REVIEW ARTICLE

Contemporary Treatment Strategy for Spinal Metastasis: The "LMNOP" System

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ABSTRACT: The choice of treatment for spinal metastasis is complex because (1) it depends on several inter-related clinical and radiologic factors, and (2) a wide range of management options has evolved in recent years. While radiation therapy and surgery remain the cornerstones of treatment, radiosurgery and percutaneous vertebral augmentation have also established a role. Classification systems have been developed to aid in the decision-making process, and each has different strengths and weaknesses. The comprehensive scoring systems developed to date provide an estimate of life expectancy, but do not provide much advice on the choice of treatment. We propose a new decision model that describes the key factors in formulating the management plan, while recognizing that the care of each patient remains highly individualized. The system also incorporates the latest changes in technology. The LMNOP system evaluates the number of spinal Levels involved and the Location of disease in the spine (L), Mechanical instability (M), Neurology (N), Oncology (O), Patient fitness, Prognosis and response to Prior therapy (P).

RÉSUMÉ: Stratégie contemporaine de traitement des métastases spinales : le système "LMNOP". Le choix du traitement des métastases spinales est complexe parce que 1) il dépend de plusieurs facteurs cliniques et radiologiques qui sont inter-reliés et 2) une grande variété d'options thérapeutiques ont été développées depuis quelques années. Bien que la radiothérapie et la chirurgie demeurent la base du traitement, la radiochirurgie et la vertébroplastie percutanée ont maintenant un rôle bien établi. Des systèmes de classification ont été développés pour aider le processus décisionnel et chaque traitement a des forces et des faiblesses différentes. Les systèmes de pointage développés jusqu'à maintenant fournissent un estimé de l'espérance de vie, mais peu de conseils sur le choix du traitement. Nous proposons un nouveau modèle de décision qui décrit les facteurs clé pour élaborer le plan de traitement, tout en reconnaissant que les soins prodigués à chaque patient demeurent très individualisés. Ce système tient également compte des changements technologiques les plus récents. Le système LMNOP évalue le nombre de niveaux spinaux atteints et le Lieu de la maladie dans la colonne vertébrale (L), l'instabilité Mécanique (M), la Neurologie (N), l'Oncologie (O), l'état du Patient, le Pronostic et la réponse aux traitements antérieurs (P).

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The vertebral column is the most common site of bone metastases.[1-3] An estimated 5-10% of patients with cancer will develop symptomatic spinal metastasis at some point in their disease,[4] and more than one-third of patients dying from neoplastic disease have spinal metasases.[5] From most common to least common, metastases are found in the thoracic, lumbar, cervical and sacral regions.[6] The most common primary pathologies are lung, breast, marrow (lymphoma and multiple myeloma), kidney and prostate.[7,8]

The treatment of spinal metastasis is palliative. The cornerstones of care are radiation therapy and surgery, but options have broadened in recent years with the development of radiosurgery[9] and percutaneous vertebral augmentation.[10] General indications for surgery, vertebral augmentation and radiosurgery are listed in Table 1.

Classification systems have been developed to assist in treatment decision-making.[11-15] Some of these schemes employ scoring systems that are complicated and are not easily remembered or put into practice.[14,16] The scores provide an estimation of life expectancy using the treatments that were available at the time the scoring system was described.

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Table 1: General indications for surgery, vertebral augmentation, and radiosurgery in spinal metastasis*

Surgery	Symptomatic spinal cord compression by tumor that is not highly radiosensitive (e.g., lymphoma, multiple myeloma)
	Mechanical instability
	Uncertain diagnosis (CT-guided trocar biopsy recommended)
Vertebral augmentation	Painful vertebral body fracture without significant epidural spinal cord compression
Radiosurgery	Failure of radiation therapy to control disease (previous radiation exposure of the spinal cord to maximum tolerance)

*Patients without any of the above are generally candidates for radiation therapy; CT=computed tomogram

Although life expectancy is one factor that influences the choice of treatment, it does not tell you which treatment is indicated. The treatment options are also somewhat poorly defined in these articles. For example, in the system described by Tomita et al[15] the prognostic score determines whether the patient should receive "supportive care", "palliative surgery", "marginal or intralesional excision" or "wide or marginal excision." Similarly, in the system described by Tokuhashi et al[14], the surgical strategies include "conservative treatment," "palliative surgery" and "excisional surgery" depending on the estimated prognosis. As we will see, prognosis is one of the key elements in determining treatment, but there are many others, and each can have a significant impact on the treatment choice.

