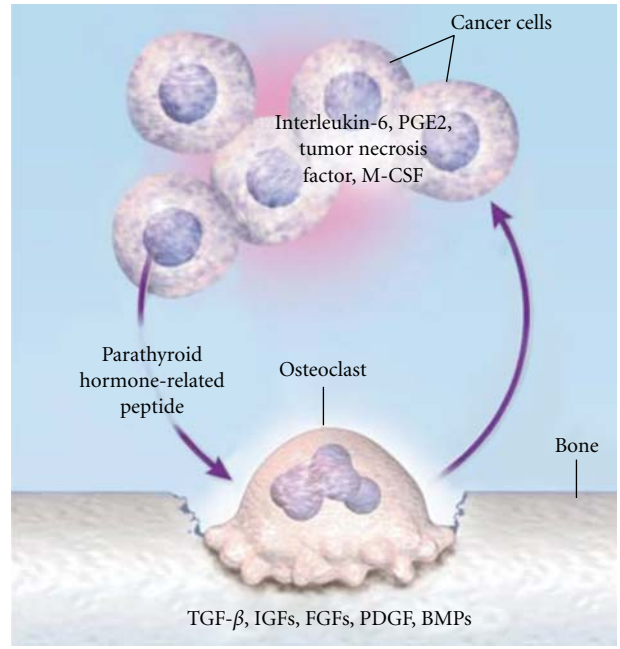


Figure 3: The Vicious Circle of Osteolytic Metastasis, from Roodman G. D., "Mechanisms of bone metastasis," *N Engl J Med.*, 15; 350 (16): 1655–64, Apr 2004.

lesions. After the tumour progression, the balance between Wnt and its inhibitors is shifted towards the first, promoting osteoblastic lesions [95, 96]. Nevertheless, PSA tumour-induced can block PTHrP [97] and then bone resorption and activating osteoblastic growth factors as TGFβ, l'IGF-1 released by bone during metastastic development, leading to a vicious circle also for osteoblastic lesions [13].

Abbreviations

ACS:	American Cancer Society
PTHrP:	Parathyroid-related peptide
uPA:	Urokinase-tipe plasminogen activator
MMPs:	Matrix metalloproteinases
BSP:	Bone sialoprotein
OPN:	Osteopontin
IL:	Interleukins
PGE2:	Prostaglandin E2
TGF:	Transforming growth factor
EGF:	Epidermal growth factor
VEGF:	Vascular endothelial growth factor
TNF:	Tumor necrosis factor
CSF:	Colony stimulating factor
GM-CSF:	Granulocyte macrophage-colony stimulating factor
M-CSF:	Monocyte-colony stimulating factor
RANK:	receptor activator of nuclear factor
IGF:	Insulin-like growth factor
FGF:	Fibroblast growth factor
PDGF:	Platelet-derived growth factor
BMP:	Bone morphogenetic protein
OPG:	Osteoprotegerin
ET:	Endothelin.

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Review Article

Imaging of Spinal Metastatic Disease

Lubdha M. Shah and Karen L. Salzman

Neuroradiology Division, Department of Radiology, School of Medicine, The University of Utah, 1A71 SOM, 50 N. Medical Drive, Salt Lake City, UT 84132, USA

Correspondence should be addressed to Karen L. Salzman, karen.salzman@hsc.utah.edu

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Metastases to the spine can involve the bone, epidural space, leptomeninges, and spinal cord. The spine is the third most common site for metastatic disease, following the lung and the liver. Approximately 60–70% of patients with systemic cancer will have spinal metastasis. *Materials/Methods*. This is a review of the imaging techniques and typical imaging appearances of spinal metastatic disease. *Conclusions*. Awareness of the different manifestations of spinal metastatic disease is essential as the spine is the most common site of osseous metastatic disease. Imaging modalities have complimentary roles in the evaluation of spinal metastatic disease. CT best delineates osseous integrity, while MRI is better at assessing soft tissue involvement. Physiologic properties, particularly in treated disease, can be evaluated with other imaging modalities such as FDG PET and advanced MRI sequences. Imaging plays a fundamental role in not only diagnosis but also treatment planning of spinal metastatic disease.

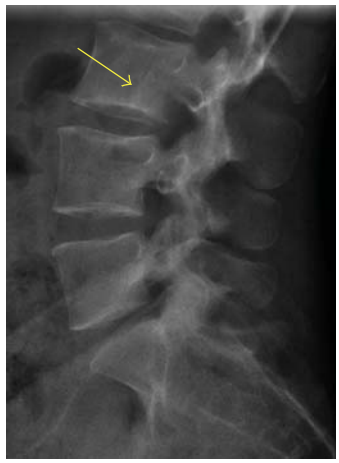
1. Introduction

Metastases to the spine can involve the bone, epidural space, leptomeninges, and spinal cord. The spine is the third most common site for metastatic disease, following the lung and the liver [1] and the most common osseous site [2]. Approximately 60–70% of patients with systemic cancer will have spinal metastasis. Fortunately, only 10% of these patients are symptomatic. The frequency with which spine metastases are detected varies considerably with the type of primary tumor. Common tumors with a high rate of metastasis to bone include tumors of the breast (72%), prostate (84%), thyroid (50%), lung (31%), kidney (37%), and pancreas (33%). Together, these account for more than 80% of primary tumors in patients presenting with metastases [3, 4]. The extradural lesions account for up to 95% of spinal lesions and can be divided into pure epidural lesions and those originating from the vertebra extending to the epidural space and subsequently impinging on the thecal sac [5]. The thoracic spine is most commonly involved. Intradural extramedullary and intramedullary seeding of systemic cancer is unusual, accounting for 5–6% and 0.5–1% of spinal metastases, respectively. In general, the prognosis for patients presenting with bone metastases is poor [6].

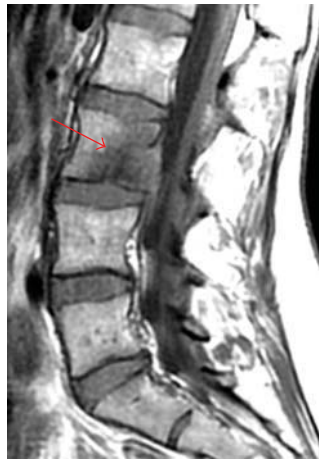
2. Imaging Techniques and Pitfalls

2.1. Radiography. Radiographs are an ubiquitous modality for the evaluation of back or neck pain in the setting of trauma or in the evaluation of degenerative changes. However, X-rays necessitate a 1 cm diameter mass and 50% bone mineral loss at minimum for detection. Up to 40% of lesions will be unidentified by X-rays, presenting false-negative results [7] (Figure 1). Radiography may be a crude assessment of the risk of pathologic fracture, which is said to be high if 50% of the cortex is destroyed by tumor [6]. Epidural lesions may demonstrate osseous erosion along the posterior vertebral body margin or pedicles. Rarely, metastases may cause scalloping of the adjacent bone.

2.2. Nuclear Medicine. Nuclear medicine bone scans (bone scintigraphy) have been the standard initial imaging method for screening for skeletal metastases. Tracer accumulates in the reactive new bone that is formed in response to the lesion (Figure 2). The amount of accumulation is sensitive to the level of blood flow. Although most metastatic lesions are "hot," lesions that are cold due to the complete absence of reactive bone or poor blood flow may be encountered in



(a)



(b)

Figure 1: (a) Lateral radiograph is poor at delineating the L3 vertebral body metastatic lesion, which appears as a faint lucency with a subtle sclerotic margin (yellow arrow). (b) This lesion is better seen on the sagittal T1-weighted MRI as an ill-defined hypointensity (red arrow) within the L3 marrow.

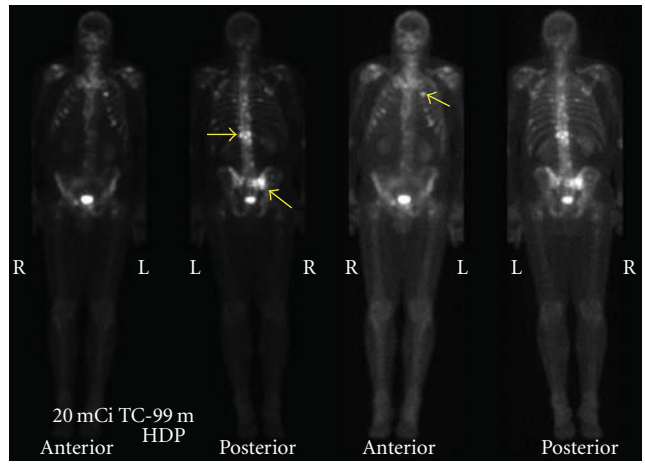


Figure 2: Anterior and posterior bone scan planar images reveal multiple foci of increased radionuclide uptake, not only in the thoracic and lumbar spine but also in the ribs and sacrum (yellow arrows).

particularly aggressive metastases. Diffuse accumulation of tracer throughout the skeleton (super scan) may occasionally occur in disseminated skeletal disease, leading to the false impression of a normal scan. This is most common with prostate carcinoma. False-negative studies are most common with multiple myeloma (up to 25% of cases), leukemia, and anaplastic carcinomas. Single-photon-emission computed tomography (SPECT) scanning. SPECT imaging has improved both the sensitivity and the specificity of bone scanning [8], particularly with larger lesions and cortical involvement. Because tracer accumulation may occur at any skeletal site with an elevated rate of bone turnover, radionuclide uptake may be nonspecific and may accompany trauma, infection, arthropathy, or osteopenia of disuse. In a patient with a known primary tumor, a scan showing multiple lesions strongly suggests metastases. However, only 50% of solitary foci represent metastases, even in patients with cancer [6]. Positive scans should be correlated with contemporaneous radiographs because of this lack of specificity.

[^{18}F]fluoro-2-deoxy-d-glucose positron emission tomography (FDG-PET) can detect increased glucose metabolism of neoplastic cells nested in the bone marrow, making it a sensitive method for assessment of bone and bone marrow metastases. [^{18}F]-FDG PET alone and [^{18}F]-FDG PET registered with CT have a reported sensitivity of 74% and 98%, respectively, in the detection of spinal metastasis [9]. [^{18}F]-FDG PET is reportedly more sensitive than bone scintigraphy in patients with lung cancer and lymphoma and was shown to detect early bone marrow involvement before cortical changes could be seen by bone scintigraphy [10, 11]. [^{18}F]-FDG PET is more sensitive for detection of osteolytic metastasis than of osteoblastic metastasis [12]. Schmitz et al. demonstrated that [^{18}F]-FDG PET is able to differentiate between osteoporotic and malignant vertebral compression fractures in patients with [^{18}F]-FDG-avid tumors [13].

2.3. Computed Tomography. Computed tomography (CT) scans can recognize a bony metastatic lesion up to 6 months earlier than an X-ray [7]. CT gives superb osseous delineation and enables detection of cortical destruction (Figure 3). An epidural mass may present as amorphous soft tissue displacing the thecal sac or filling the neural foramen (Figure 4).

Although 16/64-row-MDCT provides excellent image quality and a high spatial resolution in the assessment of bony structures, metastatic lesions without significant bone destruction may be missed. Buhmann et al. found the diagnostic accuracy of MRI (98.7%) to be significantly superior to 16/64-row-MDCT (88.8%) for the detection of osseous metastases [14]. Sensitivity was significantly lower for MDCT (66.2%) than for MRI (98.5%) ($P < 0.0001$). The specificity was not significantly different for both methods (MDCT: 99.3%; MRI: 98.9%). One disadvantage of CT is the beaming hardening artifact that obscures the adjacent soft

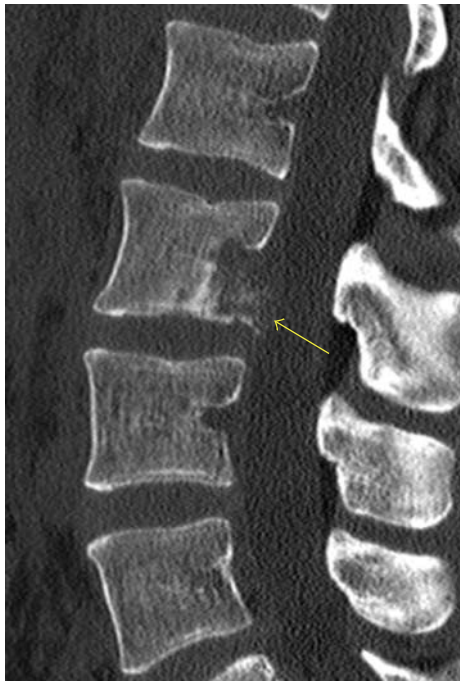


Figure 3: Sagittal CT reformation in bone algorithm depicts a cortical break in the posterior cortex of the L3 vertebral body (yellow arrow) due to a metastatic focus.

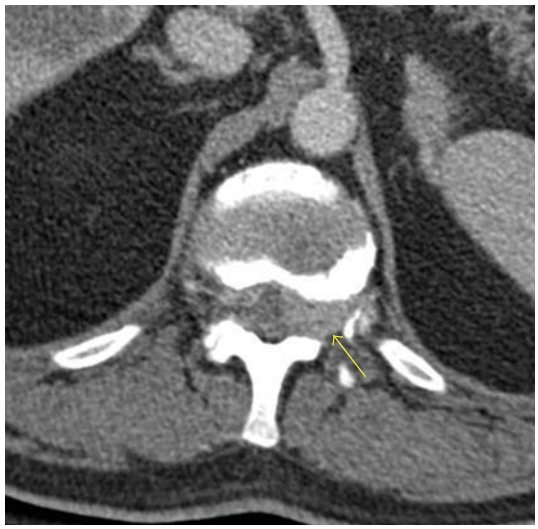


Figure 4: Axial CT in soft tissue algorithm displays slightly hyperdense soft tissue in the ventrolateral epidural space filling the left neural foramen (yellow arrow) and causing mass effect on the thecal sac.

tissues and bones. Another disadvantage of CT is that cortical destruction may be difficult to detect when osteoporosis or degenerative changes occur [15]. Finally, there is an inherent associated risk of radiation exposure from the CT.

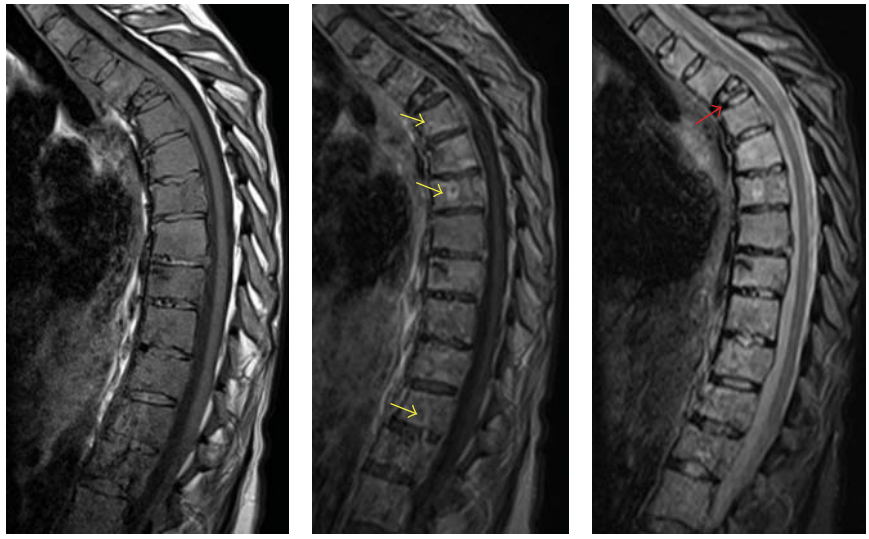
2.4. CT Myelography. CT myelography is a helpful technique in those patients who cannot undergo an MRI (e.g., patients with pacemakers, extreme claustrophobia). It allows assessment of osseous integrity as well as the thecal sac contents and has the added benefit of allowing CSF sampling at the same time as the diagnostic test is performed. Soft tissue characterization is better performed with MRI. CT myelography may show metastatic disease as thickened nerve roots, subarachnoid masses, and/or blockage of the subarachnoid space.

2.5. Magnetic Resonance Imaging. Unlike CT, which detects bony abnormalities, particularly cortical destruction, magnetic resonance (MR) imaging can detect early bone marrow deposits (Figure 5). Studies have shown that MR imaging has a significant impact on spinal tumor evaluation [16]. Specific relevant diagnostic information that can be gleaned from MR imaging of the spine includes the diagnosis of metastasis, the characterization of the levels of involvement, and the diagnosis of any associated cord compression. Both bony involvement and neural compression from epidural tumor are demonstrable by MR imaging. MRI is the only imaging technique that allows direct visualization of bone marrow and its components with high spatial resolution. The combination of unenhanced T1-weighted-spin echo- and STIR-sequences have shown to be most useful for the detection of bone marrow abnormalities and are able to discriminate benign from malignant bone marrow changes. Because of its sensitivity to bone marrow abnormalities, MRI may serve to guide biopsy of areas of abnormal signal intensity [17].

2.6. MR Sequences. Normal marrow contains both fat and water (yellow marrow 80% fat, but also 15% water, and red marrow 40% fat and 40% water). In infiltrative disorders, fat disappears in a diffuse, disseminated or solitary way. Sequences displaying differences between fat and water signal are thus useful.

2.7. T1-Weighted Spin-Echo (SE) Sequences. Fat has a shorter signal than water and the highest signal. Thus, fatty marrow containing 80% fat exhibits a high signal and any focal lesion showing a lower signal is easy to detect. This explains why this sequence is very useful and usually the first used. Hematopoietic marrow, containing water but also fat, is hypointense to fat, but hyperintense to normal muscles. At 1.5 T, a marrow signal which is hypointense to the muscles and discs in the spine is abnormal with an accuracy of 94% and 98%, respectively [18]. The study by Zhao et al. showed a higher diagnostic accuracy using signal intensity of muscle (89%) versus disk (78%) at 3 T field strength [19]. Replacement of the bone marrow always appears hypointense relative to normal marrow on T1-weighted images [17, 20]; however, this hypointensity is nonspecific. Extensive replacement of the vertebral bone marrow may initially create the impression of a normal study (Figure 5).

2.8. T2-Weighted Sequences. Conventional spin echo (SE) and fast spin echo T2 sequences have been shown to detect the same number of lesions [21] with the latter being a much more rapid sequence. On T2-weighted images, metastatic



(a) (b) (c)

Figure 5: Sagittal T1-weighted MR image (a) of the thoracic spine illustrates diffuse marrow hypointensity, which is slightly hypointense relative to the discs. Given the diffuse marrow involvement, it may be difficult to discern this marrow abnormality. Gadolinium-enhanced T1-weighted MR image (b) depicts multiple heterogeneously enhancing lesions (yellow arrows). The STIR MR image (c) shows abnormally increased signal in the posterior elements and the vertebral bodies. A compression fracture is seen in the upper thoracic spine (red arrow).

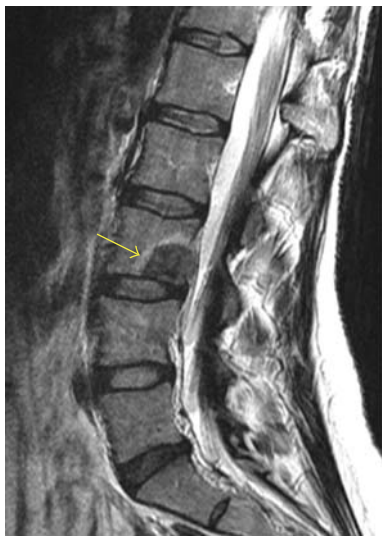


Figure 6: Sagittal T2-weighted MR image depicts the "halo sign" with a hypointense metastatic lesion and a surrounding hyperintense rim in the L3 vertebral body (yellow arrow).

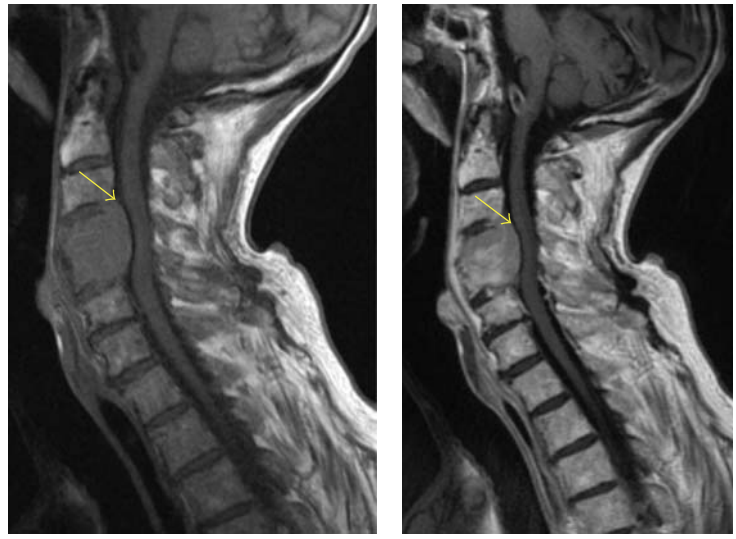
lesions are usually much brighter than bone marrow, due to their high water content. Metastases often (but not consistently) have a rim of bright T2 signal around them (a halo sign) [22] (Figure 6). The halo sign and diffuse signal hyperintensity were shown to be a strong indicator of metastatic disease (sensitivity, 75%; specificity, 99.5%). The bull's-eye sign (focus of high signal intensity in the center of an osseous lesion) is a specific indicator of normal hematopoietic marrow (sensitivity, 95%; specificity, 99.5%) [22].

Contrast is typically administered in standard tumor imaging as it allows for identification of intramedullary and intradural extramedullary abnormalities and extradural lesions (particularly in the epidural space) that may result in compression of the spinal cord and alter treatment [23] (Figure 7). However, on T1-weighted sequences, enhancing metastases may become isointense with normal bone marrow and become obscured. Sequences that suppress the signal intensity of normal fatty bone marrow allow clear identification of the enhancing metastatic foci [24]. T1 postcontrast with fat saturation can increase the conspicuity of enhancing marrow lesions by suppressing the background bright fatty marrow signal.

2.9. Fat Suppression Techniques. A 180 inversion pulse is used initially for short tau inversion recovery (STIR) sequences [25]. The inversion time is chosen to cancel the signal of fat. This sequence can be obtained on any MR unit, but it is unfortunately time consuming and only a limited number of slices can be acquired. This can be overcome by using fast STIR sequences.

Although the conspicuousness of lesions is similar on fat-saturation T2-weighted and STIR images, the former sequence has several practical advantages, including acquisition of more slices per unit time and improved tissue specificity [25]. The combination of T1-weighted and either fat-saturation T2-weighted or STIR images is highly effective for the evaluation of bone marrow lesions. On fat-suppressed, T1-weighted images, metastases demonstrate mixed-to-high signal intensity, whereas nonneoplastic lesions have low signal intensity [26]. Fat saturation techniques are particularly sensitive to susceptibility artifact from spinal hardware.

