Management of Metastatic Spine Disease

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INTRODUCTION

In the United States alone, nearly 1.66 million new cases of cancer will be diagnosed in 2013 [1], with over 500,000 deaths resulting from metastatic disease [2]. While advances in technologies, especially in the field of diagnostics, pharmaceuticals, radiotherapy, and surgery, have prolonged survival, cancer patients are experiencing more long-term complications [3].

Spinal metastases, one such complication, is present in 10-30% of cancer patients at initial presentation [4], and 30-90% at post-mortem analysis [5,6]. Those 40-65 years of age are most prone to develop spinal metastases. Most commonly, breast (21%), lung (14%), prostate (8%), gastrointestinal (5%), renal (5%) and thyroid (3%) primary tumors metastasize to the spine [7-9], with prognosis largely dependent on tumor histology. The thoracic spine is the most frequent location of spinal metastases (60%) followed by lumbosacral (30%) and cervical (10%) regions [10]. Moreover, it is estimated that nearly half of all patients with this condition require medical therapy, with 5-10% specifically requiring surgery [5,11]. Though treatment for spinal metastases is ultimately palliative, treatment strategies have become increasingly aggressive and have led to improved clinical outcomes [12,13]. Current management involves collaboration of numerous specialties including neurosurgery, surgical oncology, medical oncology, interventional radiology, pain specialists, and rehabilitation therapy [3,5].

MECHANISM OF METASTASIS

Common to all metastasis are the following steps: dissociation from the primary tumor mass, penetration of the local extracellular matrix (ECM), migration through vessels, adherence to/invasion of distant ECM, and neoangiogenesis at the seeded site [14,15]. Specifically, the migratory phase of the primary tumor to distant site occurs through 1. hematogenous, 2. direct extension, 3. cerebrospinal fluid, and 4. lymphatic pathways [14,15]. The first is the most common way in which tumor cells spread to the skeleton, and consists of arterial and venous routes. Segmental arteries deliver significant amounts of blood to vertebral bodies and therefore play a crucial role in the dissemination of malignant tumor cells. In addition, the Baston’splexus, a longitudinal network of extradural, valveless veins running parallel to the spinal column, is the primary venous means of spinal metastasis due to its connectivity with the spine, vena cava, portal, azygous, intercostal, pulmonary, and renal systems [3]. Metastasis via direct extension describes the local infiltration of primary tumor from paravertebral soft tissues to adjacent vertebrae. Furthermore, cerebrospinal fluid spread occurs following surgery for metastatic brain tumors, in which tumor cells inadvertently travel down the central canal of the spinal cord [3,16]. Finally, there is some evidence suggesting that the lymphatic system may also play a role in metastasis [17].

CLINICAL PRESENTATION

Pain

Pain is the most common symptom in patients with symptomatic with spinal metastases, with approximately 10% presenting it as the initial symptom and roughly 90% at some point in the course of the disease [5]. Because pain can manifest weeks to months before other symptoms, it should be investigated thoroughly. In particular, pain in the thoracic spine should raise suspicion, as degenerative changes of the spine, which are a common source of pain in the middle-aged and elderly populations, typically occur in the cervical and lumbosacral regions [18].
Pain can be subcategorized into local, mechanical, and radicular etiologies, though patients generally present with a combination. Local pain is thought to result from inflammation and intrinsic tumor mediators at or surrounding the metastatic site. Tumor growth may further contribute by physically stretching the nerve-dense periostuem and thus stimulating pain receptors [18]. Local pain is described as aching, and is frequently cited in many patients as worsening at night [5,19-21] as a result of increased direct pressure on the posterior elements when lying supine [19]. Percussion over the spinous process of the suspected region may aggravate it and therefore confirm local pain. Fortunately, NSAIDS and corticosteroids are effective palliative measures [5,22].