Most of the classification systems predate the use of vertebroplasty and radiosurgery.[12,14-16] Few consider the patient response to previous therapy, which may help to predict the response to future treatments and the risk of complications (e.g. high rates of wound infection with surgery performed through previously irradiated fields). Overall, the treatment of spinal metastasis is complex, and decisions have to be made on a case-by-case basis.

We present a novel framework for decision-making in spinal metastases (Table 2). The mnemonic "LMNOP" refers to Location and spinal Levels of disease (L), Mechanical instability (M), Neurology (N), Oncology (O), Patient fitness, Prognosis and response to Prior therapy (P). Each element must be considered for the comprehensive formulation of a treatment plan (Figure 1).

Our LMNOP system developed as an improvement on the NOMS system described by Bilsky and Smith.[17] In NOMS, the decision points are Neurologic (N), Oncologic (O), Mechanical stability (M) and Systemic disease (S). The alphabetical LMNOP mnemonic is not just easier to remember than NOMS. It also includes two additional key considerations: (1) the location and spinal levels of disease, and (2) the response to previous therapy. The first is important in determining the role and type of surgery. The second is important for several reasons, including recognition of the emerging role of radiosurgery for patients who fail radiation therapy.

Please note that this review is not a substitute for other articles where the investigation and initial treatment of spinal metastatic disease (e.g. intravenous corticosteroids) is discussed.[18-20] Appropriate clinical, radiologic and histologic diagnosis (and how it is achieved) is beyond the scope of this paper; however, each is required before LMNOP can be utilized to help define the goals of treatment and determine the most appropriate therapeutic approach.

Location/Level

The vast majority of spinal metastases are entirely extradural and most (80%) involve the well-vascularized vertebral bodies rather than the posterior vertebral elements.[6] Epidural compression of the neural structures is therefore most often ventral. The local extent of tumor has a direct effect on the surgical options for decompression or stabilization. A method to classify the local extent of spinal tumor invasion has been devised by Tomita et al.[15]

Many patients with spinal metastases have multilevel involvement, although this is usually localized to adjacent vertebral segments. In up to 30% of patients, two or more noncontiguous levels of disease are identified.[21] Even in patients with multilevel disease, only one particular level is usually symptomatic.[22] That being said, multilevel disease negatively affects prognosis and may be a deciding factor regarding whether or not surgery is indicated.[14,16]

Table 2: Key determinants of the LMNOP system for spinal metastasis

L	Location	Extent of disease at symptomatic level(s): involvement of anterior and/or posterior columns
	Levels	Solitary or multilevel
M	Mechanical stability	Stable (SINS = 0-6)
		Potentially unstable (SINS = 7-12)
		Unstable (SINS = 13-18)
N	Neurology	Symptomatic epidural cord compression
O	Oncology	Highly radiosensitive
		Radiosensitive
		Radioresistant
P	Patient fitness	Medical fitness for surgery
	Prognosis	Mostly dependant on tumor type (O)
	Prior therapy	Previous radiation therapy at symptomatic levels
		Failed multiple systemic treatments

*SINS = Spine Instability Neoplastic Score (see text)