2.10. Diffusion-Weighted Imaging (DWI). DWI evaluates the tissue-specific molecular diffusion of protons. In tissues with



(a) (b)

Figure 7: Sagittal T1-weighted MR image (a) shows a hypointense expansile lesion involving the C4 and C5 vertebral bodies with extension into the ventral epidural space (yellow arrow). The lesion enhances homogeneously on postcontrast T1-weighted MR (b); however, the degree of normal marrow enhancement is similar to that of the metastatic myeloma lesion.

high cell densities (neoplasm), a decreased ADC can be expected due to restricted diffusion according to an exaggerated amount of intra- and intercellular membranes (i.e., diffusion barriers). The utility of DWI on differentiating benign from metastatic spinal lesions is controversial in the literature. One study using DWI found all benign vertebral compression fractures from hypo- to isointense to adjacent normal vertebral bodies and pathologic compression fractures were hyperintense to normal vertebral bodies [20]. However, Castillo et al. show in their series of 15 patients that DWI of the spine showed no advantage in the detection and characterization of vertebral metastases as compared with noncontrast T1-weighted imaging, but was considered superior to T2-weighted imaging [27]. Others have demonstrated that rather than qualitative assessment, the quantitative evaluation of the ADC in vertebral bodies may be an objective and comparable parameter for differentiating malignant from benign vertebral tissue [28].

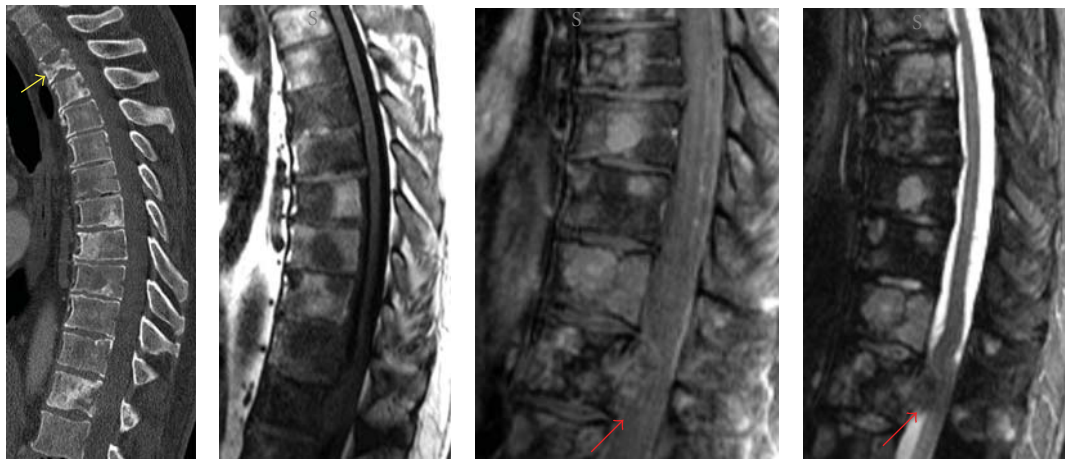
Unfortunately, MRI often cannot distinguish among changes that are due to treatment, fracture, and tumor. Hanna et al. compared MRI scans with histologic specimens at 21 sites, 7 of which contained tumor and 14 of which did not. For all of the tumor positive sites, abnormalities were revealed on MRI scans. However, for the sites shown to be free of tumor, there was a significant false-positive rate, presumably because tumor could not be distinguished from the effects of treatment [29]. DWI sequences may show decreased signal intensity of metastatic disease of the vertebral marrow with successful treatment [30].

2.11. Whole Body MRI. Whole-body MRI represents a new alternative to the stepwise multimodality concept for the detection of metastatic disease, multiple myeloma, and lymphoma of the bone with high diagnostic accuracy [24]. The introduction of a rolling platform mounted on top of a conventional MRI examination table facilitates whole body MR imaging and—with the use of fast gradient echo, T1-weighted, and STIR-imaging techniques—allows whole body imaging within less than one hour. With the development of parallel imaging techniques in combination with global matrix coil concepts, acquisition time is reduced substantially without compromises in spatial resolution, enabling the implementation of more complex and flexible examination protocols.

3. Pathology

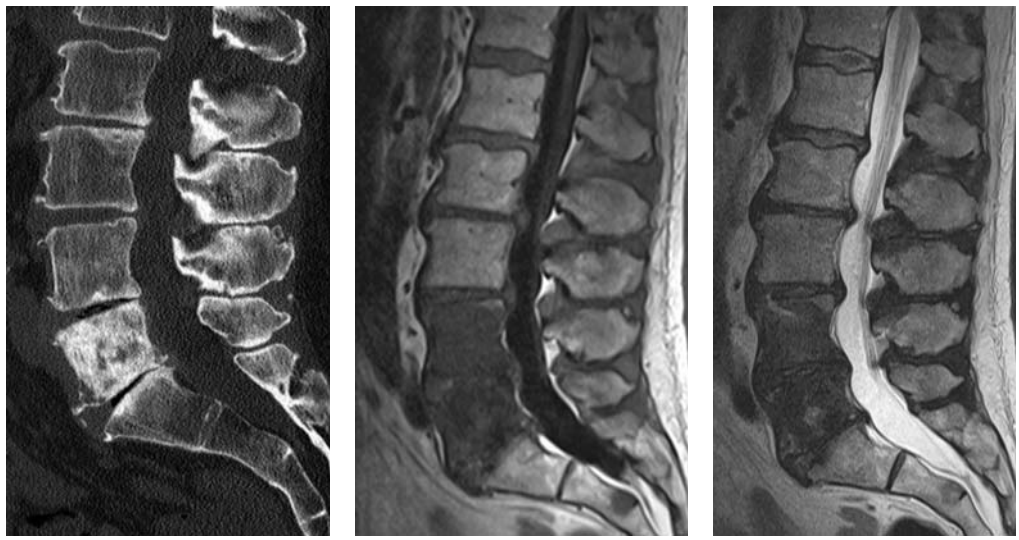
Bone destruction, secondary to metastases, is caused by the activation of osteoclasts rather than by the direct destruction of bone by tumor cells. Mundy and Yoneda proposed that cells from the primary site migrate or through the process of neovascularization attach to the basement membrane of the vessel wall and produce proteolytic enzymes that disrupt the basement membrane [31]. The tumor cells then migrate to a distant site hematogenously attaching to the basement membrane of the vessel wall using proteolytic enzymes (integrins/cadherins). After disrupting the receptor site basement membrane, they migrate into the substance of the distal host tissue. Producing the chemotactic factors, as well as RANK ligand, these cells stimulate osteoclast activity to produce bone resorption. A feedback relationship, such as that present in myeloma cells, produces continued osteoclast stimulation for bone resorption and tumor cell growth. This continued growth and survival of the metastatic cells progressively des troys cancellous and cortical bone at the distant osseous site.

Primary tumors which typically have lytic spinal metastases are breast, lung, kidney, thyroid, oropharyngeal, melanoma, adrenal, and uterus. Breast and lung cancer may also



(a) (b) (c) (d)

Figure 8: Sagittal CT reformation (a) shows multiple lytic and blastic metastatic breast cancer lesions in the thoracic spine with a compression fracture in the upper thoracic spine (yellow arrow). Sagittal T1-weighted image (b) shows multiple hypointense lesions, many of which enhance on the postcontrast T1-weighted MR (c). The STIR image (d) depicts both hyperintense (lytic) and hypointense (blastic) lesions. A mildly enhancing epidural component compresses the thecal sac (red arrows).

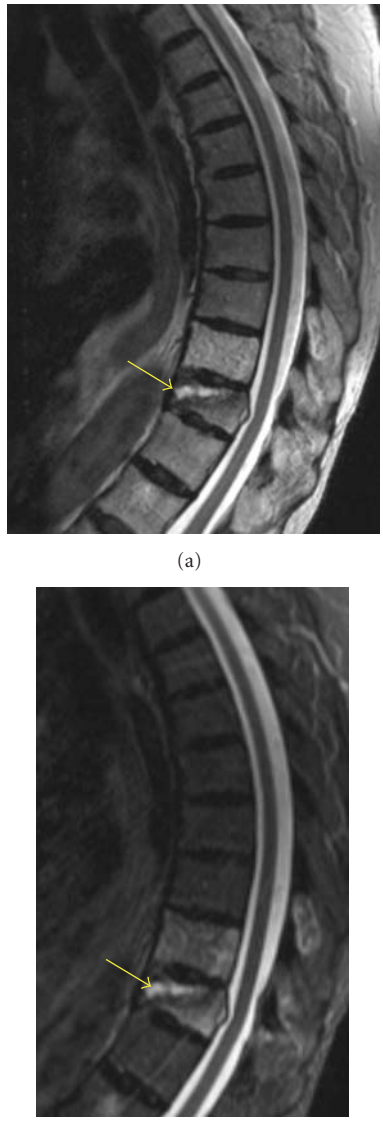


(a) (b) (c)

Figure 9: Sagittal CT reformation of the lumbar spines (a) shows a large sclerotic lesion nearly completely involving the L5 vertebral body. Sagittal T1-weighted (b) and T2-weighted (c) images show abnormal hypointense marrow signal in not only the L5 vertebral body but also the L4 vertebral body, corresponding to blastic metastatic lesions.

show mixed lytic and sclerotic lesions, which are seen with ovarian, testicular, and cervical carcinomas (Figure 8). Lytic lesions involve the posterior cortex almost always with destruction of the posterior cortex and pedicle. If the discs appear brighter than bone on T1-weighted MR, it is concerning for diffuse marrow infiltration. Lytic lesions typically exhibit diffuse enhancement. Progressive sclerosis of a lytic focus generally indicates a positive response. However, if there is persistently low T1 signal in marrow after therapy, this may indicate either active tumor or fibrosis. Functional techniques such as DWI and in phase/opposed phase are being investigated as potential MR sequences for such diagnostic dilemmas [32].

Prostate, bladder, nasopharynx, medulloblastoma, neuroblastoma, and bronchial carcinoid primaries commonly have blastic-appearing spinal metastases. The areas of sclerosis may be nodular or mottled in appearance. Occasionally, there may be diffuse areas of increased density on radiographs and CT with corresponding hypointensity on all MR sequences (Figure 9). Blastic metastases tend to destroy the posterior cortex and involve the pedicle. It is important to assess for an associated paraspinal or epidural component.



(a)

(b)

Figure 10: Sagittal T2-weighted (a) and STIR (b) MR images reveal abnormal hyperintense signal in a lower thoracic vertebral body due to fracture-related edema. A "fluid sign" is demonstrated in this vertebral body (yellow arrow), which is characteristic of a benign osteoporotic fracture.

Tumor may spread into the anterior epidural space with sparing of the meningovertebral ligament, resulting in the "draped curtain sign." The enhancement pattern is variable depending on the degree of sclerosis. Fat-suppression increases the conspicuity of enhancing lesions. It may be difficult to evaluate the therapeutic response of sclerotic lesions as tumor progression with osteolytic conversion appears similar to fading, which is seen in good response.

Hematogeneous spread of metastatic disease is far more frequent than lymphatic spread or direct invasion. The venous route, especially Batson's paravertebral plexus, appears to be more important than the arterial route. The distribution of Batson's venous plexus, as well as the overall skeletal vascularity, results in a predilection for hematogenous spread to the axial skeleton and the proximal long bones.

Metastases may reach the skeleton by direct invasion from the primary tumor or by extension from a secondary site, such as a lymph node. True lymphatic spread to the skeleton is rare. Direct invasion is usually accompanied by a detectable soft tissue mass, an unusual feature of metastases that occur by hematogenous spread.

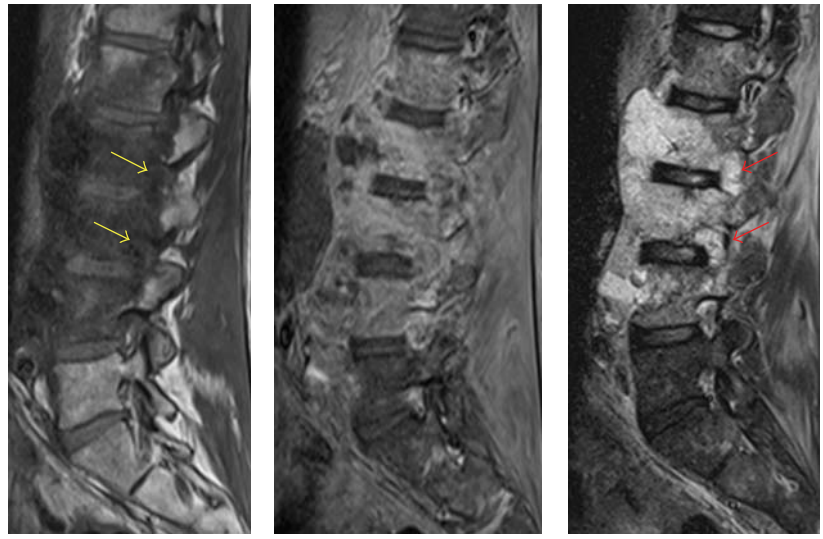
However, hematogeneous spread of metastatic disease is far more frequent than lymphatic spread or direct invasion. The venous route, especially Batson's paravertebral plexus, appears to be more important than the arterial route. The distribution of Batson's venous plexus, as well as the overall skeletal vascularity, results in a predilection for hematogenous spread to the axial skeleton and the proximal long bones.

3.1. Disease Progression. Symptomatic spinal cord compression is seen in approximately 10%–20% of cases with metastatic spinal involvement [2]. Research has shown that noncontrast T1-weighted images are probably the most useful type of images in adult patients with clinically suspected cord compression, because vertebral metastases are most often appreciated with this MR imaging sequence [33–35]. A study comparing different MR protocols found unenhanced T1-weighted images may be sufficient for evaluation of possible cord compression and guiding radiation treatment [36].

Benign compression fractures and malignant lesions can show a considerable overlap. Edema in a benign compression fracture in the acute phase replaces the normal marrow, resulting in hypointensity on T1-weighted images and hyperintensity on T2-weighted images. The vertebral body with benign fracture may show enhancement. The morphology of bone marrow replacement may be helpful for prediction of the benign or pathologic cause of a fracture. Conventional MRI features have been cited to suggest pathologic fracture: a convex posterior border of the vertebral body, abnormal signal intensity of the pedicle or posterior element, an encasing epidural mass, a focal paraspinal mass, and other spinal metastases [37]. Paravertebral soft-tissue masses and infiltration of posterior elements are the most reliable signs of a malignant fracture. MR imaging findings suggestive of acute osteoporotic compression fractures include a low-signal-intensity band on T1- and T2-weighted images, spared normal bone marrow signal intensity of the vertebral body, retropulsion of a posterior bone fragment, and multiple compression fractures [37]. The MR fluid sign has been described in avascular necrosis of the vertebral body [38, 39] and is a common finding in acute and subacute benign osteoporotic vertebral fractures [39]. Up to 40% of these fractures may show the fluid sign [40] (Figure 10). Morphologic criteria may accurately predict benign from malignant fractures of the spine in up to 94% of cases [41].

Quantitative ADC mapping, instead of qualitative diffusion-weighted imaging, may provide valuable information in differentiating benign vertebral fractures from metastatic lesions [42]. Lower ADC values have been demonstrated in pathologic fractures [42].

Vertebral metastases may invade the epidural space by direct extension from adjacent bone through the posterior



(a) (b) (c)

Figure 11: Sagittal T1-weighted MR image (a) shows abnormal hypointensity related to invasion by a paraspinal mass (spindle cell sarcoma). The cortical margins of the pedicles are attenuated (yellow arrows) in keeping with erosive changes of the mass invading through the neural foramina into the lateral epidural space. The postcontrast T1-weighted MR image with fat-saturation (b) shows heterogeneous enhancement of the mass. Marrow infiltration and neuroforaminal involvement (red arrows) is well seen as hyperintense signal on the STIR MR image (c).

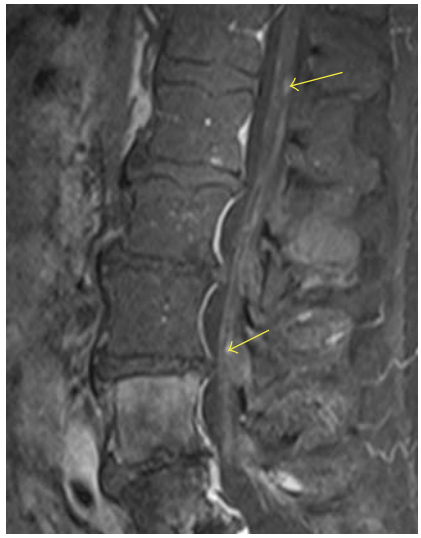
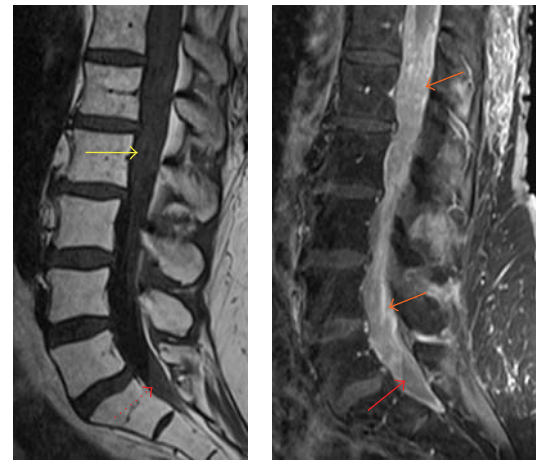


Figure 12: Sagittal contrast-enhanced T1-weighted MR image with fat saturation reveals multiple small enhancing lesions (yellow arrows) along the cauda equina, related to leptomeningeal carcinomatosis in a patient with breast cancer.



(a) (b)

Figure 13: Sagittal T1-weighted MR image (a) shows a hazy appearance of the subarachnoid space (yellow arrow) in the distal thecal sac. Fluid layers dependently in the thecal sac from blood products and/or proteinaceous debris (red arrows). Sagittal enhanced T1-weighted MR image (b) with fat-saturation shows diffuse enhancement of the CSF as well as thick sheet-like enhancement of the cauda equina (orange arrows) related to metastatic melanoma.

longitudinal ligament, by extension through the intervertebral foramina, by hematogenous dissemination, or very rarely by lymphatic infiltration. Involvement of the epidural space may result in compression of the spinal cord or cauda equina or in radiculopathy because of compression of nerve roots [43]. The neurologic symptoms due to the soft tissue material impinging upon the epidural venous plexus results in venous hypertension and vasogenic edema [44]. The epidural tumor [44] and/or the vertebral collapse [45] may have direct mass effect in the spinal cord leading to neurologic deterioration. However, occasionally the involvement may be asymptomatic.

Bone destruction is seen often, up to 86% of the time [46], at the level of epidural tumor involvement (Figure 11). Pedicular erosion on radiographs predicts epidural disease in 31% of cases [47]. Epidural metastasis is often contiguous with a vertebral body lesion. The meningovertebral ligament

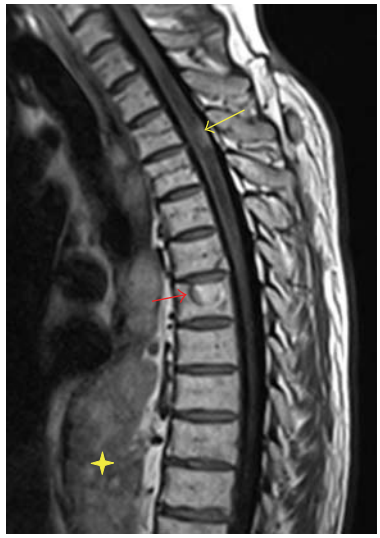
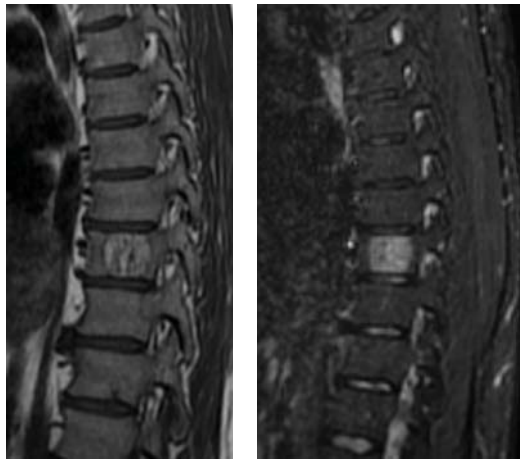


Figure 14: Sagittal T1-weighted MR image reveals an intramedullary hyperintense lesion in the dorsal upper thoracic cord from a melanoma metastasis (yellow arrow). There is extensive surrounding hypointensity due to spinal cord edema. Additionally, there is a T1 hyperintense vertebral body metastatic lesion (red arrow). Large lobulated paraspinal masses are also noted (yellow star).



(a) (b)

Figure 15: Sagittal T1-weighted (a) and STIR (b) MR images depict a well-circumscribed lesion in a mid thoracic vertebral body. The hyperintense signal and linear hypointensities, which correspond to thickened trabeculae, are characteristic of a benign hemangioma.

is characteristically spared giving the "draped curtain" appearance. Lesions tend to be T1 hypointense, T2 hyperintense, and avidly enhancing. In cases on spinal epidural lymphoma, the spinal column may actually be spared. Contrast enhancement is helpful in delineating the extent of tumor and may help in outlining regions of spinal cord compression [35]. This is particularly useful in the cervical and thoracic spine where there is relative paucity of epidural fat and prominent ligaments, which typically increase the conspicuity of epidural lesions. The thoracic spine is more often (~60%) involved in neoplastic epidural spinal cord compression as compared to ~30% in the lumbosacral spine [48]. This predilection may be due to the reduced potential space available for tumor to expand.

Leptomeningeal carcinomatosis (LC) has an incidence as high as 4–15% in patients with solitary tumors, 5–15% in patients with leukemia and lymphoma, and 1-2% in patients with primary brain tumors [40, 49]. In autopsy studies, the rate has been estimated to be 19% in patients with cancer and neurologic signs [50]. It is most commonly found in breast carcinoma, lung carcinoma, and melanoma in adults and hematogenous malignancies and primitive neuroectodermal tumor (PNET) in children. Less commonly, prostate cancer can spread to the leptomeninges. Melanoma and lung cancer have the highest rates of spread to the leptomeninges at 20% and 11%, respectively [51, 52]. The routes of dissemination to the meninges include hematogenously though Batson's venous plexus or arterial spread, direct extension from contiguous foci of tumor, and perineural or perivascular migration from systemic tumors [53, 54]. Tumor cells in the CSF are carried throughout the neural axis, particularly the base of the brain and the dorsal spinal cord surface and cauda equina [54].