Mechanical pain, also known as axial pain, is the most frequent subtype, and manifests when the structural integrity of the load-bearing spine is compromised, especially in lytic pathologies. As a result, muscles, ligaments, tendons and joint capsules experience an unusually high strain [23]. This type of pain is aggravated with movement, and is typically relieved when lying down, especially when lying on one’s side (likely due to a decrease of axial load and direct pressure on the tumorous region). However, depending on the structural elements affected by metastasis, lying prone or supine may sometimes exacerbate pain [5]. Mechanical pain is usually unresponsive to pain medications but markedly improves with stabilization either with bracing or surgical intervention [5].

Radicular pain describes nerve root impingement arising either from tumor compression or pathological fractures that compromise the neural foramina. It is characterized by shooting, stabbing, burning sensations that can be resolved via decompression, radiation therapy, or antipsychotic medications [5,18].

**Neurological deficit**

Neurological impairment is the second most frequent symptom in metastatic spine disease, and occurs at a rate of 60-85% in those with metastatic epidural spinal cord compression (MESCC) [6,24,25]. This type of deficit arises from tumor expansion or pathological fractures, which may result in the compression of the spinal cord, nerve roots, or cauda equina. In particular, motor deficits present at a rate of 35-75% [6,24,25]. Patients typically complain of heaviness and demonstrate motor deficits upon physical examination. Autonomic abnormalities with respect to bowel, bladder, and sexual functions, may also exist, with bladder dysfunction being the most common [2,5]. Sensory impairments, which usually accompany motor deficits, may include anesthesia, hyperesthesia, and paresthesia, in expected dermatomal distributions [3]. Because prognosis correlates with neurological status at the time of diagnosis, it is crucial to determine the presence of spinal metastasis before deficits emerge [5,26].

**IMAGING MODALITIES**

Numerous imaging modalities exist in the assessment of metastatic spinal tumors, each varying with respect to sensitivity, cost, and information revealed. Plain radiographs are the typically the first imaging modality employed due to their inexpensive, widespread, and technically-underdemanding nature [5]. Unfortunately, x-rays are not very useful in detecting early phases of metastases, as they require approximately 50-75% destruction of cancellous bone before detection [27]. Nonetheless, radiographs can help identify pathological fractures, spinal deformities, large masses, and relatively obvious lytic or sclerotic lesions [5,18]. The stability of the spine can also be assessed using dynamic flexion-extension views, and frank instability may be visible on standing films as well [28].

Magnetic resonance imaging (MRI) is considered the gold standard modality in the field of spinal tumors due to its superior sensitivity, specificity, and accuracy relative to standard radiographs, computed tomography, and nuclear medicine scans [5,29,30]. MRI is uniquely able to provide high resolution depictions of soft tissues of the spine, including the spinal cord, nerve roots, meninges, intervertebral discs, paraspinal musculature, ligaments, and edematous fluid with distinct interfaces between bone and tissue. Consequently, important preoperative information such as extent of tumor infiltration, degree of spinal cord compression and nerve root entrapment, as well as the condition of the stabilizing structures can be obtained. Injectable galodinium contrast agent is useful in enhancing the clarity of vasculature and tumor infiltration [18]. T1-weighted and STIR images are effective in determining fractures while T2-weighted images are useful in assessing spinal cord compression [28].

CT is an imaging modality that specializes in detecting bony structures and distinguishing between lytic and blastic lesions. It is able to identify small regions of compromised bone and extent of tumor expansion. Furthermore, the degree of neural compression can be accurately assessed when CT is performed in conjunction with myelography. Modern multidetector CT has surpassed plain radiographs as the initial imaging modality of the osseous spine, as it provides rapid two-dimensional and three-dimensional reconstructions. It should be ordered as an alternative to MRI for patients with pre-existing instrumentation in order to avoid artifacts [17]. CT angiography, such as DynaCT, can very precisely depict blood flow, which is useful in high-risk patients with hypervascular tumors (e.g. renal cell, thyroid, angiosarcoma, leiomyosarcoma, hepatocellular, neuroendocrine) [5,31]. Overall, CT is a useful tool in the surgical planning process to determine spinal stability, characterization of spinal tumor vasculature, and placement of instrumentation [18]. Postoperatively, CT is useful in confirming placement of hardware and fusion [18]. Bone scans, formally known as nuclear scintigraphy, provide full-body images based on increased regions of metabolic activity (i.e. remodeling) in the skeleton [5]. They are suggested to be the first imaging study in asymptomatic patients suspected to have bone metastases [32,33]. Notably, bone scans can provide early detection 3-18 months before standard radiographs [34], with tumor sensitivity as small as 2mm. Unfortunately, they cannot offer high-resolution imaging. Additionally, due to the nonspecific nature of imaging, bone scans may misleadingly identify regions of inflammation, infection, or fracture, and should therefore be confirmed with other imaging modalities such as MRI or CT [5,17,18].