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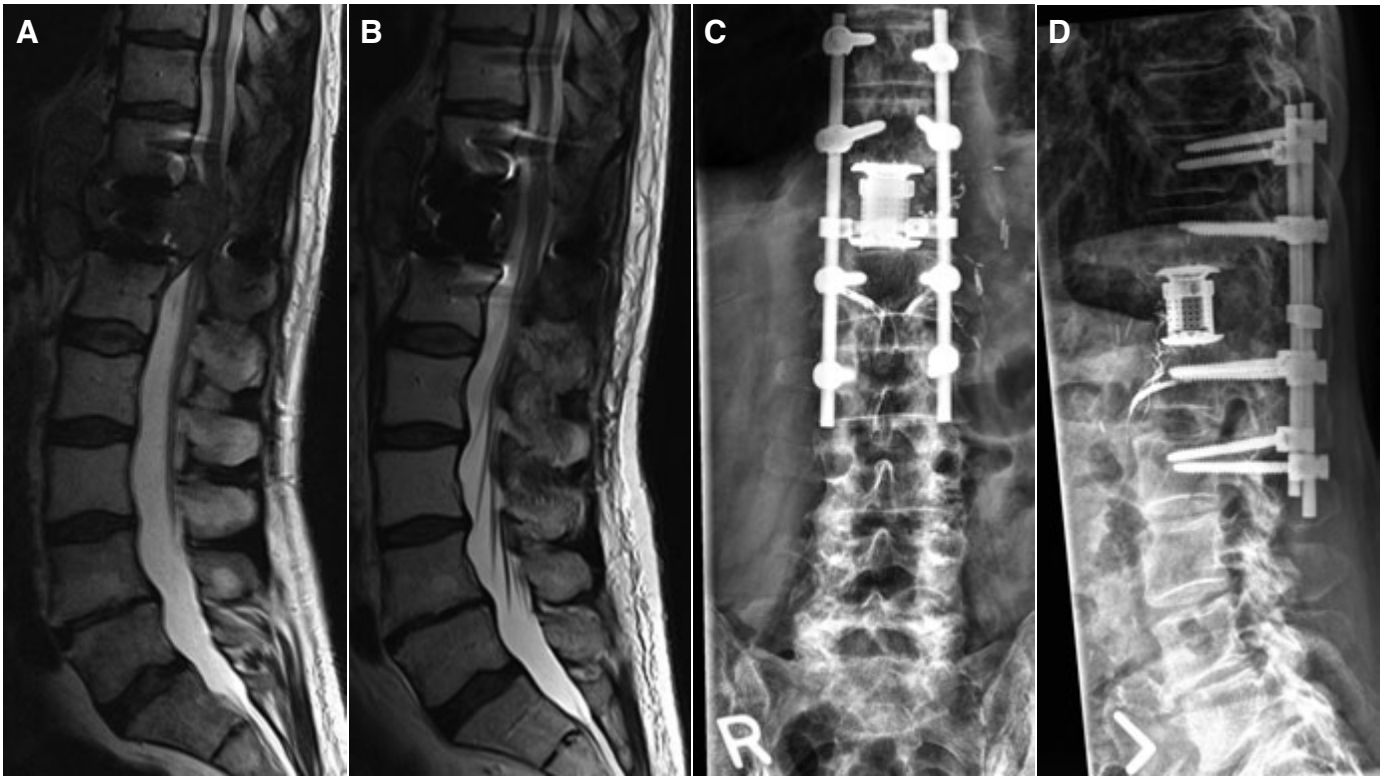

Figure 1: *This 64 year-old man underwent a T12 vertebrectomy via a left thoracotomy and T10-L2 pedicle screw fixation for renal cell metastasis. Despite postoperative radiation therapy he presented one year later with recurrent gait difficulties and pain due to local progression of disease. T2-weighted sagittal MRI shows recurrent tumor with spinal cord compression at T12 (A). Postoperative MRI shows circumferential decompression (B). Anteroposterior (D) and lateral (C) x-ray films show the final construct and the material used for preoperative embolization. The patient subsequently received stereotactic radiosurgery. LMNOP: L = Solitary, T12 anterior column; M = potentially unstable (SINS = 9); N = symptomatic spinal cord compression; O = radioresistant; P = medically fit, good prognosis, previous radiation therapy. This patient was appropriately treated with surgical resection because of symptomatic spinal cord compression due to epidural metastasis.*

When surgery is indicated, the choice of approach is significantly influenced not only by the extent of disease at each level, but the levels themselves, since each region of the spine has unique neuroanatomic features and adjacent visceral or vascular structures.