Spinal symptoms of LC include extremity weakness (greater lower extremity involvement), dermatomal or segmental sensory loss, and neck and/or back pain [49, 55]. While there are clinical signs and radiologic findings that strongly suggest LC, most cases are diagnosed by CSF cytology or leptomeningeal biopsy. As the diagnostic accuracy of lumbar puncture (LP) is only 50–60% after a single LP and 90% after 3 LPs, MRI is considered complementary and can be invaluable, detecting up to 50% of cases with false-negative LPs. It is important to note that CSF levels of protein, glucose, and malignant cells vary at different levels of the neuraxis even without an obstructive lesion [56].

Imaging the whole neuraxis is required as LC can involve the entire CNS. Detection of CNS enhancement indicates a poor prognosis [57]. MRI and CT may demonstrate multiple masses within the subarachnoid space, hydrocephalus without a discernible cause, or diffuse leptomeningeal enhancement. The latter enhancement pattern has been referred to as sugar icing or "zuckerguss" and can be found in the brain, spine, or both. The nerve roots may be thickened, particularly of the cauda equina, and there may be subarachnoid nodules (Figure 12). CSF enhancement is uncommon but when seen indicates massive tumor that coats the surface of the CNS (Figure 13). Radioisotope CSF flow studies may be performed to prior to intrathecal chemotherapy in order to ensure no obstruction of CSF flow and homogeneous distribution of the chemotherapeutic agent.

Gadolinium-enhanced T1-weighted MRI is superior to contrast-enhanced CT in detecting abnormal leptomeningeal enhancement and the complications of meningitis including cerebritis and ventriculitis. Sze et al. reported the efficacy with which gadolinum-enhanced MRI of the spine can detect even small lesions in the intradural extramedullary space [58]. However, other studies have shown that the evaluation of leptomeningeal metastasis with MRI and CT modalities may have a high incidence of false-negative

studies, 89% (31 of 35) by CT and 24% (4 of 17) by MRI [59]. The literature reports a difference in sensitivity between solid tumors and hematologic malignancies, with one study reporting a sensitivity of 90% in patients with solid tumors but only 55% in patients with lymphoma and leukemia [60].

Intramedullary spinal metastatic lesions are exceedingly rare, representing only 8.5% of all CNS metastases. They affect an estimated 0.5–2% of patients with cancer and comprise 1–3% of all intramedullary spinal cord tumors [61–63]. Intramedullary spinal cord metastases are due to lung cancer in 50–60% of cases with small cell lung cancer comprising 50% of these cases [61–63]. The presence of an intramedullary spinal metastatic lesion suggests an advanced biologically aggressively form of cancer. The metastatic deposits are usually solitary but may be multifocal in 15% of cases [63].

The mechanism of metastatic spread from the primary tumor to the spinal cord is thought to be hematogenous via an arterial route in the majority of cases. In some cases, there may be retrograde spread from the vertebral venous plexus or directly from the CSF via perivascular spaces in patients with LC. Extension from an adjacent neoplasm directly though the dura or by perineural spread has also been speculated.

The characteristic MRI finding is a small, intensely enhancing lesion, typically less than 1.5 cm, with extensive associated edema. There may be an enlargement of the cord. T1 hyperintensity may be detected with melanoma spinal cord metastases (Figure 14). Hemorrhagic intramedullary metastases may demonstrate hypointensity on T2 and T2* gradient-recalled echo images.

3.2. Spinal Metastatic Disease Mimics. The imaging differential diagnosis of vertebral body metastasis would include benign hemangioma, discogenic endplate changes, and discitis-osteomyelitis. Vertebral hemangiomas are typically well-circumscribed, benign vascular tumors, which are T1 hyperintense (Figure 15). These lesions may be dark or bright on STIR sequences dependent on the proportion of fatty and vascular elements. The coarse vertical trabeculae resemble corduroy or honeycomb of radiographs. Internal trabeculae may be subtle on MRI and may be better delineated on CT in cases of "atypical" hemangiomas. Given the vascular component of these lesions, enhancement is common. Type 1 fibrovascular discogenic endplate changes display T1 hypointensity, T2 and STIR hyperintensity, and enhancement. The signal changes parallel the endplates, and the disc space usually shows loss of height and low T2 signal due to degeneration. Similarly, acute intravertebral disc herniation or Schmorl's node will demonstrate signal abnormality related to edema, including T1 hypointensity and T2/STIR hyperintensity. In discitis-osteomyelitis, there are endplate erosions with intradisc fluid and patchy enhancement. The adjacent endplates demonstrate abnormal fluid marrow signal and enhancement. Osseous metastases typically do not cross the disc space from one vertebral body to the next. The avascular disc is resistant to tumor invasion.

Other lesions that may involve the epidural space include epidural hematoma and epidural phlegmon/abscess. Epidural hematoma is generally contained in the "less common" spectrum of intraspinal, extradural lesions, particularly in the absence of sentinel events such as surgical manipulation or trauma. Spontaneous epidural hematomas are rare but have been reported in patients on anticoagulation [64], those with vascular malformations [65] and in pregnancy [66]. A rare case report of spinal epidural hematoma associated with unsuspected metastatic lung cancer has been described [61]. Depending on the status of the hemoglobin and its intracellular versus extracellular location, the MR features will vary. In the acute stage, it will be hyperdense on CT with progressive hypodensity as the blood products evolve. The dorsal epidural space is more often involved with the multisegmental fluid collection. There may be peripheral enhancement; however, focal enhancement should be concerning for active extravasation [67].

Epidural abscess or phlegmon is often seen in association with spondylodiscitis. Hematogenous dissemination from gastrointenstinal, genitourinary, cutaneous, lung, and cardiac infection sources is also possible. Direct inoculation from iatrogenic procedures or trauma is an additional etiology of spinal epidural abscess. The posterior epidural space is involved more often than the anterior epidural space. Peripheral enhancement with a necrotic core (abscess) or diffuse enhancement (phlegmon) may be seen on contrast-enhanced T1-weighted MRI. Fat saturation techniques make lesions in the epidural space more evident by suppressing the normal epidural fat.

When evaluating an MRI with an intramedullary enhancing lesion, the differential considerations include demyelinating disease, granulomatous process, cord infarction, cord vascular malformation, and primary cord tumor (such as astrocytoma, ependymoma, hemangioblastoma). Clinical history may provide clues to narrow the differential diagnosis. For instance, CSF positive for oligoclonal bands and waxing and waning symptoms in a young female adult would favor a demyelinating process. Osseous metastases in a patient with a known primary malignancy would make an enhancing intramedullary lesion more suspicious for an intramedullary metastasis. Prominent vascular flow voids along the cord surface in addition to intramedullary edema are helpful in determining if the lesion is a spinal arteriovenous malformation.

4. Conclusion

Awareness of the different manifestations of spinal metastatic disease is essential as the spine is the most common site of osseous metastatic disease. Imaging modalities have complimentary roles in the evaluation of spinal metastatic disease. CT best delineates osseous integrity while MRI is better at assessing soft tissue involvement. Physiologic properties, particularly in treated disease, can be evaluated with other imaging modalities such as FDG PET and advanced MRI sequences. Imaging plays a fundamental role in not only diagnosis but also treatment planning of spinal metastatic disease.

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Review Article

Current Insights into Surgery for Intramedullary Spinal Cord Metastases: A Literature Review

Ondrej Kalita

Neurosurgical Department, University Hospital and Medical Faculty of Palacky University Olomouc, I.P. Pavlova 6, 77520 Olomouc, Czech Republic

Correspondence should be addressed to Ondrej Kalita, kalitao@email.cz

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Intramedullary spinal cord metastasis (ISCM) is the rarest type of CNS involvement by systemic malignant tumours. Optimal management of patients with ISCMs remains ambiguous. Based on two cases reported from our department, we focused on the strategy for intramedullary spinal cord metastases surgery.

1. Introduction

Intramedullary spinal cord metastases (ISCMs) are a rare complication of malignancy and have been identified in 0.9–2.1% of all neoplasm autopsies. ISCMs are often asymptomatic and clinically affect only 0.1–0.4% of all cancer patients. One-quarter of ISCM patients have leptomeningeal carcinomatosis, and one-third have concomitant brain metastases [1–5]. Additionally, ISCMs commonly create solitary lesions, constitute 8.5% of all central nervous system metastases, and comprise 4% to 9% of all spinal cord tumours. On the contrary, intracerebral metastases occur in 20–50% of all cancer patients, and multiple lesions develop in 30–50%. Despite the existence of tissue perfusion differences, the distribution of metastases in the brain and spinal cord has not been satisfactorily explained.

Optimal management of patients with ISCMs is difficult due to the wide variety of clinical situations and the lack of controlled studies on the results of different therapeutic options. Therapeutic options for ISCMs include microsurgical excision; radiotherapy, currently mainly stereotactic radiotherapy; chemotherapy; palliative therapy, particularly steroids. Many authors have advocated radiation therapy, preferably for radiosensitive metastases such as small cell carcinoma, breast cancer, or lymphoma[1, 4, 6, 7]. From our point of view, surgery could be considered an optimal therapeutic approach for ISCMs, even accompanied by an acceptable postoperative functional outcome.

2. Materials and Methods

In the recent ten years, there has been substantial progress in oncotherapy, microsurgery, and MRI availability. We researched ISCM cases in Pubmed during this period, including retrospective analyses and meta-analyses. This resulted in limited bias due to the inclusion of ISCM surgery cases from the previous period. Both spinal extradural and primary brain metastases were beyond the scope of this paper and were excluded. Finally, cases of ISCMs managed by surgery were selected.

3. Results and Discussion

Eleven papers concerned with ISCM surgery have been published in the last ten years. Except for one review article, only case reports were found. However, two more abundant studies with 13 and 19 patients were also discovered. To sum up, a total of fifty-four patients underwent surgery. Laminectomy or osteoplastic laminotomy with tumour excision was performed in all but one. In this single case, only palliative decompressive laminectomy was done [8]. None of these developed new neurological deficits, and partial neurological improvement was achieved [1, 2, 4].

In the literature, tumour removal was identified as complete in 47 patients and incomplete in 5 patients, and surgical biopsy was done in 2 patients [1–10].

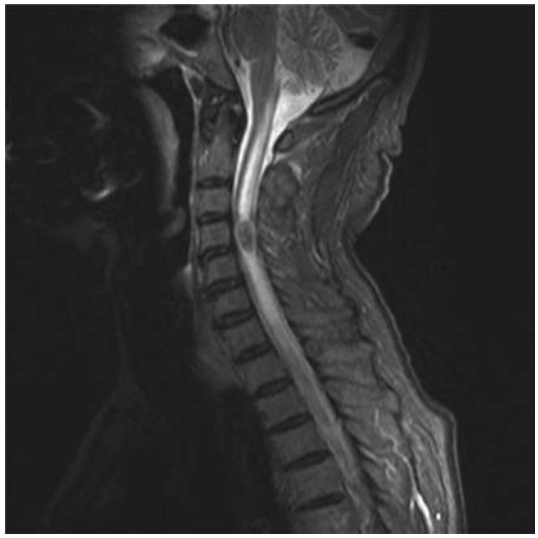

Figure 1: Intramedullary metastasis of colorectal carcinoma.

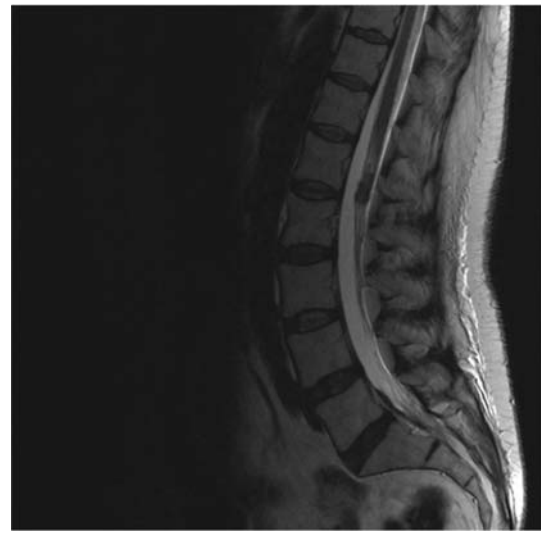

Figure 2: Cauda equine infiltration by breast carcinoma.

3.1. Incidence and Pathophysiology. Lung metastases, which account for about half of the ISCMs, were by far the most common source. The incidences of the various tumour primaries were lung (especially small cell carcinoma) 29–54%, breast 11–14%, kidney 6–9%, colorectal 3–5%, melanoma 6–9%, lymphoma 4%, thyroid 2%, ovarian 1%, and approximately 3% were categorized as secondary to an unknown primary [11].

ISCMs are mainly disseminated by the arterial route (Figure 1). Meningeal carcinomatosis occurs by CSF seeding. Tumour cells infiltrate the Virchow-Robin spaces of vessels, penetrating the spinal cord and pial membrane and invading the spinal cord parenchyma (Figure 2). A third mechanism is the direct invasion from contiguous structures. Spread through the vertebral venous plexus (Batson's plexus) during Valsalva manoeuvre enabling retrograde blood flow to the spinal cord is also possible. ISCMs concurred with meningeal carcinomatosis in 15–55% of cases. Finally, direct invasion from contiguous structures is also conceded. Although the dura protects the cord from invasion by malignant tumours, metastasis expansion from the spinal extradural space or nerve roots through the dura and into the cord has been suggested (Figure 3) [1, 12].

The above-mentioned discrepancy between the frequencies of brain and intramedullary metastases would be partly explained as follows. One-third of the cardiac output through the large vessels under high pressure directs to the brain, while the spinal cord receives arterial supply from small, low-pressure, and convoluted vessels. The medullary arteries branch off the aorta at right angles, while the cerebral arteries are almost a direct extension of the aorta, thus favouring embolic seeding [9].

3.2. Symptoms. Due to the advances in imaging and therapeutic modalities prolonging the survival of cancer patients, the probability of discovering ISCMs increases.

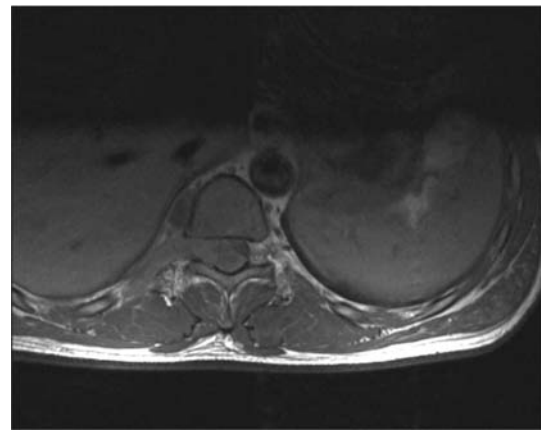

Figure 3: Direct intraspinal cancer invasion along nerve root.

ISCMs may be considered as an infrequent finding at advanced stage of disease, usually accompanying rapid progression of systemic cancer. But in much rarer cases, ISCMs are the initial presentation of malignancy. This occurred in 22.5% to 39% of ISCM cases [1, 4, 7].

Prompt diagnosis is important for treatment rationale. However, exact diagnosis of ISCMs may be difficult despite a positive history of malignancy, because clinical findings do not help to distinguish ISCMs from other lesions such as epidural metastasis, paraneoplastic necrotizing myelopathy, radiation myelopathy, or from a coincidence of nutritional, demyelinative, inflammatory, or vascular myelopathies [1, 7].

The published median intervals between the onset of ISCM-related neurological symptoms and the final diagnosis varied from 1 week to 2 weeks to 7 weeks to 9 weeks, with the greatest range being 17 months [1, 2, 4, 6, 7].

At diagnosis, about 20% of patients are ambulatory independent, 40% are ambulatory with assistance, and the remaining 40% are nonambulatory. Nevertheless, one author

somberly reported that three-fourths of patients developed a complete neurological deficit during less than one month from the onset of neurological symptoms [1, 2]. The described rapid symptom progression is elicited by the limited resistance of spinal cord tissue and vascular structures involved by an increasing tumour size and perifocal oedema. ISCMs predominantly affect elderly patients who commonly have serious comorbidities and, thus, myelopathy presents more acutely in them.

The range, pattern, and deterioration of the neurological status are based on ISCM location and volume. Clinically, ISCMs are manifested by pain, weakness, sensory loss, and incontinence. Brown-Sequard syndrome or complete spinal cord transection is nearly equally present. Pain is usually followed by sensory and sphincter disturbance [1, 2, 11].

Weakness was present in 91% of patients at diagnosis of ISCMs. Sensory loss (79%), sphincter dysfunction (60%), back pain (38%), and radicular pain (24%) were also common. Brown-Sequard syndrome or pseudo-Brown-Sequard syndrome was seen in 23–45% of cases. Asymptomatic cases have also been described (1%) [1, 2, 7, 10, 11].

3.3. Diagnosis. Currently, spinal magnetic resonance imaging (MRI) is applied routinely for the diagnosis of ISCMs. Before the era of MRI, only 5% were recognized before death. Other imaging techniques (CT, PET/CT, and angiography) are of marginal significance. Single ISCM is most commonly seen (94%) although multiple ISCMs (6%) are also encountered [1, 7].

Due to the general infrequency of ISCMs and the time elapsed from the first cancer attack, tumour duplicity, that is primary intraspinal neoplasm, would be the preferred diagnosis. ISCMs are typically characterized by rapid progression of symptoms in contrast to the relatively slow growth of primary intramedullary tumours (gliomas, ependymomas, etc.).

At the time of diagnosis, 55% of ISCM patients had systemic metastases, and an additional 41% had brain metastases. The other types reported included bone (24%), leptomeningeal (17%), pulmonary (13%), lymph node (12%), hepatic (8%), adrenal (2%), splenic, sacral, and rib metastases.

Cytological investigation of CSF is usually negative. Retrospectively, malignant cells in CSF were confirmed only in 11 patients. Nearly, in all ISCM patients (95%), CSF protein level was abnormally elevated. In older studies, one-half to two-thirds of meningeal carcinomatosis cases had malignant cells in CSF analysis. Thus, lumbar puncture and CSF analysis have limited significance for the diagnosis of ISCMs [1, 2, 4, 7].

3.4. Surgery and Survival. Currently, surgical approach is more precise and less invasive and thus allows spinal cord tumour excision with an acceptable morbidity rate. The purpose is decompression of functional neural tissue and histological confirmation of the tumour. Some authors documented that complete neurological deficit developed in 75% of ISCM patients within approximately one month. Given this result, surgical resection can be performed in these selected cases [1, 2].

Advanced technologies such as MR/CT navigation or ultrasound for tumour location, cavitron ultrasonic surgical aspirator and laser for dissection, and intraoperative monitoring of somatosensory evoked potentials have allowed limited myelotomy and a relatively safe tumour removal. Radicality also depends on tumour histology. Patients with adenocarcinoma had longer survival rates than those with poorly differentiated carcinomas. Poorly differentiated carcinomas and sarcomas are difficult to be managed by radical surgery due to the absence of a clear cleavage plane. In these cases, some authors recommend biopsy, decompressive laminectomy, and adjuvant therapy [2, 7, 13].

Many reports favoured radiotherapy (RT). However, given the rarity of ISCMs, no controlled studies comparing surgery and RT were undertaken.

The median survival of patients with ISCMs depends on several conditions. The survival was influenced by the preoperative neurological status, nature of the primary cancer, and presence of systemic and/or CNS metastases, but the differences were mostly without statistical significance. Nevertheless, surgery statistically prolonged survival more than doubly (7.4 versus 2.6 months). According to other authors, the median survival extends beyond 9.4 months when patients undergo surgery versus 5 months when conservative treatment is performed. Regarding primary cancer, the median survivals are 5.5 months and 1.0 month for breast cancer and lung cancer, respectively. Most patients succumbed to progression of the primary cancer [2, 8, 9].

The neurological status improved in 58% (11/19) of operated patients. On the contrary, ISCM patients with brain metastases have a life expectancy of about 3 to 4 months from the time of diagnosis [14].

3.5. Adjuvant Therapy. Focal radiation is used as an adjunct treatment for residual disease within the resection cavity. Postoperatively, RT (30 Gy) is used in the resection site.

The majority of ISCMs published were only treated with radiotherapy or chemotherapy. The aim of RT is to arrest tumor growth and prevent further neurological deficit. RT is considered for radiosensitive carcinomas such as small cell lung carcinoma, breast carcinoma, or lymphoma. The reported six-month survival rate of the cases treated with radiation therapy is less than 20%. The response to RT is minimal if paraplegia supervenes [14, 15].

Moreover, RT is controversial in many cases. The risk of radiation myelitis can occur after significant radiation exposure. The radiation tolerance of the spinal cord alone is substantially limited, and knowledge of the safe amount of radiation delivered to the spinal cord involved by metastasis is lacking [16]. Fractionated radiotherapy is effective particularly when the patients are not neurologically compromised. Currently, much more targeted RT such as stereotactic radiotherapy is recommended. Some authors even advise to irradiate the entire spinal cord, but with unknown bone marrow toxicity and a questionable improvement in the outcome.

Most of these patients underwent chemotherapy and biological therapy during the first cancer attack, but these are not applicable in ISCM management. These modalities do not pass through the blood-spinal cord barrier. Chemotherapy has no further effect on survival [7, 17–19].

Another therapeutic modality is steroid therapy. Patients with rapidly progressive symptoms of cord compression and a high risk of rapid deterioration are suitable for treatment with high-dose steroids. This may decrease the pain and cause transient improvement in neurological conditions. Steroids suppress perifocal oedema and normalize the blood-spinal cord barrier, which decreases tumour size but does not influence survival. Steroid therapy provides additional time for the diagnostic process as well as controls or minimizes the oedema after surgery or RT [2].

4. Conclusion

Diagnosis should be made as early as possible and surgical resection should be considered as the primary treatment whenever feasible, particularly in the case of rapidly progressive neurological deficits.

Our strategy involves aggressive surgery in selected ISCM patients, particularly those presenting with previously undiagnosed or limited primary tumours. Before choosing surgery, the clinical condition, age of the patient, primary tumour pathology, and presence of other secondary lesions have to be assessed. Finally, the expected survival is estimated, and the rationale for the surgical procedure as well as the approach and extent of resection are obtained. An intraoperative monitoring is auxiliary method to facilitate safe and radical tumour resection.

CNS metastases are extra-axial tumours. The neoplasm characteristics play a major role. ISCMs are often well circumscribed, cystic or with a cystic part, and encapsulated. Cystic tumours or cystic tumour components facilitate surgical extirpation because the cystic component often reaches the spinal cord surface. Therefore, the tumor can be easily removed without disruption to normal neural structures. However, gross total resection of solid tumour with preservation of neurological functions is possible. In the selected patients, the quality of life can be improved. Surgery should not be undertaken in cases of complete paraplegia.

The author has had two published experiences of ISCMs. Firstly, there was a patient with solitary ISCM as initial sign of colorectal carcinoma. Due to fast neurological deterioration the patient underwent ISCM surgery followed solution of primary tumour and extraneuronal metastases. Secondly, there was a patient with history of breath carcinoma. She has been already treated for extraneuronal metastases several years. A neurological deficit evolved, and solitary ISM was revealed. For relatively good prognosis of this carcinoma, the patient underwent surgery.

Although the number of cases is small, analysis of literature data suggests that, in some patients with ISCMs, surgical treatment is of relevance.

The median progression-free survival was 13 weeks (range 3–96 weeks), and the median survival time after surgery was 27 weeks (range 3–148 weeks). The median survival of patients with adenocarcinoma metastases was 42 weeks. The median survival was 21 weeks and 8 weeks for sarcomas and poorly differentiated carcinomas, respectively [1, 2, 7, 20].

RT is considered as an adjunct treatment after surgery.

Some authors have proposed the possibility that chemotherapy for intracerebral metastases can cross the disrupted blood-brain barrier and extrapolated this to ISCMs [17–19]. When compared, the blood-brain barrier and the blood-spinal cord barrier are not entirely identical. For example, their permeabilities are reduced by steroids.

Patients with ISCMs have a limited response to treatment and a very unfavourable prognosis. Every effort should be made for effective palliation and prevention of paraplegia. In our view, it is of essential importance to minimize the time from the first symptoms to diagnosis and to select patients who would benefit most from surgery. Ultimately, cooperation among the neurosurgeon, neuroradiotherapist, neuro-oncologist, neuropathologist, and physiotherapist is absolutely mandatory for an effective therapeutic process.

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Review Article

Stereotactic Body Radiosurgery for Spinal Metastatic Disease: An Evidence-Based Review

William A. Hall,[1] Liza J. Stapleford,[1] Costas G. Hadjipanayis,[2] Walter J. Curran,[1] Ian Crocker,[1] and Hui-Kuo G. Shu[1]

[1] *Department of Radiation Oncology, Winship Cancer Institute, Emory University, 1365 Clifton Road NE, Suite CT-104, Atlanta, GA 30322, USA*
[2] *Department of Neurosurgery, Winship Cancer Institute, Emory University, Atlanta, GA 30322, USA*

Correspondence should be addressed to Hui-Kuo G. Shu, hgshu@emory.edu

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Spinal metastasis is a problem that afflicts many cancer patients. Traditionally, conventional fractionated radiation therapy and/or surgery have been the most common approaches for managing such patients. Through technical advances in radiotherapy, high dose radiation with extremely steep drop off can now be delivered to a limited target volume along the spine under image-guidance with very high precision. This procedure, known as stereotactic body radiosurgery, provides a technique to rapidly treat selected spinal metastasis patients with single- or limited-fraction treatments that have similar to superior efficacies compared with more established approaches. This review describes current treatment systems in use to deliver stereotactic body radiosurgery as well as results of some of the larger case series from a number of institutions that report outcomes of patients treated for spinal metastatic disease. These series include nearly 1400 patients and report a cumulative local control rate of 90% with myelopathy risk that is significantly less than 1%. Based on this comprehensive review of the literature, we believe that stereotactic body radiosurgery is an established treatment modality for patients with spinal metastatic disease that is both safe and highly effective.

1. Introduction

Spine column tumors, both primary and metastatic lesions, are quite often seen in cancer patients. For a variety of tumors, the spine is the most common site of metastatic disease. It is estimated that 20,000–25,000 patients per year in the US develop spinal cord or root compression as a manifestation of their metastatic disease [1, 2]. Further estimates conclude that 5–10% of cancer patients will develop spinal metastasis [3]. In cancer patients with acute onset of back pain or other clinical suspicion for spinal metastatic disease, rates of spinal metastasis exceeding 25% have been reported [3, 4]. Radiotherapy has long been established as an effective treatment modality for spinal tumors [5–8]. With the advancement of image-guided radiation therapy technology, extracranial spinal radiosurgery has emerged as an effective and safe treatment modality for spinal tumors, both primary and metastatic.

Extracranial radiosurgery, or stereotactic body radiosurgery (SBRS) was developed in the mid 1990s at various institutes around the world. Possibly the earliest experience describing the procedure came from the Karolinska Institute in Sweden [9]. Around the same time, Hamilton et al. published their early experience treating spinal tumors with linear accelerator-based radiosurgery in the setting of failure of other surgical or radiotherapy interventions [10]. Since the early days of SBRS development, the technique has become increasingly important and common in the management of both primary and metastatic spinal tumors. Today, stereotactic radiosurgery has come to be defined as "a distinct discipline that utilizes externally generated ionizing radiation in certain cases to inactivate or eradicate (a) defined target(s) in the head or spine without the need to make an incision. The target is defined by high-resolution stereotactic imaging [11]." The purpose of this review is to summarize the growing body of literature for spine radiosurgery focusing

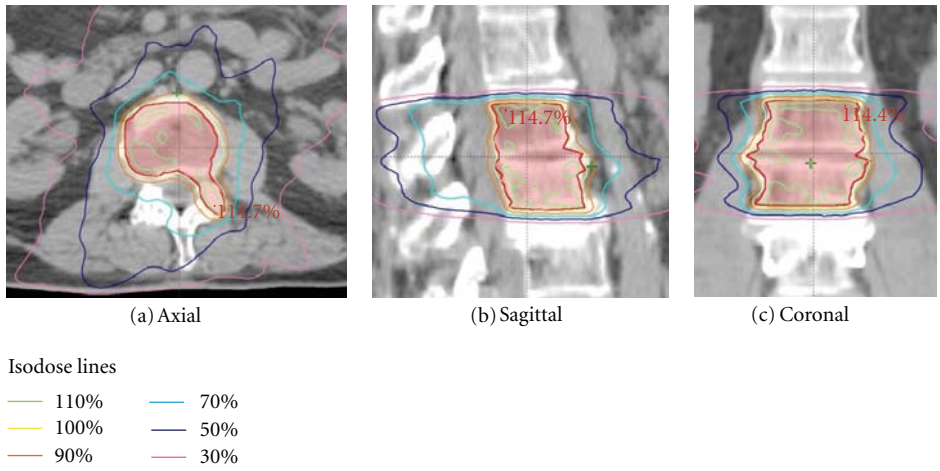

Figure 1: Dose distribution for a patient treated with spinal radiosurgery to L1-L2. The planning target volume (PTV) is outlined in red.

on prospective case series available that have led to the current standards, and will influence future directions in spinal radiosurgery.

2. Technical Aspects of Spine Radiosurgery

Essential to the delivery of stereotactic radiation to the spine is a very steep dose gradient outside of the target volume [12]. An example of a spine radiosurgery plan for a patient with this type of steep dose fall off and conformal dose distribution is shown in Figure 1. Equally important to the dosimetric considerations is rigid immobilization of the patient. The essential elements required for spinal radiosurgery can be achieved through different commercially available, turn-key or institution-specific, in-house systems. Currently, several available systems, each utilizing slightly different immobilization techniques and methods for accurately delivering focused spinal radiation doses, can be used for this purpose. Some of the more common systems are detailed below.

The CyberKnife, (Accuray, Inc., Sunnyvale, CA) is a frameless robotic radiosurgical system that is used to deliver extracranial radiosurgery and plays an important role in spinal radiosurgery. The design of the CyberKnife consists of a lightweight linear accelerator (LINAC) mounted on a robotic manipulator that serves to deliver several independently targeted (nonisocentric) and noncoplanar treatment beams. These beams are delivered under continual X-ray image guidance with corresponding shifts in the positioning of the robotic arms to maintain accurate targeting [13]. Early versions of the CyberKnife system required implanted radiopaque markers that were used to accurately localize the spinal target. Recent advancements in the ability of the Cyberknife technology to track the spine (a tracking system called Xsight, Accuray, Inc.) have eliminated the need for implanted fiducials. The treatment positioning for this system compared with use of implanted radioopaque fiducials was found to be 0.61 mm ± 0.27 mm as measured in a a realistic, anthropomorphic head-and-neck phantom and 0.49 mm ± 0.22 mm in 11 patients treated with SBRS [14]. Typical immobilization devices used for the Cyberknife system consist of head thermoplastic masks for cervical spine tumors, and body alpha cradles for thoracic and lumbar tumors.

A second major commercially available system used to perform both cranial and extracranial radiosurgeries is the Novalis LINAC (BrainLAB, Inc., Munich, Germany). The device consists of a single-energy 6 MV LINAC mounted on a standard gantry with a built-in micromultileaf collimator. As a consequence of being single energy, this treatment unit has a lower mass than typical general purpose LINAC's thus facilitating gantry isocentricity [15]. Similar to the Cyberknife, the Novalis system is equipped with in-room kilovoltage X-ray imaging equipment consisting of two orthogonally mounted 80–100 kiloelectron volt (keV) X-ray tubes with corresponding amorphous silicon digital detectors and a computerized control and image analysis system. The acquired keV images are then fused with the reference images from the CT simulation to ensure accurate patient positioning. The information regarding the location of the isocenter is forwarded to the ExacTrac system, a computerized system that uses two infrared cameras to detect infrared-sensitive markers. This allows the system to automatically compare this marker information with reference information to move the treatment couch to the desired position [16, 17]. The precision for the Novalis system, which was defined on this study as the degree of isocenter variation from CT simulation to portal imaging at the time of treatment, has been measured at 1.36 mm ± 0.11 mm [16]. Both the value measuring variability of the Novalis ExacTrac and the values from the previous paragraph measuring variability of the Cyberknife Xsight show that each system is highly precise. However, their absolute values cannot be directly compared since the gold standard for patient positioning in each study was different (image fusion of digitally reconstructed radiographs (DRRs) from the simulation CT with orthogonal port films for ExacTrac and matching positions of 4 fiducial markers on DRRs with orthogonal X-rays).

In addition to the above dedicated radiosurgery systems, modern linear accelerators equipped with image-guidance hardware such as the Trilogy system (Varian Medical Systems, Inc., Palo Alto, CA) or the Synergy system (Elekta AB, Stockholm, Sweden) can be used for spinal radiosurgery. Given our experience with the Trilogy, we will discuss that system in greater detail. Like the above systems, the Trilogy utilizes the dosimetric advantage of multiple noncoplanar treatment beams [18]. It is the angular distribution of these beams that enables a conformal dose distribution around a nonspherical target. With this system, the user can select either dynamic mode (also known as sliding window) or segmental mode (also known as step and shoot) to deliver an intensity modulated treatment plan. Each of these treatment modes has their advantages that have been previously described [19–21]. With regards to patient immobilization, any number of solutions can be adapted for use with the Trilogy. For treatment in the mid-lower thoracic and lumber regions, we use BodyFIX (Elekta AB) which consists of a vacuum bead cushion that is set to conform to the patient's treatment position with an overlying plastic wrap that is affixed under vacuum suction over the patient to ensure reproducible setup and reduce potential motion. For treatment in the lower cervical and upper thoracic spine, we use a customized head and shoulder thermoplastic mask with body immobilization. Finally, for treatment in the upper cervical spine, we use a thermoplastic mask that is fitted over the head on an indexed head extender that permits adjustments in all six degrees of freedom (3 translational and 3 rotational). Central to any spinal radiosurgery system is the image guidance system used to confirm patient setup and tumor location with normal anatomical landmarks. The Trilogy features three different imaging/localization systems on the treatment machine, namely, optical, kilovoltage X-rays, and megavoltage X-rays. While each of these image modalities have their advantages and can be used to guide patient positioning either alone or together depending on the situation, we primarily use the kilovoltage on-board imager to obtain both paired orthogonal images and cone-beam CT images for verification of positioning. The kilovoltage imager for Trilogy is mounted on the Trilogy gantry with 2 robotically controlled arms that each operate on three axes of motion which enables optimal positioning for imaging of the target volume [18]. For patient setup, paired orthogonal images are first obtained using this system to guide initial positioning. Next, this same imager is used to obtain a 3D cone-beam CT image set which can subsequently be matched to the simulation CT scan using either automated or manual image registration. A second cone-beam CT scan may then be obtained to confirm final positioning before patient treatment. Beam shaping with the Trilogy is achieved with the 120-leaf Millennium multileaf collimator (MLC). The Millennium MLC has been previously described and its advantages with respect to beam penumbra are established [22, 23]. Finally, the Trilogy features dual beam energies (6 and 18 MV photons) providing greater flexibility in the type of treatment plans that can be used. These features combine to make the Trilogy a versatile machine that is well suited for spinal radiosurgery.

3. Dosimetric Considerations in Spinal Radiosurgery

The safety of any course of radiotherapy is dependent on the tolerance of the normal tissues in the vicinity of the tumor that is being treated. Of paramount importance when considering spinal radiosurgery is the dose to the spinal cord. Classically, the tolerance of the spinal cord, according to Emami and colleagues, is expressed in terms of TD 5/5 (tolerant dose of radiation, dose at which the severe complication rate is 5% at 5 years) and is estimated at 50, 50, and 47 Gy for cord lengths of 5, 10, and 20 cm, respectively, for a conventionally fractionated course (1.8–2.0 Gy/fraction) [24]. An important consideration for this report is that its conclusions were based on extrapolation of data going back to the 1940s. In the setting of modern day conformal radiotherapy technologies, many view the stated tolerance of the spinal cord of 45–50 Gy as conservative. More recent data has supported the possibility of a higher spinal cord tolerance [25–29]. In particularly, Kirkpatrick et al. showed that for patients treated with conventional fractionation, the risk of myelopathy is less than 1% at 54 Gy and less than 10% for 61 Gy [29].

When discussing spinal radiosurgery, the spinal cord tolerance to hypofractionated RT becomes more important than the spinal cord tolerance to conventionally fractionated radiation (1.8–2.0 Gy). Some information regarding the dose tolerance of the spinal cord to high-dose radiation fractions has emerged. It is well established that common hypofractionation schemes in the dose range of 8 Gy $\times$ 1 fraction to 4 Gy $\times$ 5 fractions is safe with essentially 0% risk of radiation myelitis [30, 31]. Macbeth and colleagues estimated the risk of radiation myelopathy based on information from three randomized trials of palliative radiotherapy for nonsmall cell lung cancer [28]. According to their review, none of the 114 patients treated with 10 Gy $\times$ one fraction developed spinal myelopathy. However, of 524 patients treated with 17 Gy in two fractions, the estimated cumulative risk of myelopathy at 2 years was 2.2%. Additionally, prospective data suggest that the spinal cord can tolerate at least 10 Gy to 10% of this volume when defined as the cord at the level of the radiosurgical target plus 6 mm above or below this region, with acceptable rates of myelitis [32].

Important to consider also is the issue of reirradiation of the spinal cord after a fractionated course of RT. While data with respect to cord reirradiation is limited, this question has been examined in a primate model by Ang and colleagues [33]. In their study, a group of 56 rhesus monkeys were initially treated to a dose of 44 Gy in 2.2 Gy fractions to the cervical and upper thoracic spinal cord. Monkeys were then reirradiated using 2.2 Gy fractions to 57.2 Gy after 1 or 2 year intervals or 66 Gy after 2 or 3 year intervals. In this long-term experiment, 45 monkeys completed the required observation period of 2–2.5 year after reirradiation (for a total of 3–5.5 years total followup). Of these monkeys, only 4 developed myeloparesis. The authors concluded that spinal cord tissue likely has a large capacity to recover from prior radiation doses. Some data is also available in regards to reirradiation of the human spinal cord. One clinical series reported on

a total of 62 patients reirradiated for an in-field recurrence of spinal cord compression from metastatic disease with 8 Gy × one fraction or 3 Gy × 5 fractions after initially being treated with 8 Gy × one fraction or 4 Gy × 5 fractions. This approach results in a biologically equivalent dose (BED) of 80–100 Gy (by standard linear-quadratic modeling) to the spinal cord and, at a median of 8 months of followup, there were no cases of radiation myelopathy observed [34–36]. Higher incidences of myelopathy have been reported in patients receiving higher BEDs to the cord. In a series of 40 patients reported by Nieder et al., myleopathy was only observed in patients receiving higher than 102 Gy of cumulative BED with no observed cases of myleopathy below that dose [37]. In a recent analysis by Sahgal et al., the dosimetric data in five cases of myelopathy was analyzed per the BED and these were compared to a subset of 19 patients with no radiation myelopathy [38]. The thecal sac was contoured to represent the spinal cord, and doses to a maximum volume of 0.1, 1, 2, and 5 cc were analyzed. Radiation myelopathy was found to occur with a maximum point dose of 14.8, 13.1, and 10.6 Gy in a single fraction, 25.6 Gy in two fractions, and 30.9 Gy in three fractions. The authors concluded from their series that for single fraction SBRT, a maximum point dose of 10 Gy is safe. It should be noted that the data regarding spinal cord tolerance in the setting of reirradiation is still limited and should be clinically applied with caution.

4. Selection of Case Series

PubMed, a service of the US National Library of Medicine, was searched for English language publications up through December, 2010 on stereotactic radiosurgery for spinal tumors. Radiosurgery was defined as 5 or fewer fractions of radiation delivered to both primary and metastatic spinal tumors. Treatment in the primary and reirradiation setting were both included in this review. To evaluate only more sizeable experiences, series that had fewer than 20 patients were excluded. A total of fifteen series were identified that met these criteria, and details about these reports are summarized on Table 1.

5. Review of the Literature

In a phase II trial from the University of Florida by Amdur and colleagues, 21 patients were treated with a single fraction of 15 Gy with spinal cord dose limited to 12 Gy to no more than 0.1 cc in previously unirradiated patients and 5 Gy to no more than 0.5 cc in previously irradiated patients [39]. A primary objective of this study was to evaluate toxicity. The authors demonstrated that with these dose constraints, patients experienced only minor grade 1-2 acute toxicities consisting primarily of nausea or dysphagia and no late toxicities. Overall, this series demonstrated that, with clearly defined spinal cord dose constraints, spinal radiosurgery given as 15 Gy in a single fraction is very well tolerated.

Gerszten et al. reported on multiple case series from the University of Pittsburgh about the safety and effectiveness of spinal radiosurgery in patients with different types of metastatic lesions [40–44]. In 77 patients with metastasis to the spine from nonsmall cell lung cancer treated with a mean dose of 20 Gy with a range of 15–25 Gy in a single fraction, pain improved in 89% of patients and the local control rate was 100% [40]. In addition with a followup of 12 months, no acute or chronic radiation toxicities were noted despite treatment being given to a mean volume of 25.7 cc (range: 0.2–264 cc). In the spine radiosurgery series with the longest median followup of 37 months, Gerszten et al. demonstrated similar efficacy of this treatment for renal cell carcinoma metastasis in 48 patients with little observed toxicity [41]. Again, a mean dose of 20 Gy in a single fraction (range: 17.5–25) was used to treat relatively large volumes (mean: 61.9 cc, range: 5.5–203 cc). Finally, in the largest published spine radiosurgical series to date consisting of 393 patients with a range of histologies, Gerszten and colleagues found, with a median followup of 21 months, that they achieved 88% tumor control and excellent palliation of pain with a mean dose again of 20 Gy (range: 12.5–25 Gy) [44]. Based on these series, spinal radiosurgery appears to be feasible, safe, and effective for the treatment of spinal metastatic disease of various histologies.

In another series, Yamada and colleagues reported the Memorial Sloan-Kettering experience for spinal radiosurgery [45]. Here, 93 patients were treated to a median dose of 24 Gy (range: 18–24 Gy) with the spinal cord constrained to maximal point dose of 14 Gy. With a median followup of 15 months, the actuarial 1-year local control rate was 90% and, despite the relatively high single fraction dose of radiation, no myelopathy or other late toxicities were seen. Because a range of doses was used in this cohort, the impact of radiation dose on tumor control could be evaluated. This analysis revealed a dose-response relationship with higher doses being a statistically significant predictor of local control.

In a phase I/II trial conducted at the MD Anderson Cancer Center by Chang et al., 63 patients underwent a hypofractionated course of spinal radiosurgery to a median tumor volume of 37.4 cc (range: 1.6–358 cc) [47]. Treatment given with a fractionation schedule of 6 Gy delivered in 5 fractions to half of the patients in the series that was later modified to 9 Gy delivered in 3 fractions to further reduce treatment time. With a median followup of 21 months, the one-year actuarial progression-free rate was 84%. The pattern of failure tended to be marginal being either in the bone adjacent to the site of previous treatment or in the epidural space adjacent to the spinal cord. No grade 3/4 neurologic toxicity was reported. Based on the pattern of failure in the posterior elements, the authors recommended inclusion of the pedicles and the posterior elements of the vertebrae in the target volume due to the possibility of direct extension to these structures.

Ryu and colleagues at Henry Ford Hospital published a series consisting of 177 patients treated with single fraction radiosurgery with doses ranging from 8–18 Gy [32]. With a relatively short median followup of 6.7 months, they demonstrated that a dose to 10% of the spinal cord of 9.8 Gy was well tolerated with respect to acute toxicity. Of note, in the subgroup of eighty-six patients that survived more than 1 year, one case of spinal cord injury at 13 months

Table 1: Spine radiosurgical series through December 2010.