For lesions from C0 through C2, posterior stabilization alone is the preferred surgical approach, since pathology in this region generally presents with mechanical pain.[23] Spinal cord compression is rarely symptomatic in this region, and the morbidity associated with anterior approaches (i.e., transoral, transpharyngeal) may be excessive given the palliative goals of surgery.[24] Others have advocated non-operative interventions for C0-C2 lesions, as long as spinal alignment is maintained.[25]

From C3 through C6 the anterior approach is preferred in most cases undergoing surgical resection. A combined anterior/posterior is preferred for multilevel disease, circumferential tumor involvement, severe instability, and poor bone quality.[23] At C7-T1 anterior or posterior approaches may be employed. Supplemental posterior stabilization is often required at this junctional level.[23]

For lesions from T2 to T5, a systematic review by the Spine Oncology Study Group (SOSG) concluded a strong recommendation for posterolateral approaches.[26] Anterior approaches in this region are complicated by the great vessels and the heart. Lesions from T6 through L5 may be approached anteriorly, posteriorly or circumferentially: there is little evidence-based literature to conclude overall superiority of any single approach.[26] Fourney and Gokalsan[27] described an algorithm for determining the optimal surgical approach to these lesions. Ultimately the choice depends on the goals of surgery as well as the experience and preference of the surgeon.

Surgical treatment of sacral metastases is rarely indicated due to (1) the capacity of the sacral canal to accommodate large tumor volumes before the development of neurologic symptoms, (2) the degree of bony destruction required to cause instability, and (3) difficulty to effectively stabilize the lumbosacral junction when significant lytic disease has taken hold in this area. Most often, sacral metastases do not cause significant instability and can be effectively palliated with radiation therapy. When surgery is indicated, it is most often performed via posterior approaches.[28-30]

Mechanical Instability

Spinal instability due to tumor has been defined by the SOSG as the "loss of spinal integrity as a result of a neoplastic process that is associated with movement-related pain, symptomatic or

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progressive deformity and/or neural compromise under physiological loads."[31] Mechanical instability due to spinal metastasis is a common indication for surgery or percutaneous vertebral augmentation,[10] but it has not been studied as much as spinal cord compression. The lack of data may reflect the disagreement that exists regarding tumor-related instability as evidenced by a wide variety of criteria published in the literature and significant differences of opinion suggested by spine surgeons.[32-36]

Some authors have suggested movement-related pain as a surrogate for mechanical instability.[17] However, one must remember that pain is the most common symptom of metastatic spinal disease, occurring in 83-95% of symptomatic patients.[37-41] Mechanical pain may occur alone or in combination with two other commonly encountered pain patterns: local (or "biologic") pain and radiculopathy. The mechanisms of biologic pain are unclear, but may be related to local inflammatory mediators or periosteal stretching with tumor growth. It is unrelated to movement. Treatment of the disease, either with radiation therapy or corticosteroid administration, may provide relief.[20,42] Radicular pain is related to nerve root irritation and follows a characteristic dermatomal pattern. Radicular pain may respond to radiation therapy or chemotherapy in the setting of tumor types that are sensitive to these treatments; however, surgical decompression is often required for radioresistant tumors.[20]

Tumor-related instability may be graded using a combination of clinical and radiologic criteria called the Spine Instability Neoplastic Score (SINS).[31] The details of this scoring system is beyond the scope of this review. The major clinical criterion is movement-related pain. Radiologic criteria include bone quality (lytic, blastic or mixed), vertebral alignment, extent of vertebral body collapse, and extent of involvement of the posterolateral complex of the spine (pedicles, facet joints, and costovertebral joints). In a retrospective analysis, SINS demonstrated near-perfect inter- and intraobserver reliability in determining three clinically relevant categories of stability: stable (SINS score = 0 to 6), potentially unstable (SINS score = 7 to 12) and unstable (SINS score = 13 to 18). The sensitivity and specificity for detecting potentially unstable or unstable lesions was 95.7% and 79.5%, respectively.[43]

Assigning a numerical grade to instability is attractive because it recognizes that unlike in trauma, spinal stability due to tumor is not lost suddenly in an "all or none" fashion: rather it is gradual process that at a certain point will result in pathologic fracture. By being able to reliably define the severity of instability we come closer to understanding the indications for less invasive forms of stabilization such as vertebroplasty or kyphoplasty.[10] In the appropriate clinical setting, patients with potentially unstable lesions (SINS scores of 7 to 12) may be candidates for percutaneous vertebral augmentation, while those with higher scores may be better treated with spinal instrumentation (Figure 2).