Authors and year	Institution	No. of pts/ tx sites	Prior RT	Treatment system	Dose/fraction No./coverage	Spinal cord dose limits	Histology	Median F/U (in months)	Local control rate (percent)	Pain improved (percent)	Rate of myelopathy (percent)
Amdur et al., 2009 [39]	U of Florida	21/25	12/21	In house (Elekta Synergy-S)	15 Gy/1/100% to 95% of PTV	12 Gy to < 0 .1 cc, 5 Gy to < 0.5 cc if prior RT	Many	8	24/25 (96%)	6/14 (43%)	0/21 (0 %)
Gerszten et al., 2006 [40]	U of Pittsburgh	77/87	70/77	CyberKnife	20 Gy (mean)/1/80% IDL	9 Gy max (mean), range: 4–12 Gy	Lung	16	87/87 (100%)	65/73 (89%)	0/77 (0%)
Gerszten et al., 2005 [41]	U of Pittsburgh	48/60	42/48	CyberKnife	20 Gy (mean)/1/80% IDL	9.7 Gy max (mean), range: 2.4–14.0 Gy	Renal	37	54/60 (90%)	37/38 (97%)	0/48 (0%)
Gerszten et al., 2005 [42]	U of Pittsburgh	28/36	23/28	CyberKnife	21.7 Gy (mean)/1/80% IDL	>8 Gy to 0.3 cc (range: 0–0.7 cc)	Melanoma	13	26/28 (93%)	27/28 (96%)	0/28 (0%)
Gerszten et al., 2005 [43]	U of Pittsburgh	50/68	48/50	CyberKnife	19 Gy (mean)/1/80% IDL	13 Gy max dose	Breast	16	68/68 (100%)	55/57 (96%)	0/50 (0%)
Gerszten et al., 2007 [44]	U of Pittsburgh	393/500	344/500	CyberKnife	20 Gy (mean)/1/80% IDL	NR	>50% breast, lung, melanoma, renal	21	440/500 (88%)	290/336 (86%)	0/393 (0%)
Yamada et al., 2008 [45]	Memorial Sloan-Kettering	93/103	0/93	In house [46]	24 Gy (median)/1/92% IDL (average)	11.7 Gy max (median), range: 1.8–14 Gy	Many	15	90% (actuarial at 1 year)	NR	0/93 (0%)
Chang et al., 2007 [47]	MD Anderson	63/74	35/63	In house (Varian 21EX)	tx 1 : 6 Gy/5/80–90% of PTVtx 2 : 9 Gy/3/80–90% of PTV	10 Gy max in 5 fractions for tx 1 9 Gy max in 3 fractions for tx 2	Many (40% renal)	21	84% (actuarial at 1 year)	NR	0/63 (0%)
Ryu et al., 2007 [32]	Henry Ford Hospital	177/230	0/177	Brainlab Novalis system	8–18 Gy/1/90% IDL	9.2 Gy (mean) to <10% of cord volume	Many (25% breast)	6	NR	NR, 41/49 (84%) separate report [48]	1/177 (0.5%)
Nelson et al., 2009 [49]	Duke U	32/33	22/32	In house (Varian 21EX)	18 Gy (median)/3 (median)/	12 Gy to 1% of cord, BED < 83 for retreatment	Many (31% renal)	7	29/33 (88%)	30/32 (94%)	0/33 (0%)
Gibbs et al., 2007 [50]	Stanford U	74/102	50/74	Cyberknife	16–25 Gy/1–5/77% IDL (mean), 98% of PTV	Max dose range 3–28 Gy in 1–5 fractions	>50% breast, lung, melanoma, renal	9	NR	52/62 (84%, includes other neuro sxs)	3/74 (4%)
Choi et al., 2010 [51]	Stanford U	42/51	42/42	Cyberknife	20 Gy (median)/2 (median)/77% IDL (median)	19.3 Gy max (median) in 1–5 fractions	>50% breast, lung	7	38/51 (75%)	15/23 (65%)	1/41
Degen et al., 2005 [52]	Georgetown U	51/72	38/72	Cyberknife	21 Gy (mean)/3.6 (mean)/71% IDL (mean)	11 Gy max (mean) to <1% of cord volume	Many (19% breast)	12	69/72 (96%)	37/38 (97.3%)	0/51 (0%)
Gagnon et al., 2009 [53]	Georgetown U	200/274	137/274	Cyberknife	21, 26.4 or 37.5 Gy/3, 3 or 5/75% IDL	NR	Many (18% breast)	12	NR	55/152 (36%) became pain-free	0/200 (0%)
Sahgal et al., 2009 [54]	UCSF	39/60	25/39	Cyberknife	24 Gy/3/67% or 60% IDL (no RT or prev. RT)	16.8 Gy or 12.8 Gy max (median) (no RT or prev RT)	Many	9	85% (actuarial at 1 year)	NR	0/39 (0%)

Abbreviations: pts, patients; tx, treatment; F/U, followup; RT, radiation therapy; Gy, Gray; cc, cubic centimeter; PTV, planning target volume; IDL, isodose line; NR, not reported; BED, biologically equivalent dose.

after radiosurgery was seen. One conclusion of this series was that the tolerance of the spinal cord is at least 10 Gy to 10% of the cord volume as defined as 6 mm above and below the target lesion. While efficacy outcomes was not reported on the above study, this group published a followup paper showed excellent pain palliation with 41 of 49 patients who had significant pain prior to the procedure subsequently reporting on reduction in discomfort [48].

Nelson et al. described their clinical experience at Duke University for the treatment of spinal and paraspinal tumors in 32 patients with 33 spinal lesions [49]. In this series, the safety and efficacy of spinal radiosurgery was again demonstrated with a median followup of 7 months. Among the treated patients, 94% had improved pain control with 40% describing complete resolution of their pain. Moreover, no radiation-induced toxicity was observed. Interestingly, the authors used BED as calculated using the linear-quadratic model with a spinal alpha/beta ratio of 3 to define strict spinal cord limits in patients that had prior RT. Additionally, they utilized a model involving time-discounted BED recovery of the spinal cord based on prior published data [33]. Specifically, a dose recovery of 25%, 33%, and 50% at 6 months, 1 year, and 2 years, respectively, was accounted for in previously irradiated patients. While the authors conclude that spinal radiosurgery appears effective and safe when performed as prescribed, they caution that the time-discounted BED model of recovery will require further validation.

Gibbs and colleagues at Stanford University reported on their series of 74 patients with 102 spinal metastasis treated with SBRS. Like the multiple other series reviewed here, they found that a high percentage of their patients (84%) had symptom improvement with an acceptable rate of toxicity [50]. A more recent report of the Stanford experience by Choi et al. focused on the safety and efficacy of spinal radiosurgery after previous irradiation [51]. Their series included 41 previously irradiated patients with recurrent metastatic spine disease. SBRS was delivered to the spine at a median marginal dose of 20 Gy in 2 fractions (range: 1–5 fractions). With a median followup of 7 months, the actuarial local control rate at 6 months and 1 year was 87% and 73%, respectively. Time to retreatment of less than or equal to 12 months was a significant predictors of local failure. While overall, the radiosurgery appeared to be well tolerated, one patient with metastatic breast cancer did develop a grade-4 neurotoxicity. At 81 months prior to retreatment, this patient had received a fractionated course of radiation (39.6 Gy in 1.8 Gy fractions) from T4 to L1 for spine disease resulting in a cord dose of 40 Gy. SBRS consisted of 20 Gy in 2 fractions to a 10.3 cc volume for a T5 recurrence with a maximum cord dose of 19.25 Gy. After experiencing LE weakness, paresthesias, and urinary retention 6 months after SBRS, the patient was diagnosed with a spinal cord injury, initiated on aggressive management without success, and ultimately became wheelchair dependent. Here, the authors also applied a time-discounted BED method, again extrapolating from Ang data similar to that used by Nelson et al. for choosing cord tolerances [33, 49, 51]. Similar to the other reports, they conclude that SBRS can be safely and effectively delivered for the treatment of spinal metastasis in previously irradiated regions.

Table 2: Pooled results of spinal radiosurgery series.

Description	Values
Total patients	1388
Total lesions	1775
Patients with previous RT	888
Mean F/U time (months)	15
Pain improvement rate ($n = 902$)	79%
Local control rate ($n = 1169$)	90%
Myelopathy rate ($n = 1388$)	0.4%

Abbreviations: RT, radiation therapy; F/U, followup.

Degen et al. at Georgetown University published a series on 51 patients with 72 lesions that focused on pain control and quality of life assessments [52]. The visual analogue scale (VAS) and the 12-item Short Form Health Survey (SF-12) prior to and after treatment were used to assess these factors. In this cohort, the average VAS score decreased significantly from 51.5 to 21.3 at 4 weeks to 17.5 at 1 year indicating a very good initial reduction in pain that remained durable. Also, average SF-12 scores did not vary in either the physical or mental well-being domains over time, indicating quality of life maintenance after treatment. Gagnon et al. reported results of the followup study of similar design where this cohort was expanded to 200 patients and confirmed earlier results with respect to control of pain and maintenance of quality of life [53]. Overall, these studies were able to more objectively quantify the improvement in pain provided by radiosurgery and contribute to the growing body of evidence regarding the durability of response.

Sahgal et al. reported on the results of spinal radiosurgery in 39 consecutive patients (with 60 tumors) at UCSF [54]. The median followup of patients in this study was 8.5 months. The median total dose prescribed was 24 Gy given in 3 fractions. Overall, the 1-year and 2-year progression-free probability was 85% and 69%, respectively. Of note, the great majority of failures had tumors that were less than or equal to 1 mm from the thecal sac. Finally, of the tumors followed for longer than 6 months (39 of 60), no radiation-induced neurotoxicity was noted. This study gives further support for the safety and efficacy of spinal radiosurgery.

Pooling of the case series presented in this review results in a total of 1388 patients with 1775 lesions who underwent spinal radiosurgery. The combined result of these treatments is summarized on Table 2. The weighted (based on number of patients in each series) mean value of the median followup times for patients on all the series was slightly more than 15 months. In the series where pain relieve was examined, 79% of patients ($n = 902$) experienced some reduction in discomfort associated with their spinal lesions. The weighted overall local control rate, defined as lack of progression of the gross disease on surveillance imaging, was 90%. These results were obtained with an extremely low crude incidence of myelopathy of less than 0.5%. In summary, pooling the results of these case series further illustrates that spinal radiosurgery is a safe and effective treatment modality when performed as outlined by the various cited authors.

6. Clinical Recommendations

Numerous published series have now reported the results collectively on significantly more than 1000 patients treated with radiosurgery for spine metastatic disease thus establishing this treatment modality as a safe and effective therapy. However, certain standards need to be established to assure that treatment results are in line with what has been reported to date. We recommend that the procedure be a collaborative effort between the spine surgeon (neurosurgery or orthopedics) and the radiation oncologist with strong medical physics support. Since this procedure has many intricacies including issues with patient immobilization, treatment planning, accurate positioning, and so forth, it should be performed only at institutions that have made the commitment to establish a program that will see and treat a reasonable number of patients (e.g., >25 patients/year) in order to maintain proficiency with this procedure. Adequate quality assurance specific for the radiosurgery system used needs to be performed by the physics staff on a regular basis to assure that the equipment is performing according to specification.

Patients need to be carefully selected, and informed consent obtained regarding the risks, benefits, and alternatives to spinal radiosurgery. Conventionally fractionated RT should be presented to the patient as a viable alternative to radiosurgical treatment. The site of treatment should be limited, and we recommend that disease involvement be at two or less contiguous vertebra(e). Based on the literature, a dose of 15–20 Gy delivered in a single fraction should be safe and effective. The spinal cord should be constrained so that no more than 10% of the cord, defined to include the target level and 6 mm above and below this region, receives 10 Gy. This dose constraint should be achievable in the great majority of cases unless there is epidural disease that is <3 mm from the edge of the spinal cord. In such cases, a hypofractionated approach utilizing between 2–4 treatment fractions to deliver 18–24 Gy may still be possible depending on spinal cord dosimetric considerations. Patients with frank cord compression, spinal instability secondary to compression fracture, or bony retropulsion causing neurologic symptoms should be considered for surgery, if possible.

7. Summary

The role of radiation therapy for the treatment of spinal tumors, whether metastatic or primary, is well established. While conventional radiation therapy delivered without the use of high-precision localization techniques has been used for decades [6, 7, 55, 56], over the past fifteen years, new radiotherapy technologies now enable the delivery of high doses of focal radiation therapy with steep dose fall-off and millimeter accuracy in sites other than the brain. The safety and efficacy of these new technologies for use in spinal tumors have been increasingly demonstrated. The concept behind spinal radiosurgery is extrapolated from the long-standing experience of radiosurgery in the brain as a treatment modality [57–60]. Given the majority of tumors in this review series were metastatic in nature; spinal radiosurgery should be considered as an emerging essential part of the treatment armamentarium for spinal metastatic disease.

As illustrated in this review, numerous recently published series have shown that spinal radiosurgery can be given with high probability of tumor control and symptom relieve with a correspondingly low incidence of long-term toxicities. This treatment relies on high precision and highly conformal radiation doses delivered in 1–5 fractions, often very close to the spinal cord. It is important to note that each of the reviewed series is at a larger academic center that can perform this type of procedure at high volume and with adequate quality assurance. Application of these techniques at smaller radiotherapy centers where procedure volume will be lower and less physics/technical support is available should be approached with caution.

Several questions remain about the application of the spinal radiosurgery procedure. These include the precise definition of the dose tolerance of the spinal cord at radiosurgical doses, the influence of fraction number when giving high-dose, multifraction treatments, the most effective dose schedule to use with respect to symptom reduction and tumor control, and how spinal radiosurgery compares with more conventional radiation therapy treatments for safety and efficacy. Based on the case series presented in this review, a dose of nearly 21 Gy delivered in an average of 1.6 fractions can be safely delivered with rates of myelopathy of less than 0.5% and results in excellent rates of tumor control and pain relief. Overall, the future of spinal radiosurgery continues to evolve. With an increasing number of new heavy particle accelerators, proton-based spinal radiosurgery may be increasingly considered. Clearly, proton-based therapy for spinal tumors will have several dosimetric advantages when compared to traditional photon-based techniques [61]. These dosimetric advantages could potentially result in even lower toxicity and risk associated with the spinal radiosurgery procedure. However, there is currently a lack of high-quality evidence to support or refute the clinical applicability of the dosimetric advantages that protons may provide. Finally, as stated above, spinal radiosurgery has not yet been compared to more conventional radiation therapy techniques in the prospective setting. This question is now the subject of the current cooperative group trial (RTOG 0631) examining 8 Gy in a single fraction to a wider field compared with 16 Gy in a single fraction to a more limited radiosurgical volume for spinal metastatic disease. Results of this trail are awaited with anticipation.

8. Conclusion

Stereotactic body radiosurgery for spinal tumors is increasingly assuming a larger role in the treatment of metastatic spinal lesions. It has been shown in numerous prospective cohort series and retrospective case series that spinal radiosurgery is both safe and effective. In addition, the minimally invasive nature of spinal radiosurgery and its ability to be performed on an outpatient basis lends itself extremely well to the patient population in which it is most frequently used. Because patients with metastatic disease to the spine often have large burdens of systemic disease and poor performance

status, radiosurgery provides them with an attractive option to relieve their suffering quickly with very low risk.

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Review Article

A Systematic Review of the Current Role of Minimally Invasive Spine Surgery in the Management of Metastatic Spine Disease

Camilo A. Molina, Ziya L. Gokaslan, and Daniel M. Sciubba

Department of Neurosurgery, Johns Hopkins University School of Medicine, 600 N. Wolfe Street, Meyer Building 5-185a, Baltimore, MD 21287, USA

Correspondence should be addressed to Daniel M. Sciubba, dsciubb1@jhmi.edu

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Although increasingly aggressive decompression and resection methods have resulted in improved outcomes for patients with metastatic spine disease, these aggressive surgeries are not feasible for patients with numerous comorbid conditions. Such patients stand to benefit from management via minimally invasive spine surgery (MIS), given its association with decreased perioperative morbidity. We performed a systematic review of literature with the goal of evaluating the clinical efficacy and safety of MIS in the setting of metastatic spine disease. Results suggest that MIS is an efficacious means of achieving neurological improvement and alleviating pain. In addition, data suggests that MIS offers decreased blood loss, operative time, and complication rates in comparison to standard open spine surgery. However, due to the paucity of studies and low class of available evidence, the ability to draw comprehensive conclusions is limited. Future investigations should be conducted comparing standard surgery versus MIS in a prospective fashion.

1. Introduction

It is estimated that nearly 10 million people worldwide were diagnosed with cancer in 2000, with the incidence expected to increase to 15 million by 2020 [1]. The most commonly diagnosed neoplasms are breast, lung, and prostate cancers [2, 3]. Metastatic invasion of the spinal column can occur via various mechanisms that are dependent on both the biological behavior and physical location of the primary tumor [4]. Given the predilection of the breast, prostate, and lung neoplasms to metastasize to bone, it is not surprising that spinal metastases occur in 30–90% of patients, with 10% of such patients experiencing symptomatic metastatic epidural spinal cord compression (MESCC) [4, 5]. The most common symptom at presentation is pain that can be both radicular (exaggerated by percussion or palpation) and/or mechanical (exacerbated by movement) [6, 7]. Neurological dysfunction including motor, sensory, and autonomic dysfunction is the second most common presentation modality and is indicative of metastatic epidural spinal cord compression (MESCC) [3, 8–10].

Ideal management is multidisciplinary and involves various medical specialties such as neurosurgery, surgical oncology, medical oncology, radiation oncology, interventional radiology, pain specialists, and rehabilitation therapy [4, 5]. Management strategies involve a combination of surgery (for candidate patients), radiotherapy, and pharmacotherapy [4, 5, 11]. Due to both the short life expectancy of afflicted patients and high systemic tumor burden [8, 9, 12–14], with the exception of solitary metastatic lesions such as in the setting of renal cell carcinoma, treatment regimens are most often palliative rather than curative [10]. Afflicted patients frequently present with infiltration of the spinal column with tissues that lack weight bearing properties resulting in spinal instability, particularly ventral column instability given that most metastatic lesions localize to the anterior elements [11]. Optimal treatment of such patients requires stabilization in addition to traditional (surgical or nonsurgical) decompression [4, 15]. The most efficacious modality for restoring column instability is reconstructive surgical intervention. Unfortunately, numerous patients are not considered candidates for surgical intervention due to

neoplasm-associated comorbidities such as malnourishment and diminished immune system that make extensive surgical procedures unfeasible [4]. Such patients can be managed with vertebral augmentation, as it can provide some degree of restabilization [11]. However, surgical advances in the field of minimally invasive spine surgery (MIS) have opened the door for not only extended surgical candidacy to patients who were previously ineligible, but it has also established the setting for surgical intervention with minimal perioperative morbidity such as decreased pain, less blood loss, and shorter hospital stays [11, 15–23]. This paper aims to describe the current role of MIS in the treatment of metastatic spine disease. The overall objectives of this paper are to present a systematic review of literature with regard to the following clinical questions:

(1) the efficacy of MIS in improving neurological and pain-associated outcomes in the setting of metastatic spine disease;
(2) the incidence of complications associated with MIS in the setting of metastatic spine disease.

2. Methods

2.1. Search Strategy. A systematic review of literature was performed employing Pubmed and a review of bibliographies of reviewed articles. The search query was broad and formulated to combine a number of subheadings and keywords that included the therapies and pathology of interest. The search string employed was the following:

("Minimally Invasive Surgery" OR "MIS" OR "VAST" OR "endoscopic thoracoscopy" OR "mini-open spine surgery" OR "minimal access spine surgery" OR "MASS") AND (("bone neoplasms" (Mesh) OR "spinal neoplasms" (Mesh)) OR ("spin*" AND "metasta*") OR ("Spinal Cord Compression" (Mesh) OR "spinal cord compression") OR ("epidural neoplasms" (Mesh) OR "epidural neoplasm")).

2.2. Eligibility Criteria

(i) Criteria for possible inclusion were the following:
   (a) articles published between 1980 and 2011,
   (b) all articles in English or with an English translation,
   (c) adult age group (18 years and older),
   (d) articles describing the use of minimally invasive spine surgery modalities in the treatment of metastatic disease,
   (e) fully published peer reviewed studies including RCTs, nonrandomized trials, cohort studies, case control studies, case series, and case reports. Both prospective and retrospective studies were considered.

(ii) Criteria for exclusion were the following:
   (a) iontradural spine tumors,
   (b) primary spine tumors,
   (c) pediatric age groups,
   (d) articles with no extractable data specific to metastatic spine disease.

2.3. Study Eligibility and Quality Assessment. Abstracts were screened by two independent reviewers using the above-stated inclusion and exclusion criteria. Cases of reviewer disagreement were resolved by a third reviewer. Full-text versions of acceptable article were gathered and subjected to more detailed screening for inclusion. After finalizing a collection of eligible studies, the studies were analyzed in detail, and the data pertaining to the research questions was extracted and tabulated by one reviewer. The second reviewer checked the extracted information.

3. Results

A total of eleven publications were ultimately found eligible to evaluate the clinical outcomes associated with MIS as a treatment for metastatic spine disease. All of the publications available were retrospective in nature. Nine of the publications were retrospective case series, and two of the publications were case reports. Although case reports are normally excluded in systematic reviews, they were included in this review due to the paucity of evidence evaluating MIS in the setting of metastatic spine disease. The main outcomes extracted from the selected publications included mean operating time (MOT), mean blood loss (MBL), hospital length of stay (LOS), rate of neurological improvement (NI), pain alleviation rate (PA), and complication rate (CR). Collected outcomes are tabulated in Tables 1 and 2.

3.1. Video-Assisted Thoracostomy (VAST). There were a total of five publications addressing the use of VAST or endoscopy-assisted posterior decompression to manage patients with metastatic spine lesions. Four of the publications were retrospective case series, and one was a case report. The earliest description of VAST for managing metastatic vertebral was published by Rosenthal et al. [20] in 1996. The authors described the development of an endoscopic procedure to achieve anterior vertebrectomy, reconstruction, and stabilization of the thoracic spine in 4 patients afflicted with metastatic spine lesions. All patients were in good health condition but were experiencing progressive neurological decline and radiological evidence of bone destruction and cord compression. The study reported a 6.5 hr MOT, 7.5 day LOS, and 1450 mL MBL. The authors found that MBL was correlated to MOT and extent of vertebrectomy. Additionally, all of the patients were ambulatory with assistance on postoperative day 1, ambulatory with a Jewett brace during the first 4 weeks, and independently ambulatory at 11-month followup (NI: 100%). Patients were pain-free following chest drain removal on day 3 or 4 and remained pain-free at

Table 1: Endoscopic video-assisted thoracoscopy (VAST) outcomes. MOT: Mean operating time; LOS: Length of stay; NI: Neurological improvement rate; PA: Pain alleviation rate; CR: Complications rate; MBL: Mean blood loss.

Study	Design and procedure	Outcome results
Rosenthal et al. [20]; 1996	Retrospective analysis ($n = 4$) of outcomes associated with VAST MIS management of thoracic metastatic spine disease	MOT: 6.5 hours LOS: median 7.5 days NI: All patients experienced neurological improvement; in addition, all were independently ambulatory at time discharge and followup (mean 11 mo.) PA: All patients free of pain at time of discharge and followup (mean 11 mo) CR: none MBL = mean 1450 mL
Huang et al. [24]	Retrospective analysis ($n = 41$) to analyze the complication rate in VAST MIS	MOT: 3.1 hours CR: 54% MBL: mean 775 mL
Le Huec et al. [25], 2001	Case series ($n = 2$) to report outcomes associated with the use of VAST to manage spinal metastases at the cervicothoracic junction	MOT: 2.6 hours NI: Both patients experienced neurological improvement and were independent at followup (mean 9.5 mo) PA: Both patients experienced pain relief and only one required narcotics postoperatively CR: 1 patient suffered a progressive recurrent laryngeal nerve palsy MBL: 350 mL
McLain [21], 2001	Retrospective case series ($n = 8$) to evaluate outcomes of endoscopy-assisted posterolateral approach to manage thoracic metastatic spine disease	MOT: 6 hours LOS: 6.5 days NI: All 8 patients experienced neurological improvement PA: All 8 patients experienced pain relief. Additionally 63% of patients experienced complete pain relief CR: none MBL: 1677 mL
Mobbs et al. [26], 2002	Case report ($n = 1$) of endoscope-assisted posterior decompression of a solitary renal cell carcinoma metastatic lesion	NI: Patient was neurologically intact at two-month followup. Patient initially presented with hyperreflexia PA: Patient was pain-free at two-month followup CR: Patient experienced no procedural complications

11-month followup (PA: 100%). The study reported no complications (Table 1).