Several authors have advocated vertebroplasty or kyphoplasty to treat so-called "impending collapse" but the indications are unclear.[44] Theoretically, vertebral body collapse may be prevented by non-surgical treatments if the metastatic tumor is radiosensitive and/or chemosensitive and its growth (and therefore lytic destruction of the vertebra) can be inhibited. Once the tumor reaches a critical size, which can be defined as "impending collapse", only surgical stabilization or vertebral augmentation can prevent fracture.[34] Proof that SINS can actually predict vertebral body collapse will have to await the results of prospective studies, but this scale will hopefully lead to a more consistent therapeutic approach among spine surgeons and aid scientific study of the problem.

Neurology

Approximately 5-14% of patients with metastatic spine tumors develop epidural spinal cord compression (MESCC).[4,41,45,46] Historically, the surgical treatment of MESCC was laminectomy, which often did not provide benefit,[47-52] and in many patients, further compromised spinal stability.[38,39] The development of instrumentation to treat instability resulted in the development of better surgical techniques for direct decompression.[38,53-55]

A randomized prospective trial of 101 patients conclusively confirmed these observations, showing that direct decompressive surgery plus postoperative radiotherapy is superior to radiotherapy alone for treatment of MESCC restricted to a single area with at least one neurological symptom.[56] Significantly more patients in the surgery group (42/50, 84%) than in the radiotherapy group (29/51, 57%) were able to walk after treatment (OR 6.2 [95% CI 2.0-19.8], p=0.001). Surgery patients also maintained the ability to walk longer (median 122 days versus 13 days, p=0.003). The study had to be stopped after an interim analysis showed clear superiority to surgical treatment.

Patchell et al[56] also showed that surgically treated patients had a substantial reduction in the use of corticosteriods and analgesics. Surgery did not result in prolonged hospitalization as the median length of hospital stay in both groups was ten days.

Ten patients in the radiation group had a substantial decline in motor strength and crossed over to the surgery group (20%). Of these crossover patients, four had surgical complications, three of which were wound infections. This confirmed previous studies that showed a very high rate of wound complications when operating on the spine through previously irradiated fields.[38,57-59] The key point to take away is that if surgery is indicated, it is best to perform it first, and then follow with radiation therapy (rather than the reverse).

Along with the knowledge that direct decompressive surgical resection can provide relief from the symptoms of MESCC, it should be noted that there is a correlation between neurological status at the time of diagnosis, especially motor function, and prognosis.[14,60] Patients in the surgically treated arm of the randomized trial had slightly longer survival (100 days versus 126 days; p=0.033), which is presumably a side effect of being able to walk.[56] On the other hand, the rate of ambulatory recovery in patients who are paraparetic at presentation is less than 5%[49] and as such, surgical decompression is generally not offered when deficits are severe, especially if they have been present for more than 24 to 48 hours.[37] Conversely, a patient without MESCC will not benefit from decompression, and unless there is significant mechanical pain and instability, these patients are usually treated nonoperatively.