Huang et al. [24] published a retrospective case review of 90 patients who had undergone VAST for various spinal pathologies, of which 41 cases were due to metastatic lesions. The main goal of the study was to evaluate MIS complication rates. Procedures performed for the metastatic lesion afflicted subgroup included biopsy only, corpectomy for decompression, and corpectomy with interbody fusion. Although the study did not stratify MOT (3.1 h) or MBL (775 mL) according to neoplastic or nonneoplastic etiologies, the study did stratify complication rates. The authors reported a total of 30 complications in 22 patients (overall CR: 33%) for the 90 procedures performed. Importantly, 22 of those complications occurred among the 41 patients treated for metastatic spine disease (CR: 54%). Additionally, the authors also noted that the most common complication was excessive intraoperative bleeding, with all 5 instances occurring in patients with metastatic disease. The additional complications encountered were intercostals neuralgia (7%), superficial wound infection (7%), atelectasis (5%), pericardial penetration (2%), implant failure (2%), and death (2%). Notably, none of the complications occurred due to injury to the spinal cord, a great vessel, or internal organ (Table 1).

Le Huec et al. [25] published a small case series of two patients in which VAST was used to manage metastatic spine disease encompassing the cervicothoracic junction. The goal of the authors was to develop an alternative approach to the traditional lateral approach that requires mobilization of the scapula to visualize the T1, T2, and T3 spinal levels. The technique was technically feasible and allowed for ample access to achieve corpectomy and visualization of the posterior longitudinal ligament, thereby allowing for complete release of the cord. MOT was 2.6 hours, MBL was 350 mL, and mean LOS was 6.5 days. Both patients presented with progressive neurological decline but were independently ambulating at last followup (7 and 12 months) (NI: 100%). Both patients experienced substantial pain relief (PA: 100%), but one required narcotics at the followup due to having undergone additional surgeries for other metastases. One

patient acquired a progressive recurrent laryngeal nerve palsy (CR: 50%) (Table 1).

3.2. Endoscopy-Assisted Posterior Decompression. McLain [21] reported a retrospective case series of 8 patients afflicted with metastatic spine lesions to demonstrate the feasibility of endoscopically assisted (transpedicular) decompression and stabilization through a single, extrapleural, and posterolateral approach. MOT was 6.5 hours, and MBL was 1677 mL. All 6 of the patients that presented with neurological deficit recovered completely and maintained neurological integrity until the last followup or terminal care (3–36 months) (NI: 100%). The other 2 patients not presenting with neurologic compromise retained neurological function until the last followup or terminal care (3–36 months). All 8 patients experienced pain relief (PA: 100%), and 5 patients (62.5%) did not require any analgesics at the last followup. The authors concluded that endoscopy augmented the efficacy of the posterolateral approach by improving the visualization of structures that were traditionally difficult to access through a standard posterolateral approach (Table 1).

Mobbs et al. [26] published a case report of endoscope-assisted posterior decompression of a solitary renal cell carcinoma metastatic lesion. The patient initially presented with hyperreflexia and back pain but was neurologically intact and pain-free at two-month postoperative followup. The patient's course was uncomplicated throughout the procedure and postoperative recovery (Table 1).

3.3. Minimal Access Spine Surgery (MASS). There were a total of six publications addressing the use of MASS to manage patients with metastatic spine lesions. Muhlbauer et al. [27] published the first description of MASS for managing metastatic spine disease in 2000. The authors reported a small retrospective case series regarding the management of 5 patients with compression fractures from osteoporosis or metastatic lesions. Reported MOT was 6 hours, and MBL was 1120 mL. All 5 of the patients presented preoperatively with both pain and neurological dysfunction. At followup, all patients had experienced neurological improvement (NI: 100%) characterized by either progressing from ambulating with a cane to ambulating unassisted, or from being nonambulatory to ambulating with a cane. Additionally, all patients experienced significant pain relief (PA: 100%) with 40% of the patients not utilizing analgesics at followup (6–12 months) (Table 2).

Huang et al. [23] published a retrospective analysis of 46 patients to compare outcomes in MASS ($n = 29$) and standard thoracotomy (ST, $n = 17$) in the setting of metastatic spine disease. There was no significant difference in MOT, MBL, NI, or CR. MOT for MASS was 179 minutes versus 180 minutes for ST ($P = .54$). MBL for MASS was 1,100 mL versus 1,162 mL for ST ($P = .63$). Neurological outcome was reported as the postoperative reacquisition of ambulation. NI for MASS was 70.8% versus 69.2% for ST ($P = .6$). CR for MASS was 24% versus 29% for ST ($P > .05$). Complications encountered from MASS included dural tears (2), femoral fracture (1), pneumothorax (1), tumor recurrence (1), implant failure (1), and metastasis (1). Complications encountered from ST included sepsis (1), postoperative pneumonia (1), pneumothorax (1), GI bleeding (1), and UTI (1). Additionally, 2 year survival rates were also not significantly different (MASS: 24% versus ST: 29%, $P = .69$). However, the authors found that the percentage of patients requiring at least a 2-day postoperative admission to the intensive care unit (ICU) was significantly different when comparing MASS to ST, with MASS resulting in significantly less admissions (MASS 6.9% versus ST: 88%, $P \leq .001$) (Table 2).

Deutsch et al. [28] reported a retrospective case series of 8 patients undergoing MASS posterolateral vertebrectomy and decompression to treat symptomatic thoracic MESCC. The patient population was compromised of patients not deemed candidate for conventional open thoracotomy due to age (mean 74 y), limited life expectancy, and/or systemic metastatic burden. MOT was 2.2 hours and MBL was 227 mL. All patients presented with substantial neurologic deficit (mean Nurick grade: 4.35 (range 3–5)) and pain (mean numerical pain score (NPS) 5.5 (range 3–8)). Postoperatively, 5 patients experienced neurologic improvement (NI: 62.5 %), and the mean Nurick grade of all patients decreased to 3.13. 5 patients experienced pain alleviation (PA: 62.5%), with the group mean NPS decreasing to 3.10. There was no incidence of complications reported (Table 2).

Kan and Schmidt [29] published a retrospective case series of 5 patients with metastatic disease of the thoracic spine who underwent ventral decompression via MASS. The procedure included a corpectomy, interbody fusion, expandable cage-mediated reconstruction, and stabilization via anterior plating through MASS techniques. MOT was 4.3 hours, MBL was 610 mL, and mean LOS was 6.25 days. All patients who presented with neurological deficits were neurologically intact at 6-month followup (NI: 100%). The preoperating mean VAS score for the group was 6.8, and it decreased to 3 at 6-month followup. Additionally, all patients experienced some degree of pain relief (PA: 100%) (Table 2).

Payer and Sottas [30] published a case series of 37 patients, 11 of which were afflicted with thoracic metastasis to the spine and managed via MASS using the SynFrame (Stratec Medical; Obendorf, Switzerland) table mounted retractor. The authors stratified results according to tumor and nontumor etiology. MOT for tumor patients was 188 minutes versus 178 minutes for nontumor patients. MBL for tumor patients was 711 mL versus 598 mL for nontumor patients. There were 4 complications (15%) in the nontumor group and 2 complications in the tumor group (18%). Neurological outcomes were not stratified according to etiology. However, it was reported that of the 22 patients presenting with neurological deficits, 20 patients demonstrated recovery (NI: 92%). Preoperative and postoperative pain outcomes were not compared (Table 2).

Taghva et al. [31] published a case report describing a T4 and T5 vertebrectomy with expandable cage placement coupled with T1–T8 screw fixation and fusion using MASS. The patient was afflicted with metastatic adenocarcinoma of the lung and presented with back pain for more than 4 months. On neurological examination, the patient was found

Table 2: Minimal access spine surgery outcomes. MOT: Mean operating time; LOS: Length of stay; NI: Neurological improvement rate; PA: Pain alleviation rate; CR: Complications rate; MBL: Mean blood loss, SVR: 2-year survival rate.

Study	Design and procedure	Outcome results
Mühlbauer et al. [27], 2000	Retrospective case series ($n = 5$) of patients undergoing lumbar corpectomy and anterior reconstruction via MASS in the setting of osteoporotic or malignancy-related compression fractures	MOT: 6 hours NI: All patients experienced neurological improvement and were ambulatory at followup (6 mo to 1 yr) PA: All patients experienced pain relief. 40% of patients did not utilize analgesics at 1-year followup CR: Segmental vessel nick via a high-speed drill. Bleeding was adequately controlled MBL: 1120 mL
Huang et al. [23], 2006	Retrospective analysis ($n = 46$) comparing MASS ($n = 29$) to standard thoracotomy (ST) ($n = 17$) in the management of thoracic spinal metastasis	MOT: MASS = 179 mins versus ST = 180 mins; $P = .54$ % Requiring 2-day ICU stay: MASS = 6.9% versus ST = 88%, $P \leq .001$ NI: Reacquisition of ambulation postoperatively; MASS = 70.8% versus ST = 69.2%, $P = .6$ SVR: MASS = 27.4 mo versus ST = 24.8 mo, $P = .68$ CR: MASS = 24% versus ST = 29% MBL: MASS = 1,100 mL versus ST = 1,162 mL, $P = .63$
Deutsch et al. [28], 2008	Retrospective case series ($n = 8$) of patients undergoing MASS posterolateral vertebrectomy and decompression for the management of thoracic spinal metastasis	MOT: 2.2 hours LOS: 4 days NI: 62.5% of patients PA: 62.5% of patients CRs: none MBL: 227 mL
Kan and Schmidt [29], 2008	Retrospective case series ($n = 5$) of patients undergoing MASS anterior corpectomy and decompression for the management of thoracic spinal metastasis	MOT: 4.3 hours LOS: 6.25 NI: All patients experienced neurological improvement PA: All patients experienced pain alleviation CR: none MBL: 610 mL
Payer and Sottas [30], 2008	Retrospective case series ($n = 11$) analyzing operative outcomes of MASS conducted with the SynFrame (Stratec Medical, Obendorf, Switzerland) table mounted retractor in the setting of thoracic metastatic spine disease	MOT: 188 mins NI: All patients neurologically intact, at presentation remained intact and 91% of patients with preoperative deficit experienced neurological improvement CR: 18% (2/11; one dural tear and one superficial wound infection) MBL: 711 mL
Taghva et al. [31], 2010	Case report of a man undergoing vertebrectomy and expandable cage reconstruction for the management of metastatic lung adenocarcinoma localized to the thoracic spine	MOT: 7 hours LOS: 5 days NI: Patient experienced myelopathy relief and was ambulatory on postoperative day 1 PA: at 9-month followup, patient remained back pain-free with no use of analgesic medications CR: none MBL: 1200 mL

to have decreased strength and sensation. Operative time was 7 hours, and blood loss was 1200 mL. The patient was discharged 5 days following surgery. Neurological outcome was positive, with the patient being ambulatory postoperatively on day 1 and completely recovering strength and sensory function at 9-month followup. Similarly, pain alleviation was satisfactory with the patient reported to be pain-free at 9-month followup (Table 2).

3.4. Summary. There were a total of 5 publications, encompassing a total of 105 patients, selected to review the outcomes of VAST and endoscopy-assisted posterior decompression in the setting of metastatic spine disease. Data was compiled and yielded a median MOT of 4.6 hours (2.6–6.5 hours), a median MBL of 1113 mL (350–1677 mL), 7-day median LOS (6.5–7.5 days), 100% median NI (92%–100%), 100% median PA (94%–100%), and 0% median CR (0%–54%) (Table 3) Data gathered from the 6 publications, totaling 76 patients, to evaluate MASS outcomes in the setting of metastatic spine disease yielded similar results with a median MOT of 3.7 hours (2.2–7 hours), a median MBL of 905 mL (227–1200 mL), 5-day median LOS (4–6.25 days),

Table 3: Minimally invasive spine surgery outcomes summary. VAST: Video-assisted thoracoscopy; MASS: Minimal access spine surgery; mMOT: Median mean operating time; mLOS: Median mean length of stay; NI: Median neurological improvement rate; PA: Median pain alleviation rate; mCR: Median complication rate; mMBL: Median mean blood loss.

	VAST (median (range))	MASS (median (range))
N =	105 patients	76 patients
mMOT	4.6 hours (2.6–6.5 hours)	3.7 hours (2.2–7 hours)
mLOS	7 days (6.5–7.5 days)	5 days (4–6.25 days)
mNI:	100% (92%–100%)	95% (62.5%–100%)
mPA:	100% (94%–100%)	100% (62.5%–100%)
mCR:	0% (0%–54%)	9% (0%–24%)
mMBL	1113 mL (350–1677 mL)	905 mL (227–1200 mL)

95% median NI (62.5%–100%), 100% median PA (62.5%–100%), and 9% median CR (0%–24%) (Table 3). In comparing VAST to MASS (Table 3), the data suggests that VAST was associated with longer operative times, increased hospital length of stay, and increased blood loss. However, VAST compared favorably when looking at median neurological improvement and median complication rates. Despite appearing clinically significant, it is uncertain whether these differences are statistically significant.

4. Discussion

Surgical intervention in the setting of metastatic spine disease commenced prior to the advent of radiotherapy, and the initial goals of treatment were to achieve decompression of the spinal cord. This was most commonly performed via a dorsal laminectomy, as it was believed that this would relieve the pressure on the cord resulting in a reversal of neurologic deficits. However, the majority of metastatic neoplasms affect the anterior column and thus when combined with destabilization of the posterior column via a laminectomy, patients experienced rapid destabilization of the entire spinal column along with both cord vascular insufficiency and radicular compression due to the loss of spinal column integrity [2, 32].

With the advent of radiotherapy, evidence accrued demonstrating no neurological benefit to surgical intervention, specifically laminectomy alone, in comparison to radiotherapy alone, and thus surgery as a primary treatment modality was abandoned [33–36]. However, spine surgery in the setting of the metastatic spine disease continued to advance as surgeons continued to operate in patients whose neurological function was not improved following radiotherapy [11]. During the 1980s, rapid advances in both surgical technique and advances in spinal instrumentation resulted in the publication of the studies that re-established a role for surgical intervention as an addition to radiotherapy [37, 38]. In 1983, Constans et al. [39] published a retrospective case series of 600 patients with symptomatic MESCC and reported a neurological stabilization rate of 41% and a neurological improvement rate of 44%, both of which were rates considered to be superior to prior reported rates. In 2004, Klimo Jr. et al. [40] published a meta-analysis comparing outcomes of surgery and radiotherapy management compared to radiotherapy alone and reported superior outcomes for patients who underwent surgery in addition to radiotherapy. In 2005, Patchell et al. [41] conducted the first randomized control study comparing the efficacy of radiotherapy and surgery to that of radiotherapy alone. Similar to the results of Klimo Jr. et al. [40], the study not only found functional and survival outcomes to be superior in the surgery plus radiotherapy group but also reported that surgical intervention was cost effective, cementing the role of surgery in the management of metastatic spine disease for candidate patients.

Although surgery plus radiation has been shown to be superior to radiation alone in a class I study, the role of surgical intervention remains controversial due to the difficulty of appropriate patient selection. Numerous factors such as tumor type, extent of metastatic disease, spinal stability, neurologic status, comorbid conditions, and life expectancy are considered when evaluating a patient for potential surgical candidacy [4, 15]. Furthermore, numerous scoring systems such as that of Tokuhashi et al. [42] and Tomita et al. [38] have been created to guide patient selection and dictate the aggressiveness of the respective surgical intervention. Unfortunately, the advances in surgical technique that improved surgical outcomes in patients with metastatic lesions required aggressive methods such as circumferential decompression or combined (anterior, posterior, and lateral) approaches that were only feasible in healthier patients with respective longer life expectancies and thus were not feasible for patients with numerous comorbid conditions or contraindications such as ongoing chemotherapy [15].

Minimally invasive spine surgery was created with the purpose of minimizing soft tissue surgical trauma and thereby accelerating postoperative care [16, 18, 43, 44], without a loss of surgical effectiveness, and was thus applicable to the management of metastatic spine disease in patients not candidate for conventional surgical intervention. More specifically, patients with single or adjacent level involvement with neurologic symptoms from spinal instability or neurological structure compression and a life expectancy of at least 3 months are considered candidate for MIS [15, 16, 18].

There are two main modalities of minimally invasive spine surgery: endoscopic video-assisted thoracoscopic surgery (VAST) and mini-open surgeries otherwise known as minimal access spine surgery (MASS) [15]. VAST, first described in 1993 [45], allows for the visualization and magnification of the entire ventral spine from T1 to T12, thereby allowing for decompression, reconstruction, and stabilization similar to an open thoracotomy. However, unlike an open thoracotomy, VAST has the advantage of decreased pulmonary morbidity, preservation of chest wall motion, decreased intercostal neuralgia, and avoidance of scapular dysfunction [46]. Furthermore, VAST can be combined with laparoscopic techniques to permit similar visualization and manipulation of the lumbar spine [15, 29]. Despite advantages, VAST has not become a widely adopted procedure due to practical limitations such as a steep learning curve, increased surgical time, relative difficulty in controlling

intraoperative bleeding, and expensive equipment needed to perform the procedure [15, 47].

MASS was first described in 1997 [48] as a microsurgical approach for performing an anterior lumbar fusion, covering all levels from L2 to S1. It has since become more popular than VAST as an MIS modality as it is easier to learn, is a more familiar exposure to most spine surgeons, permits faster decompression of the spinal canal [23, 30, 49], potentially allows for safer mobilization of neurovascular structures, and provides three-dimensional direct vision allowing for easier reconstruction of the anterior column [50]. Since its introduction, the procedure has been modified to permit access from T2 to S1 via a combination of mini-open thoracotomy and/or retroperitoneal miniapproach [30, 49].

In this study, we performed a systematic review of published literature to date with the goal of evaluating the clinical efficacy and safety of MIS in the setting of metastatic spine disease. A total of 11 studies specifically reporting outcomes of metastatic spine cases managed via MIS were gathered. 5 of the studies, totaling 105 patients employed VAST, and 6 of the studies, totaling 76 patients, employed MASS. All of the collected studies were retrospective (Class IV evidence), and two of the studies were case reports. Although traditionally excluded from systematic reviews, the two case reports collected were included in our study due to the scarcity of published studies reporting on the use of MIS to treat metastatic spine lesions.

We evaluated the clinical efficacy of MIS for the treatment of metastatic vertebral lesions via neurological improvement rate and pain alleviation rate outcome data. Collected data from each study was compiled to yield median mean neurological improvement (mNI) and median mean pain alleviation rate (mPA). mNI for VAST was 100% (92%–100%) and 95% (62.5%–100%) for MASS. mPA for VAST was 100% (94%–100%) and 100% (62.5%–100%) for MASS. The neurological improvement and pain alleviation rates are similar to those provided by the Class I study conducted by Patchell et al. that evaluated surgery plus radiotherapy outcomes [41]. Given the high rates of neurological dysfunction and pain alleviation, the results suggest that both VAST and MASS are efficacious means of achieving pain and neurological dysfunction relief through decompression and stabilization.

Operative variables such as operative time, blood loss, complication rate, and hospital stay are considered markers of safety and practicality. Prolonged operating times are associated with an increased amount of complications (i.e., higher wound infection rate) and costs [51]. High blood loss leading to perioperative anemia leads to increased morbidity (i.e., surgical site infections), mortality, length of stay, and readmission rates [52]. Furthermore, patients with high blood loss often require transfusions which are associated with higher risks of infection, acute immune-mediated hemolytic reactions, and gastrointestinal complaints [52]. Longer hospital stays result in higher costs and are indicative of increased patient morbidity [15]. Smith et al. [47] compiled median operative variables of 16 studies, totaling 746 patients, reporting outcome data for open thoracotomies performed in the setting of thoracolombar spine pathology. One of the limitations commonly associated with MIS procedures is prolonged operative time. Data gathered contradicts this notion and suggests that both VAST and MASS collective median operating times (mMOT) compare favorably to open standard thoracotomy (ST) operating times collected by Smith et al. [47] (VAST: 4.6 hours (2.6–6.5 hours); MASS: 3.7 hours (2.2–7 hours); ST: 4.65 hours (2.3–10.2 hours)).

Decreased complication rates, blood loss, and length of stay are considered to be among the benefits of MIS. This was confirmed by outcomes data compiled in our study when compared to gathered data outcomes for ST [47]. Median mean complication rates (mCR) for VAST (0% (0%–54%)) and MASS (9% (0%–24%)) compared favorably to those of ST (30.5% (15%–94.4%)). Similarly, median mean blood loss (mMBL) and median mean length of stay (mLOS) for both VAST (mMBL: 1113 mL (350–1677 mL); mLOS: 7 days (6.5–7.5 days)) and MASS (mMBL: 905 mL (227–1200 mL); mLOS: 5 days (4–6.25 days)) was decreased in comparison to data gathered for ST [47] (mMBL: 2100 mL (460–3136 mL); mLOS: 14.6 days (7.2–35.5 days)). It should be noted that the paper by Huang et al. [23] included in this review performed a direct retrospective comparison of MOT, MBL, LOS, and CR for MASS versus ST and found no significant difference in rates for any of the latter. However, the study did find a significant difference in the incidence of patients that required at least a two-day admission to the ICU postoperatively (MASS: 6.9% versus ST: 88%). If there truly is not a difference in these operative variables, it is possible that the potential benefit of MIS is counteracted by the more complicated nature of operating in patients with metastatic spine disease [24]. This observation was present in the study included by Payer and Sottas [30] in which mean blood loss, operative time, and complication rates were higher in patients being operated for spinal tumors versus those operated on the spine for pathology other than tumor.