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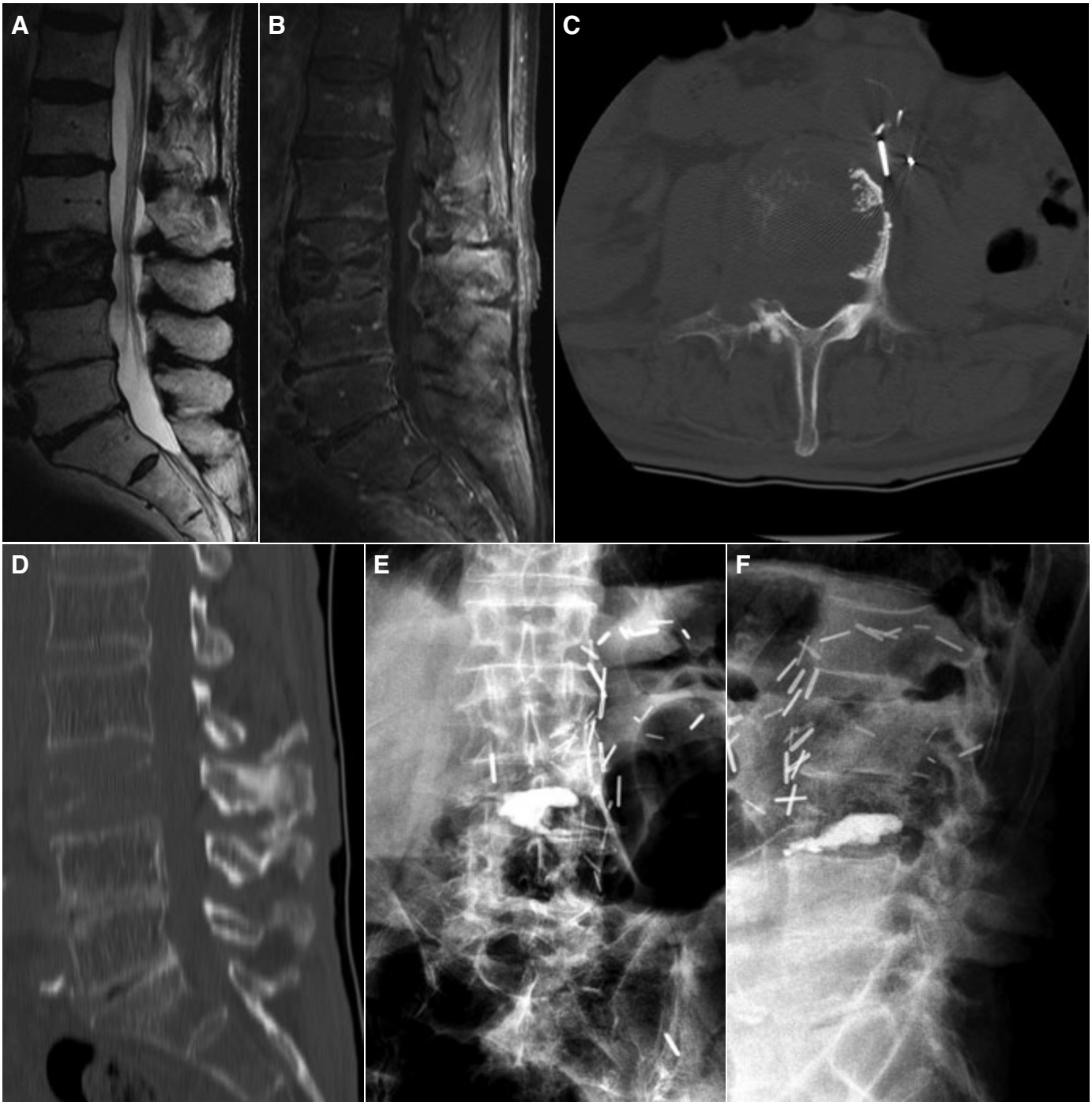

Figure 2: *This 87-year-old man who underwent nephrectomy for renal cell carcinoma ten years ago presented with mechanical back pain due to a pathologic fracture at L3. Radiation therapy and bracing failed to alleviate his pain. T2-weighted MRI (A) and T1-weighted post-contrast MRI (B) show collapse at L3 with no significant epidural disease. Renal cell carcinoma was confirmed on CT-guided biopsy. Axial (C) and sagittal (D) CT show lysis of the vertebral body including the posterior vertebral body wall. Although this is a relative contraindication to vertebral augmentation, his age and medical comorbidities made him a poor candidate for surgical stabilization. Anterposterior (E) and lateral (F) x-ray films show the final casting of kyphoplasty cement. LMNOP: L = Solitary, L3 anterior column, M = potentially unstable (SINS = 10); N = normal; O = radioresistant; P = poor fitness and prognosis (elderly), previous radiation therapy.*

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Oncology

The randomized study by Patchell at al[56] excluded patients with highly radiosensitive tumors such as lymphoma and multiple myeloma. These diseases generally respond well to urgent radiation therapy, regardless of the degree of spinal cord compression (Figure 3).[17]

Spinal metastases may be further divided into radiosensitive and radioresistant varieties. Most of the common solitary metastasis to the spine (e.g., breast, lung, prostate) respond well to radiation therapy.[61]

So-called radioresistant tumors have achieved this status as a result of their limited response to conventional radiation therapy, which is typically 30 Gy in ten fractions.[62] The recent advance of stereotactic radiosurgery to treat spinal lesions has allowed for the delivery of more biologically effective treatment while limiting the dose to the spinal cord. As such, aggressive surgical resection in an attempt to obtain best control of renal cell carcinoma may be an obsolete strategy.[63]

Tumor type is also an important determinant of survival prognosis. With regards to expected survival time, spinal metastasis may be considered in three oncologic groups: slow growth, moderate growth, and rapid growth. Slow growth tumors include breast, prostate, thyroid and carcinoid tumors. Moderate growth tumors include those arising from the kidney and uterus. Local control rates and survival time of patients for renal cell carcinoma appears to be improved with radiosurgery, although this has only been evaluated with comparison to historical controls.[64] Rapid growth tumors have a much poorer prognosis, and these include tumors of the lung, liver, stomach, esophagus, pancreas, and tumors of unknown origin.[14,15]

In addition to the type of tumor, the presence and extent of extraspinal disease affects survival time. The presence of visceral metastases in particular is associated with poorer survival.[14,15]

Patient fitness, Prognosis and Response to Prior Therapy

Nonsurgical treatments such as radiation therapy, radiosurgery, and percutaneous vertebral augmentation are most appropriate for patients with significant medical risks or limited prognosis. There is no consensus regarding the life expectancy required to justify surgical intervention. A period of at least three to six months has been proposed,[39] although it is often difficult to accurately determine life expectancy for the individual patient. Tumor histology is perhaps the single strongest predictor of survival.[14] However, the patient's general physical condition, neurological status, nutritional and hematological status (bone marrow suppression with leukopenia and thrombocytopenia is common among cancer patients who have received chemotherapy or radiation therapy) must also be considered.[59,65] Other host factors associated with poor surgical outcomes include low bone mineral density,[66] chronic corticosteroid use,[15] advanced age,[67] and serious medical comorbidity.[38]