5. Conclusions

A systematic review of the literature yielded Class IV data suggesting that both VAST and MASS MIS modalities are efficacious means of achieving neurological improvement and alleviating pain in the treatment of metastatic spine disease. However, the magnitude of neurological improvement and/or pain alleviation cannot be accurately quantified by such retrospective studies. Such studies suggest that minimally invasive surgery for metastatic spine disease offers decreased blood loss, operative time, and complication rates in comparison to standard open spine surgery. Furthermore, these studies also suggest that MIS implementation was not limited by increased operative times. Nonetheless due to the paucity of studies and low class of available evidence, the ability to draw comprehensive conclusions is limited. Minimally invasive surgery thus remains a viable *option* for the treatment of spinal metastases. Future investigations should be conducted comparing standard surgery versus minimally invasive surgery in a prospective fashion.

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Clinical Study

Minimally Invasive Treatment of Spinal Metastases: Techniques

Peter S. Rose,[1] Michelle J. Clarke,[2] and Mark B. Dekutoski[1]

[1] *Department of Orthopedic Surgery, Mayo Clinic, Rochester, MN 55905, USA*
[2] *Department of Neurosurgery, Mayo Clinic, Rochester, MN 55905, USA*

Correspondence should be addressed to Peter S. Rose, rose.peter@mayo.edu

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With improved treatments and increasingly life expectancy, the burden of metastatic disease in the spine is expected to rise. The role of conventional surgery for spinal metastases is well established but often involves procedures of large magnitude. We describe minimally invasive techniques for spinal stabilization and decompression in patients with symptomatic metastatic disease of the spine.

1. Introduction

Metastatic disease to the spine is an increasingly common clinical condition given improved cancer care and overall mortality trends. The majority of patients who die of cancer have vertebral metastases at autopsy [1, 2]. An estimated 20,000 patients per year in the United States have symptomatic epidural spinal cord compression and a much greater number have symptomatic vertebral metastases [3, 4]. The clinical burden in other areas of the world is likely similar.

Surgical management is entertained in patients who have spinal instability and/or compressive neurologic deficits [5]. Although there are rare indications for formal en bloc resection of metastatic tumors, the vast majority of patients with metastatic disease in the spine are treated with palliative intent. These patients are often weakened as a consequence of their primary disease process as well as its attendant treatments (e.g., chemotherapy and radiotherapy).

Open surgical treatment has a well-established clinical record in the treatment of patients with metastatic disease to the spine [6, 7]. However, advancements in surgical technique, instrumentation, and imaging modalities have led to the development of minimally invasive surgical techniques (MIS) in the treatment of metastatic disease to the spine. These procedures seek to decrease the physiologic insult, recovery time, and morbidity of more traditional open spine procedures. As well, they often allow more rapid initiation of other treatments (chemotherapy, radiotherapy) postoperatively than would be permitted by traditional approaches alone. MIS surgery of the spine seeks to achieve equivalent or superior outcomes to those of traditional open spine surgery with the use of these techniques. It is important to recognize, however, that the safety and efficacy of these techniques are currently under investigation and depend on surgeon experience and patient selection. This paper will review techniques commonly employed in minimally invasive spine surgery for metastatic disease. Percutaneous augmentation techniques (vertebroplasty/kyphoplasty) may be used in concert with these procedures but are not the focus of this paper.

2. Indications/Contraindications

Patients are considered for MIS treatment of spinal metastases if they require stabilization with or without tumor decompression. Relative contraindications to these techniques include circumferential tumors (in which adequate decompression may be difficult to achieve through an MIS approach alone). As well, highly vascular tumors (e.g., renal cell carcinoma) which require decompression with a high risk of resulting epidural hematoma may best be approached through open procedures in which proper hemostasis can be assured. Finally, it must be recognized that currently available MIS instrumentation is not as strong as the strongest traditional open instrumentation. Thus, patients who lack anterior column support should probably not undergo stand-alone MIS posterior instrumentation without concordant techniques to increase anterior column support

(e.g., concurrent vertebro/kyphoplasty, surgical instillation of methylmethacrylate, or cage insertion). The recent development of cobalt chrome rods for use in MIS systems improves the biomechanical profile of these instrumentation sets but does not remove these concerns.

3. Surgical Techniques

Common surgical techniques used in minimally invasive surgery for spinal metastases include posterior pedicle screw-based stabilization applied percutaneously, limited open decompressive procedures, percutaneous extracavitary/costotransversectomy type approaches accessed through a paraspinal muscle splitting mechanism, and direct lateral approaches. These techniques may be used in combination and may be further coupled with vertebro/kyphoplasty procedures to maximize the repertoire of disease which may be addressed in this manner.

Excepting rare and unique circumstances, we do not recommend decompression without instrumentation in the treatment of metastatic disease. The presence of the tumor itself is generally a destabilizing influence on the spine, and the bony removal necessary for decompression leads to further destabilization. Even if the assessment at the time of surgery is that appropriate remaining bone stock is present, with progression of disease, there is a high likelihood of spinal instability developing. Thus, posterior instrumentation is a standard part of MIS spine tumor treatment in our hands.

Spinal stabilization without formal fusion is usually the goal of these procedures. We do not pursue an extensive decortication or bone grafting in the treatment of metastatic disease. Bony fusion is unlikely to ever be achieved in the hostile environment containing a tumor which is treated by adjuvant chemo- and/or radiotherapy. The decortication used to promote bony fusion disrupts natural anatomic barriers to further tumor infiltration and spread, increases the scope of the procedure beyond its oncologic goals, and removes/weakens further stabilizing bone stock. If cavities remain which require filling for structural support, we prefer to achieve this with the use of methylmethacrylate and/or further instrumentation. Note that the United States Food and Drug Administration considers spinal instrumentation without fusion in this manner to be an "off-label" use of these devices. The authors employ this technique for the clinical reasons outlined above and inform their patients of this discrepancy between how these devices are approved and how they are used in these unique clinical situations.

3.1. Technique: MIS Posterior Pedicle Screw Instrumentation. Percutaneous pedicle screw instrumentation is used in nearly all MIS metastatic tumor surgeries by our group (Figure 1). Patients are positioned prone upon a radiolucent operating table. Imaging is usually achieved through the use of biplanar fluoroscopy. Alternatively, an intraoperative CT scanner and stereotactic navigation with appropriate reference landmarks may be used at the surgeon's discretion. We prefer to drape in two fluoroscopy units to allow efficient AP and lateral imaging to be obtained.

At the discretion of the operating surgeon, instrumentation may be placed through a series of paraspinal stab incisions, two parallel longitudinal paraspinal incisions, or a single mid-line incision. If a single mid-line incision is used, dissection is generally taken down to the level of the dorsal interfascial plane, and instrumentation is then placed through small individual fascial incisions.

Using biplanar fluoroscopy, pedicles are cannulated using a cannulated awl. Guidewires are then placed through each cannula. Cannulated taps are used to establish the pedicle screw trajectory, and pedicle screws are then placed over these guidewires. The guidewire is removed once the screw is inserted. Screwdrivers or reduction towers may remain in place as a mechanism to allow manipulation of the vertebral body (to correct deformity) and provide for locking screws to be placed once the stabilizing posterior rods are in place.

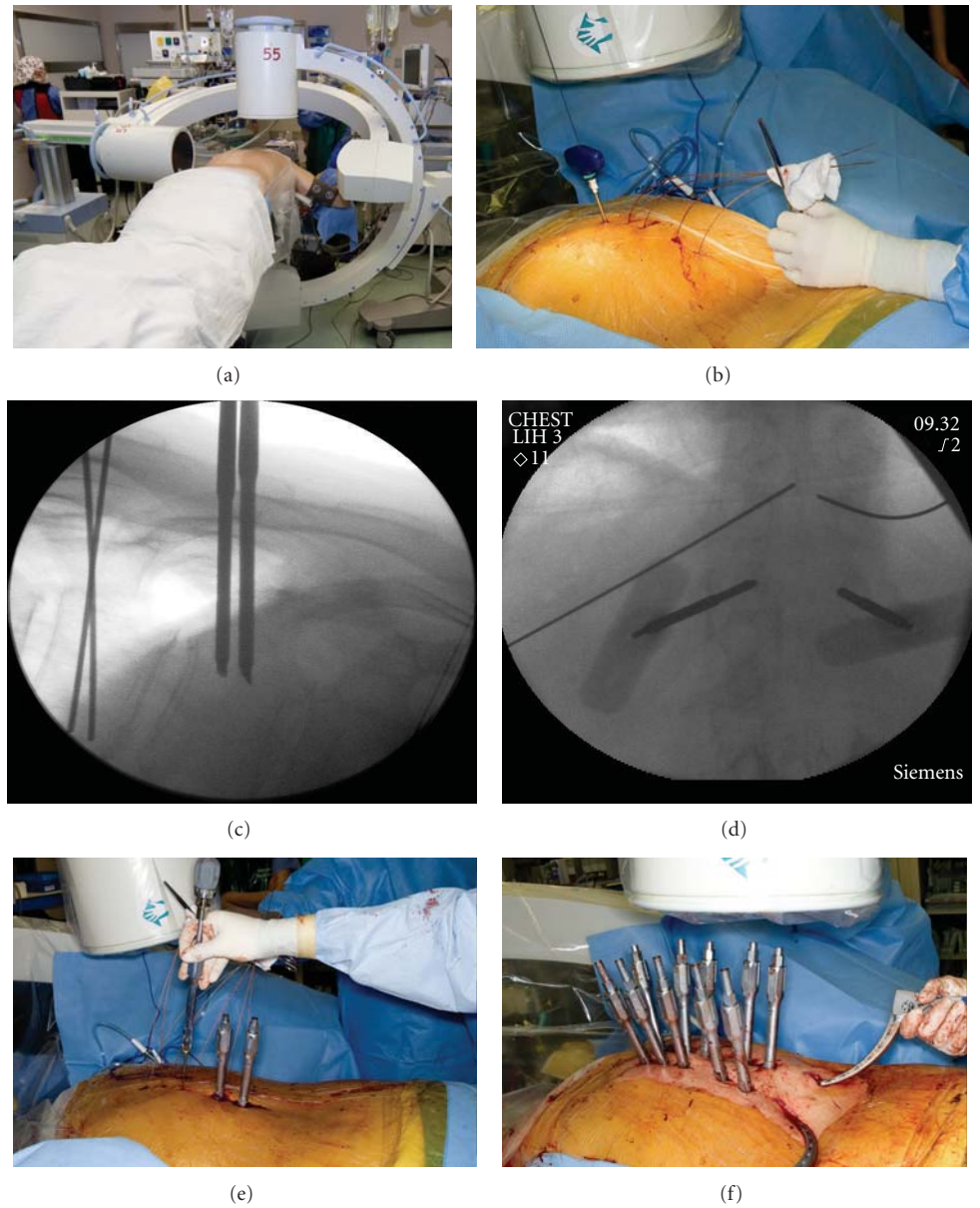
Once fixation points are all placed, rods are passed percutaneously through the screw heads and locked in place. A separate paraspinal stab incision is generally used to allow entry of the rods proximal to distal. In the lower lumbar spine, the lordotic orientation of L4-S1 sometimes makes it easier to pass rods from caudal to cranial. Once the rods are locked in place, the instruments used to place the screws are removed, the wound is irrigated and then closed in the standard fashion.

As patients with metastatic disease often have involvement at levels adjacent to the primary pathology, it is our preference to err on the side of a greater number of fixation points to distribute any stresses over a greater area, decreasing the risk of catastrophic failure. In practice, we generally instrument with bipedicular fixation two to three levels above and two to three levels below the site of disease in this manner. Instrumentation (or spannage) of six to ten levels is commonly achieved. Percutaneous instrumentation is also used to provide supplemental fixation for patients who have undergone limited open anterior procedures (Figure 2).

3.2. Combined Miniopen Decompression. In conjunction with the percutaneous instrumentation described above, miniopen decompression may be used to remove dorsal or dorsal-lateral areas of tumor compression. As well, in cases below the conus medullaris, anterolateral decompression may be achieved through this route as well with gentle manipulation of the thecal sac.

Patients undergoing a miniopen posterior decompression have a short segment mid-line incision performed over the area of offending pathology. Dissection is then taken down to allow for limited laminectomy and tumor removal (Figure 3). Any dorsal tumor is easily removed via this approach. As well, the medial portion of the pedicle on either side may be removed and angled instruments can be used to achieve a decompression of dorsal-lateral, lateral, and anterolateral tumor compression.

This approach is very helpful when the surgeon suspects the tumor may be hypervascular. This miniopen approach allows proper exposure for hemostasis and a high degree



(a) (b) (c) (d) (e) (f)

Figure 1: Percutaneous pedicle screw instrumentation. (a) Dual fluoroscopy setup; (b) percutaneous cannulation of pedicles; (c, d) lateral and anteroposterior imaging of pedicle cannulation; (e) passage of pedicle screws; (f) percutaneous passage of rod.

of confidence that a postoperative hematoma is unlikely. Limited open approaches also provide the best access if unilateral rhizotomy are necessary to access offending tumor or to repair any dural tears which occur. No special imaging capabilities beyond basic fluoroscopy for level localization and percutaneous pedicle screw placement is necessary for this technique.

3.3. Percutaneous Extracavitary/Costotransversectomy Technique. More extensive ventral and lateral tumor may be resected through the use of a percutaneous extracavitary/costotransversectomy approach. This utilizes the Wiltsie interval to access the lateral half of the dural tube as well as the ventral epidural space. This procedure requires more specialized instrumentation. Surgery relies upon the use of dilating percutaneous retractors which are docked over the surgical region of interest and held fixed by arms which attach to the operating table frame (Figure 4). These are usually used in conjunction with an operating microscope and bayoneted instruments to allow appropriate access.

Percutaneous extracavitary decompressions are coupled with posterior pedicle screw instrumentation placed percutaneously. The incision for the dilating retractor to allow the decompression is done 5 to 7 cm off the mid-line as dictated by local anatomy and the trajectory of the approach. Radiographic localization may be by fluoroscopy or via intraoperative navigation, depending on surgeon preference and facility capabilities. This technique allows more extensive

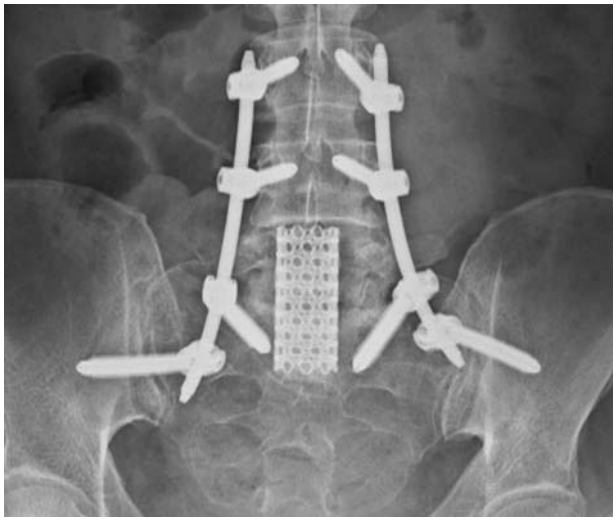
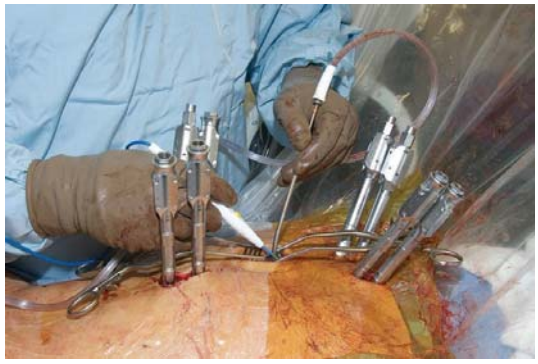
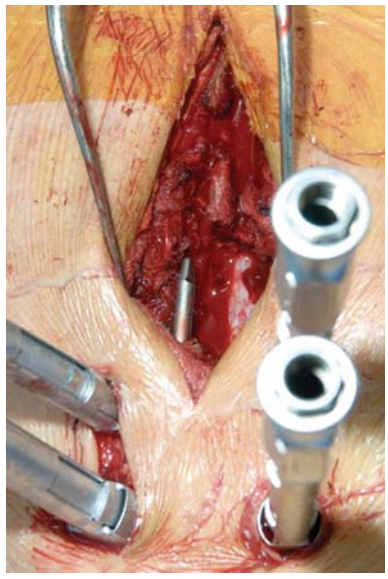


Figure 2: Use of percutaneous posterior instrumentation to stabilize open L5 corpectomy.



(a)



(b)

Figure 3: Miniopen decompression combined with percutaneous instrumentation. (a) Limited open decompression; (b) view of decompressed dural tube during rod passage.

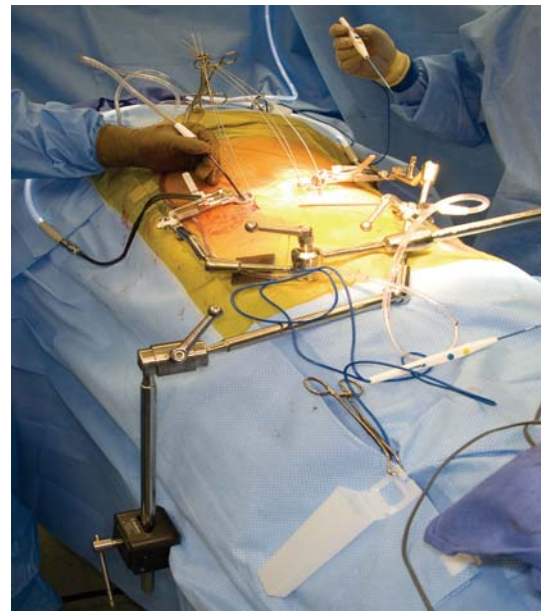


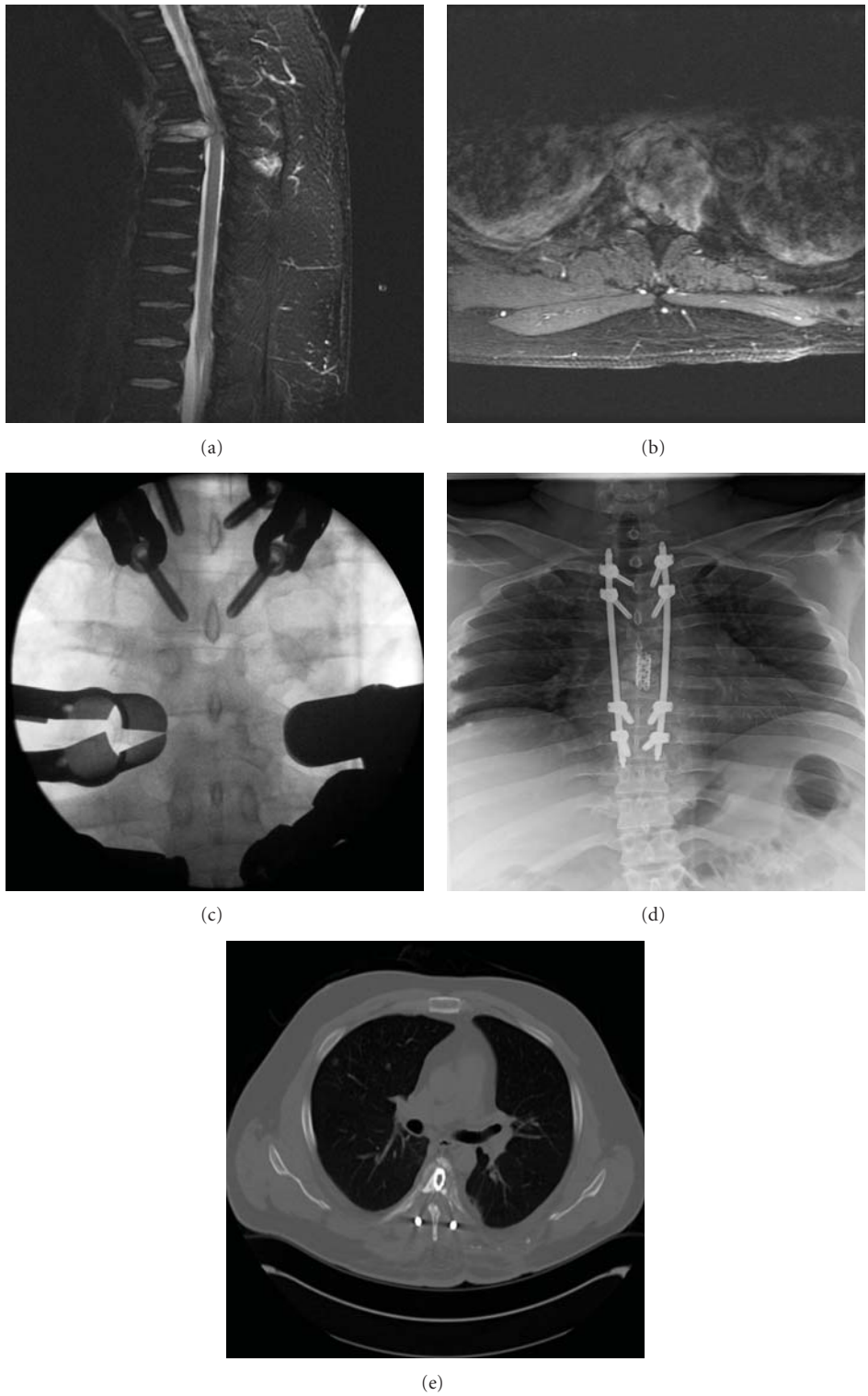
Figure 4: Setup for bilateral extracavitary approach showing dilating retractors inserted off midline rigidly attached to the operative table.

decompression of ventral tumor masses than does a miniopen posterior approach alone. Access to the posterior vertebral body may be obtained for curettage of tumor or augmentation with cement. We have found that methylmethacrylate may be easily instilled into tumor cavities in the vertebral body accessed in this manner using a conventional PMMA cement gun with a small diameter nozzle typically used for implantation of shoulder and elbow arthroplasty components. When cement is injected in this manner, a cage, Steinmann pin, or small fragment screw is placed into the adjacent bone, and the cement is placed around it. This acts as an additional anchor to prevent migration of cement.

3.4. Direct Lateral Approach for Tumor Removal. Percutaneous systems now offer direct lateral access to the L1 through L4 vertebral bodies. Similar instruments may be used in conjunction with a minithoracotomy to access disease in the thoracic vertebral bodies. In much the same manner of an MIS extracavitary approach, a direct lateral approach may be used to access vertebral body disease. It is not our preference to resect epidural tumor extension through this approach as the visualization of the thecal sac is inferior to that achieved through an extracavitary approach. This approach does allow for resection of the anterior vertebral body and reconstruction with a cage or methylmethacrylate. Because of the overhanging iliac wing, the L5 vertebral body is not well accessed in this manner.