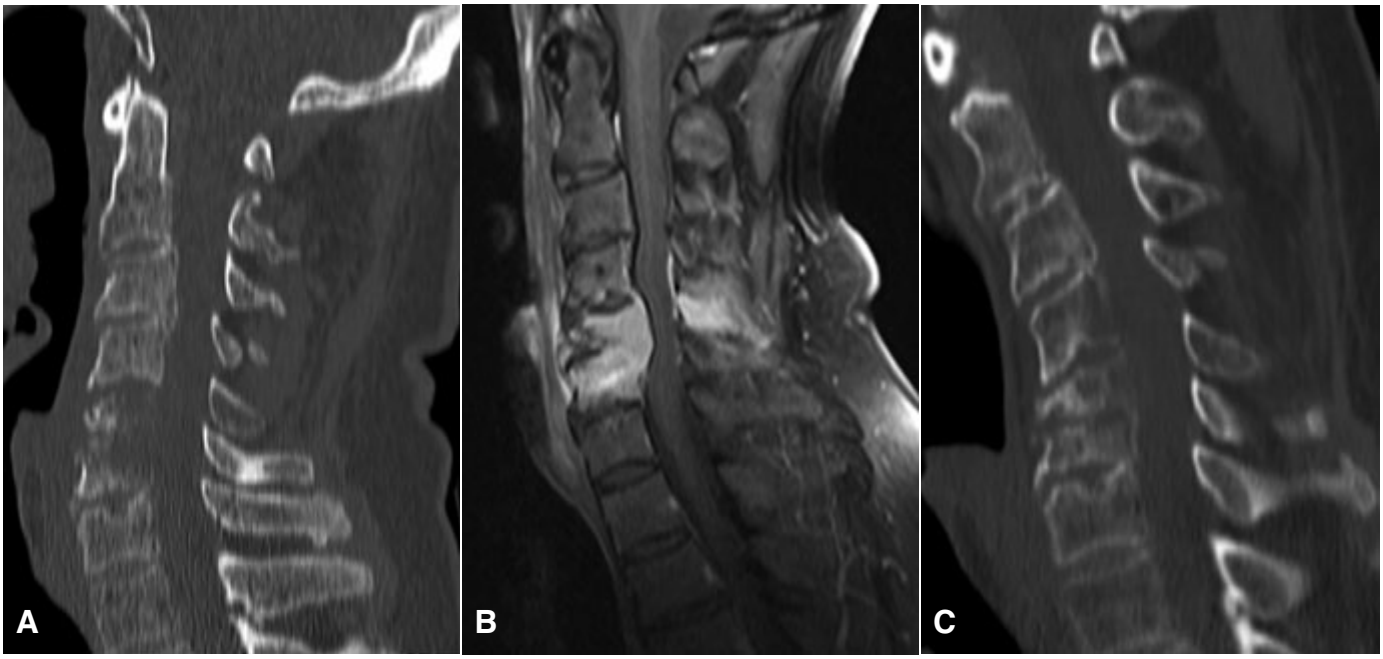

Figure 3: *This 68-year-old man presented with mechanical neck pain, poor balance and numbness in his hands. He had bilateral Babinski signs. Sagittal CT shows lytic pathologic fractures at C5 and C6 (A). Sagittal T1-weighted post-contrast MRI shows circumferential spinal cord compression (B). CT-guided biopsy showed diffuse B-cell lymphoma. He was treated with radiation therapy, 46 Gy in 23 fractions. His myelopathic symptoms and signs resolved. Although sagittal CT obtained one month after treatment shows mid-cervical kyphosis (C), he has no neck pain. LMNOP: Solitary, C5/6 circumferential; M = potentially unstable (SINS = 12); N = symptomatic spinal cord compression; O = highly radiosensitive; P = medically fit, poor prognosis (rapid growth tumor), naïve to treatment. This patient was appropriately treated non-surgically because his disease was highly radiosensitive.*

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The response of the primary tumor to previous treatment is another significant factor in determining treatment. For example, a patient with a metastatic spine tumor that is progressing despite fourth-line chemotherapy is unlikely to have as good a survival as a patient who is naïve to first-line treatments.

In the past, failure of radiation therapy to control progression of tumor was one of the primary indications for surgery. Currently, radiosurgery may be employed in this circumstance, as long as epidural compression of the spinal cord is minimal.[9] If there is significant epidural compression and surgery is considered, the surgeon should recall the high rate of infection and dehiscence when operating through previously irradiated tissue[38,50,53,57,59,63,65,67] and consider a direct anterior rather than a posterior approach if at all possible (Figure 1).[27]

Conclusion

The LMNOP is not a strict treatment algorithm but rather a useful mnemonic for the key factors that should be assessed to determine the optimal treatment for an individual patient with metastatic spine disease. It is not possible to produce a defined algorithm that shows every possible combination of variables because it would be far too complex. For example, should a patient with multilevel metastatic spine disease be considered for surgery? There is no consensus in the literature regarding multilevel disease.[10-17,21] In general, treatment is palliative, and therefore localized treatment (i.e., surgery) should only be done if the symptoms are attributable to localized disease, although the disease may be contiguous over a few levels. Any treatment should only be offered if it can be performed with acceptable morbidity given the extent of systemic disease and the prognosis. This is a good example of why such decisions can only be made on a case-by-case basis with excellent patient informed consent and cannot be reliably dictated by a flowchart or scoring system. Some examples of how LMNOP can be employed in specific cases is provided in Figures 1-3.

In general, patients with epidural spinal cord compression (N) or mechanical instability (M) are offered surgery depending on their fitness/prognosis (P) and the location/extent of disease (L). Mild-moderate instability (M) in the absence of spinal cord compression (N) may be treated with percutaneous vertebral augmentation; this strategy is particularly attractive for patients who are unfit for more extensive surgery (P), have an estimated survival less than three to six months (P) or have multiple levels of disease (L). Highly radiosensitive tumors (O) are treated with external beam radiation therapy regardless of the degree of spinal cord compression (N). Patients with radioresistant tumors (O) without significant cord compression (N) are offered stereotactic radiosurgery to control local tumor growth. Radiosurgery is also an option for tumor progression when external beam radiotherapy has failed (P).

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