4. Illustrative Case Example

Percutaneous fixation, bilateral extracavitary approach, and vertebral body reconstruction with cage and methylmethacrylate were employed in the successful treatment of



(a) (b) (c) (d) (e)

Figure 5: Bilateral extracavitary decompression for metastatic fibrosarcoma. (a) Sagittal T2-weighted, and (b) axial gadolinium enhanced MR images demonstrate pathologic fracture and metastatic epidural spinal cord compression at T5. (c) Fluoroscopy demonstrating docking of extracavitary retractors over the T5 costovertebral region. (d) Postoperate radiograph demonstrating T2–T8 fixation with cage + methylmethacrylate reconstruction of T5. (e) Postoperative CT demonstrates bilateral extracavitary decompression with cage/cement reconstruction.

a 37-year-old woman presenting with thoracic myelopathy from metastatic fibrosarcoma. Initial imaging studies demonstrate pathologic fracture of T5 with high-grade metastatic epidural spinal cord compression (Figures 5(a) and 5(b)). Patient underwent surgical treatment with percutaneous pedicle screw fixation spanning T2–T8 with bilateral extracavitary decompression at T5. Note that fluoroscopic imaging demonstrates docking of dilating retractors over the T5 costovertebral junction (Figure 5(c)). After tumor removal, a cage and methylmethacrylate were inserted to help reconstruct the weakened T5 body (Figure 5(d)). Postoperative CT demonstrates the resection achieved as well as cage/methylmethacrylate reconstruction. The patient recovered neurologic function post-operatively.

5. Discussion

Preliminary results of minimally invasive treatment of spinal metastases are encouraging [8]. Instrumentation failure is rare, and with proper adjuvant treatment, patients are unlikely to succumb to local mechanical or disease-related failure prior to demise. Most procedures can be performed with limited blood loss and modest operative times.

A benefit to the use of MIS approaches to metastatic spine tumors in our practice is a more rapid initiation of postoperative adjuvant therapies. For example, after a conventional open instrumented costotransversectomy procedure, we are hesitant to allow initiation of chemo- or radiotherapy until four to six weeks following the procedure to guard against wound dehiscence given the large approach, empty/dead space, and tissue devitalization which occurs with such procedures. In contrast, after an MIS extracavitary decompression and percutaneous instrumentation procedure, stereotactic radiotherapy may be initiated at our institution 10 to 14 days postoperatively. Although the percutaneous procedure may not allow a complete debulking of offending tumor from the vertebral body, the excellent local control (even of adverse histologies) achieved by stereotactic radiotherapy decreases the need for a gross total resection of tumor and may change the treatment paradigm of some patients with metastatic disease [9]. Our goal in the MIS treatment of these patients is to achieve a zone of decompression around the thecal sac of 2 to 4 mm followed by the rapid initiation of stereotactic radiotherapy to achieve local disease stasis.

We emphasize that the adoption of these techniques by our surgical oncology group has been in a progressive fashion. There is certainly a learning curve associated with the implementation of MIS techniques in any setting. Given the altered anatomy and tissue conditions caused by tumor, radiotherapy, and so forth in the oncologic situation, this learning curve/case progression is highlighted. Our group began using MIS techniques for stabilization procedures alone and then expanded them to the use of stabilization coupled with miniopen decompressions and now pursue MIS extracavitary decompression of metastatic epidural spinal cord compression.

To date, our experience has been encouraged with low morbidity and favorable clinical and oncologic outcomes (Clarke et al., manuscript under review). Further experience will be necessary to refine the indications and techniques for MIS surgery applied to metastatic disease. Open surgical stabilization and decompression remain the gold standard to which MIS results must be compared. Direct comparative studies of open versus MIS treatments for metastatic disease in the spine are not currently available. Acknowledging these limitations, MIS techniques offer a valuable option for consideration in patients presenting with symptomatic metastatic disease of the spine.

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Clinical Study

Minimally Invasive Posterior Stabilization Improved Ambulation and Pain Scores in Patients with Plasmacytomas and/or Metastases of the Spine

Joseph H. Schwab,[1] Alessandro Gasbarrini,[2] Michele Cappuccio,[3] Luca Boriani,[2] Federico De Iure,[4] Simone Colangeli,[2] and Stefano Boriani[2]

[1] *Department of Orthopedic Surgery, Massachusetts General Hospital, Yawkey 3, 55 Fruit Street, Boston, MA 02114, USA*
[2] *Department of Oncologic Surgery, Rizzoli Institute, 40136 Bologna, Italy*
[3] *Department of Orthopedic Surgery, Ospedale Maggiore, 40136 Bologna, Italy*
[4] *Department of Orthopaedics, Traumatology and Spine Surgery, Ospedale Maggiore AUSL, 40136 Bologna, Italy*

Correspondence should be addressed to Joseph H. Schwab, jhschwab@partners.org

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Background. The incidence of spine metastasis is expected to increase as the population ages, and so is the number of palliative spinal procedures. Minimally invasive procedures are attractive options in that they offer the theoretical advantage of less morbidity. *Purpose*. The purpose of our study was to evaluate whether minimally invasive posterior spinal instrumentation provided significant pain relief and improved function. *Study Design*. We compared pre- and postoperative pain scores as well as ambulatory status in a population of patients suffering from oncologic conditions in the spine. *Patient Sample*. A consecutive series of patients with spine tumors treated minimally invasively with stabilization were reviewed. *Outcome Measures*. Visual analog pain scale as well as pre- and postoperative ambulatory status were used as outcome measures. *Methods*. Twenty-four patients who underwent minimally invasive posterior spinal instrumentation for metastasis were retrospectively reviewed. *Results*. Seven (29%) patients were unable to ambulate secondary to pain and instability prior to surgery. All patients were ambulating within 2 to 3 days after having surgery ($P = 0.01$). The mean visual analog scale value for the preoperative patients was 2.8, and the mean postoperative value was 1.0 ($P = 0.001$). *Conclusion*. Minimally invasive posterior spinal instrumentation significantly improved pain and ambulatory status in this series.

1. Introduction

It is estimated that over 1.5 million new cases of cancer occur each year in the United States. Roughly 500,000 people die each year in the United States from cancer-related causes, most of whom have metastatic disease [1]. The three most common cancers, lung, breast, and prostate, all commonly spread to bone, and the spine is the most frequently involved segment of the skeleton [2]. The majority of spinal metastases are asymptomatic and do not require local treatment. Radiation is the standard of care for painful spinal metastases in the absence of an unstable fracture or impending fracture [3]. In cases where a fracture is unstable or there is an impending fracture, then stabilization ought to be considered.

Minimally invasive techniques offer potential advantages over open techniques particularly in the population of patients suffering from metastatic disease of bone. Minimally invasive techniques, as the name implies, are potentially associated with less soft tissue injury than their open surgical counterparts [4]. Furthermore, minimally invasive posterior stabilization has been shown to be associated with relatively low blood loss [5]. This may translate to less morbidity and possibly shorter hospital stays. In addition, the use of minimally invasive techniques may be associated with lower postoperative infections. Posterior stabilization allows

for immediate mobilization without the need for external bracing. This is particularly important in this patient population as the main goal ought to be to maintain their quality of life.

We present the short-term followup of 24 cases of metastatic disease in the spine treated minimally invasively with posterior instrumentation. We compared preoperative ambulatory status and preoperative pain levels with postoperative levels. Our goal was to determine whether minimally invasive posterior instrumentation could provide meaningful improvement in pain control and ambulatory status in the short term.

2. Materials and Methods

We performed a retrospective review of 24 consecutive cases treated with minimally invasive posterior spinal instrumentation for spine tumors. The patients were followed for an average of 9 months (range 3–21). There were 13 male and 11 female patients. The average age was 62 (range 33–86). Patients with spinal cord compression are not suitable candidates for this procedure and thus were excluded. The following cancer diagnoses were included: plasmacytoma (9), metastatic breast cancer (5), metastatic hepatocellular carcinoma (2), metastatic lung cancer (1), metastatic prostate cancer (1), metastatic colon cancer (2), metastatic angiosarcoma (1), metastatic liver cancer (1), metastatic thyroid cancer (1), and lymphoma (1). The thoracic spine was the primary site of disease in 10 cases, and the lumbar spine was the primary site of disease in 14 cases.

Only cases where instrumentation was used were included in this paper. The indications for instrumentation were made on a case-by-case basis. In general, an unstable fracture or an impending fracture were indicated for surgery. The decision to proceed with surgery was made on a case-by-case basis. Patients with mechanical back pain, defined as pain with movement which is relieved by rest, that corresponded to an area of metastases were considered for surgery.

We were interested in examining whether surgical stabilization had a statistically significant impact on ambulatory status and self-reported pain levels. We categorized patients into one of two categories with regard to ambulation. If they were able to ambulate with or without a gait aid, they were given a score of 1. If they were unable to ambulate, then they were given a score of 0. We utilized the Fisher's exact test to evaluate whether the patients' ambulatory status was improved by our intervention. We used a visual analog scale (VAS) to assess pain as reported by the patients. A score of 1 was given for mild or no pain (0–3). A score of 2 was given for moderate pain (4–6), and a score of 3 was given for severe pain (7–10). The student's t-test was used to compare the mean VAS between preoperative and postoperative groups. A P value of less than 0.05 was used to determine whether a value was statistically significant.

The procedure involves the use of fluoroscopic imaging in order to place the pedicle screws percutaneously. Adequate imaging is required to visualize the pedicles well in both the lateral as well as a/p views. This may require the radiology technician to cant the fluoroscope in order to visualize the pedicles clearly. This is particularly true in the sacrum. A radiopaque marker is placed on the skin so that the incisions are appropriately placed just lateral to the pedicles. This allows medialization of the trochar. The trochar is passed through the soft tissues down to the bony surface. Prior to penetrating the cortex with the trochar, it is important to confirm that the trochar is on the lateral border of the pedicle silhouette. In addition, it is useful to place the trochar along the superior quarter of the pedicle as seen on the a/p and lateral image. Placement of the trochar in this manner allows one to medialize the pedicle screw as it passes into the vertebral body. After the trochar has been successfully placed into the vertebral body, a guide wire is placed through it. The trochar is then removed, and a series of dilators are passed over the wire. Each system has a slightly different mechanism of screw/rod placement, and thus the technique should be tailored to the implant used as well as particular anatomy of the patient. The unifying theme behind these systems is that they provide a percutaneous/minimally invasive means by which they can stabilize the spine.

3. Results

Seven (29%) of the 24 patients were unable to ambulate secondary to pain and instability prior to surgery (Table 1). All 24 patients were ambulating within 2 to 3 days after having surgery ($P = 0.01$). The mean visual analog scale value for the preoperative patients was 2.8, and the mean postoperative value was 1.0 ($P = 0.001$).

Twenty-one of 24 patients presented with severe pain. Seven patients were unable to ambulate secondary to pain. One patient complained of radicular pain in addition to their back pain. The rest of the patients complained primarily of back pain.

The two patients who presented with minimal back pain had lytic lesions that were concerning for impending collapse. Both of them were to undergo surgery for pathologic fractures of their limbs. In one case a proximal femoral replacement was performed secondary to a pathologic fracture. The other patient underwent a proximal humerus resection secondary to pathologic fracture. Both of these patients underwent minimally invasive spinal stabilization under the same anesthetic. Both of these patients were in need of chemotherapy. It was felt that their spines were going to collapse secondary to the lytic nature of their lesions. It was determined that minimally invasive stabilization under the same anesthetic as the one used for their limb reconstructions made the most sense. If their spines became a problem in the ensuing months, then their chemotherapy would have to be interrupted in order to stabilize their spines. This decision was made in conjunction with the patients and their medical oncologists.

Another patient with metastatic hepatocellular carcinoma underwent open decompression and stabilization for high-grade spinal cord compression in the thoracic spine. They had a painful lumbar metastasis at L4 and L5, which was stabilized minimally invasively from L3-S1 under the same anesthetic.

Table 1: Minimally invasive posterior stabilization for malignancies in the spine.

Sex	Age	Diagnosis	Walking pre-op.	Walking post-op.	Pre-op. pain	Post-op. pain	Pathology level	Instr. levels	Δ Deformity	Time (min)
M	68	Plasmacy.	Y	Y	2	1	L3	L2-4		110
M	86	Metastatic prostate ca.	N	Y	3	1	L5	L4-S1	9° Kyphosis	180
F	65	Plasmacy.	Y	Y	1	1	T10	T9–T11		60
M	80	Metastatic colon ca.	N	Y	3	1	L3-L4-L5	L2-S1		80
F	44	Metastatic breast ca.	Y	Y	3	1	T7	T5–T9	10° Kyphosis	135
F	58	Metastatic breast ca.	N	Y	2	1	L5	L4-S1		80
F	55	Plasmacy.	Y	Y	3	1	L2	T12, L1–L3		105
F	66	Metastatic angiosarc.	Y	Y	3	1	T11	T9, T10–T12, L1		180
M	61	Metastatic lung ca.	N	Y	1	1	T5	T3–T7		105
M	48	Metastatic HCC	Y	Y	3	1	L4-L5	L3-S1		75
M	75	Plasmacy.	Y	Y	3	1	T10	T9–T11		60
M	33	Lymphoma	Y	Y	3	1	L1	T12-L2	13° Scoliosis	120
M	75	Metastatic HCC	Y	Y	3	1	T11	T10–T12		120
F	60	Metastatic breast ca.	N	Y	3	1	L1	T12-L2		60
F	68	Metastatic colon	Y	Y	3	1	L4	L3–L5		120
M	75	Metastatic liver	Y	Y	3	2	L1	T12-L2		180
M	64	Plasmacy.	Y	Y	3	1	L5	L4-S1		180
F	73	Metastatic breast	Y	Y	3	1	L3	L2–L4		120
M	37	Plasmacy.	N	Y	4	1	T7	T6–T8		120
F	72	Plasmacy.	Y	Y	3	1	T10	T9–T11		180
F	52	Plasmacy.	Y	Y	3	1	L5	L4-S1		180
F	75	Metastatic breast	Y	Y	3	1	T10-T11	T9–T12		180
M	45	Plasmacy.	N	Y	3	1	T10	T9–T11		120
M	59	Metastatic thyroid	Y	Y	4	1	T6-L4	T3-S1		180

Plasmacy.: plasmacytoma, angiosarc.: angiosarcoma, HCC: hepatocellular carcinoma, ca.: cancer, Δ deformity: the measured change in deformity from preoperative to postoperative images, pre and postoperative pain scale 3: severe, 2: moderate, 1: none to mild.

One 86-year-old patient with metastatic prostate cancer presented with back pain and radicular pain in an L5 distribution. He underwent a minimally invasive decompression along with minimally invasive stabilization (Figure 1).

Three patients had deformities associated with pathologic fractures. In two instances the patients had kyphotic deformities, and in the other case the patient had scoliosis. All three deformities were noted in the lumbar spine. The kyphotic deformities measured 25° and 15° over the involved lumbar vertebrae. The scoliosis measured 15° around L1. All three of these patients were managed with minimally invasive posterior instrumentation. The kyphotic deformities improved by 10° and 9°, respectively, and the scoliosis improved by 13°.

4. Discussion

We report the successful management of 24 patients treated with minimally invasive posterior spinal instrumentation for malignancies of the spine. The patients had a statistically significant improvement in ambulatory status as well as pain levels after their minimally invasive stabilization. All patients in our series were ambulatory without a brace after surgery. The rationale behind this form of treatment is that it balances the need to stabilize the spine while avoiding the morbidity associated with open procedures [4].

It is important to maintain proper oncologic perspective when managing this patient population. Many of these patients do not have long to live, and the goal must be to improve or maintain their quality of life during the remaining time. This concept is predicated on the notion that appropriate staging and diagnostic work-ups have been performed prior to rendering treatment. Anecdotally, we have had several patients sent to us for management of their metastatic disease when in fact they had spondylodiscitis. These patients had a history of cancer, and it was assumed that their spine pathology was related. The opposite situation has also occurred in which a patient was thought to have an infection when in fact they had metastatic disease. A biopsy should be performed and cultures should be sent before deciding on and rendering treatment.

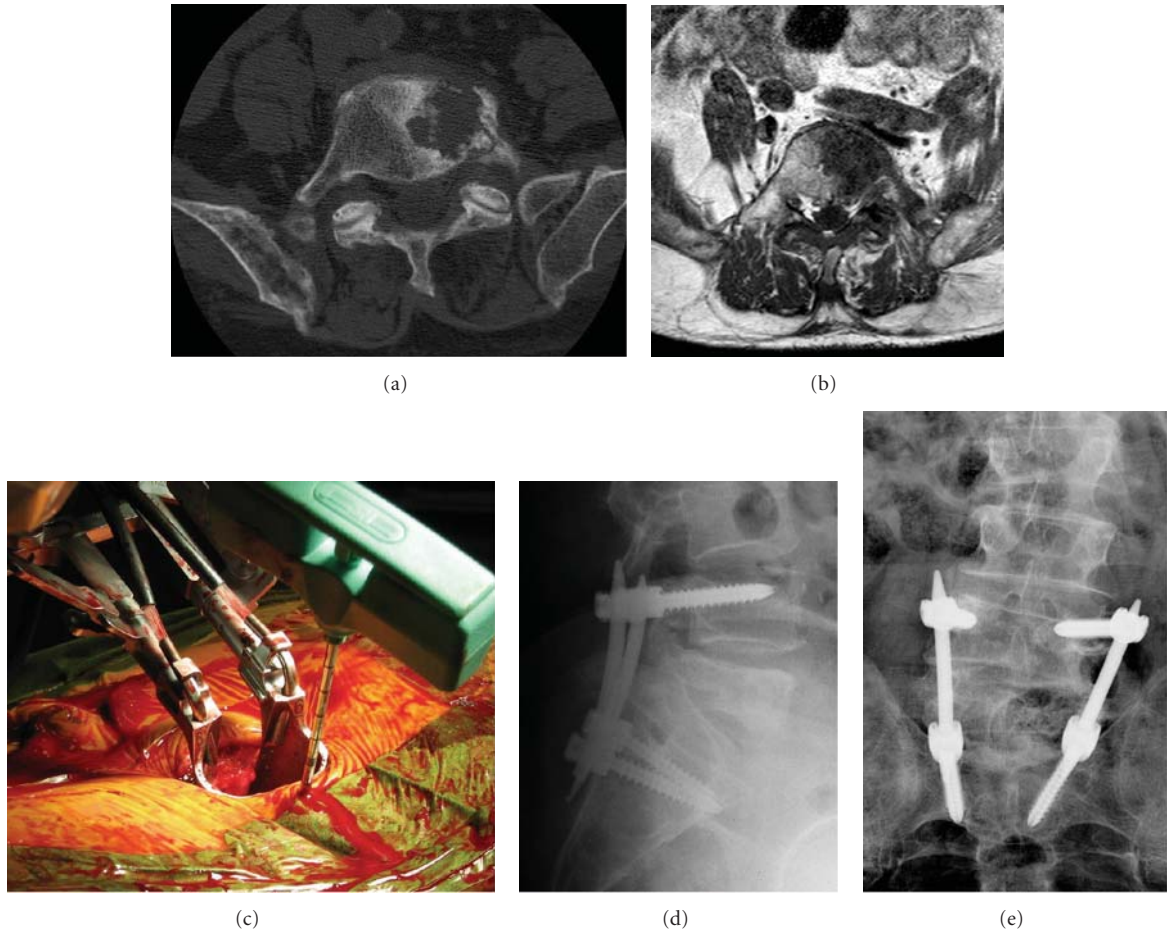

Figure 1: (a) This is a preoperative axial CT image of the L5 vertebrae demonstrating a lytic lesion from metastatic prostate cancer, (b) this preoperative axial MRI image demonstrates compression of the L5 nerve root on the left side, (c) this intraoperative photo demonstrates a trochar utilized to localize the pedicle prior to pedicle screw insertion, and it also demonstrates the minimally invasive access utilized for decompression of the L5 nerve root, (d) and (e) these are the postoperative a/p and lateral images demonstrating the L4-S1 instrumentation.

While there seems to be an important role for minimally invasive procedures in this patient population, there are instances in which minimally invasive approaches are not appropriate. In the setting of high-grade spinal cord compression, percutaneous procedures should not be entertained. At this time, percutaneous fusions are unproven and if a patient requires a fusion, they should not be treated percutaneously. Furthermore, minimally invasive instrumentation is to be used alongside other adjuvant therapies such as radiation or chemotherapy. If a tumor is not sensitive to either, then one should pause before using a minimally invasive approach.

Traumatic fractures of the thoracolumbar spine have been treated successfully using a similar approach [5, 6]. It is important to note that this procedure does not involve a fusion. The instrumentation should be considered as an internal brace. In theory the instrumentation would eventually fail, and thus it should be removed prior to this occurring, which is often done in the case of traumatic fractures. However, this is meant as a definitive procedure in the setting of metastatic disease. Surgery is meant as a means by which the quality of life of the patient can be improved, and it is not meant as curative. In this way, percutaneous instrumentation is sound from an oncologic perspective.

Recent studies have questioned the utility of percutaneous cement augmentation of osteoporotic vertebral fractures [7–9]. Currently, it is an accepted means to treat many symptomatic vertebral metastases [10]. However, further studies are needed to prove its utility in patients with spine metastases. Furthermore, the rate of polymethylmethacrylate (PMMA) leakage is between 10 and 40%, and it has been reported to be much higher when CT is routinely used following procedure [11–14]. While most cases of cement leakage are reported to be asymptomatic, there are reports of cement leakage that required urgent surgical decompression [15–18]. In addition, there are reports of symptomatic pulmonary emboli after cement augmentation [19–22]. Further, the use of PMMA is a relative contraindication when the posterior cortex of the vertebral body is breeched by tumor. There have been no trials comparing the use of PMMA augmentation with that of percutaneous fixation.

Close consultation with medical and radiation oncology is an important component care in these cases. Survival expectations must be discussed and the treatment rendered

tailored to each individual case. Local radiation is often an important adjuvant in the setting of spinal metastases, and this is particularly true when one is considering a minimally invasive approach. The goals of surgery are to stabilize and/or decompress the spine. Debulking of tumor is possible in a minimally invasive fashion, but if tumor debulking is a central part of the local control plan, then an open procedure may be more suitable. Local failure due to tumor regrowth is a concern in the setting of minimally invasive approaches, and one is relying more heavily on radiation/chemotherapy when approaching these cases in a minimally invasive fashion. Our study demonstrates the short-term successes associated with minimally invasive approaches to spine metastasis. However, longer followup is needed to assess whether local failure, whether from tumor regrowth or hardware failure, becomes a problem.

We report the successful short-term treatment of 24 patients with a minimally invasive approach for malignancies in the spine. Pain and ambulatory status were both improved after this minimally invasive approach. The role of minimal access surgery continues to evolve, and further studies are needed to elucidate the most appropriate patients for this approach.

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