Single photon emission tomography, or SPECT, is a more sophisticated nuclear bone scan that provides three-dimensional, cross-sectioning imaging of targeted locations. This modality...
Aggressive procedures are reserved for patients of more favorable tumor, extent of metastases, and patient performance status [47]; making process by generally taking into consideration primary option for MESCC [45,46]. Since then, surgery has been the favored treatment alone [44].

Since the early 1900’s, with the primary purpose of achieving pain relief and the secondary goal of regaining neurological function. Surgical techniques at the time were limited to decompressive laminectomy without stabilization and tumor resection. Postoperative outcomes were extremely poor due to the indiscriminate nature of decompression, which only served to further destabilize spine in the common case (80% occurrence rate) of anteriorly located tumors [14]. In the 1950’s, conventional radiotherapy became an established method for controlling tumor growth and providing analgesic relief, with fewer complication. Consequently, surgery fell out of favor until 1980, when a randomized controlled trial demonstrated the laminectomy followed by radiotherapy compared to radiotherapy alone demonstrated equivalent outcomes with respect to pain relief, ambulation, and sphincter function. Beginning that decade, spinal instrumentations such as pedicle screws and hooks, rods and plates, cages, and constructs to augment the spinal column were developed. Circumferential screws and hooks, rods and plates, cages, and constructs to augment the spinal column were developed. Circumferential screws and hooks, rods and plates, cages, and constructs to augment the spinal column were developed.

PET/CT exhibits a statistically significant improvement in detecting lesions compared to PET, bone scans, or SPECT [32,41]. However, cost and radiation exposure are the primary drawbacks of PET and PET/CT. For these reasons, PET-CT should not be used unless radiographs, MRI, and bone scans fail to provide sufficient information [32].

**Surgery**

Historically, spinal metastases has been treated with surgery since the early 1900’s, with the primary purpose of achieving pain relief and the secondary goal of regaining neurological function. Surgical techniques at the time were limited to decompressive laminectomy without stabilization and tumor resection. Postoperative outcomes were extremely poor due to the indiscriminate nature of decompression, which only served to further destabilize spine in the common case (80% occurrence rate) of anteriorly located tumors [14]. In the 1950’s, conventional radiotherapy became an established method for controlling tumor growth and providing analgesic relief, with fewer complication. Consequently, surgery fell out of favor until 1980, when a randomized controlled trial demonstrated the laminectomy followed by radiotherapy compared to radiotherapy alone demonstrated equivalent outcomes with respect to pain relief, ambulation, and sphincter function. Beginning that decade, spinal instrumentations such as pedicle screws and hooks, rods and plates, cages, and constructs to augment the spinal column were developed. Circumferential screws and stabilization became a common procedure, and surgeons restricted the use of laminectomy to posterior lesions. In 2005, a randomized, multicenter, nonblinded trial by Patchell et al. demonstrated a statistically significant efficacy of surgery followed by radiotherapy compared to radiotherapy alone [44]. Since then, surgery has been the favored treatment option for MESCC [45,46].

**Prognostic scoring systems**

Numerous prognostic scoring systems have been established for the purpose of providing guidance in the surgical decision-making process by generally taking into consideration primary tumor, extent of metastases, and patient performance status [47]; aggressive procedures are reserved for patients of more favorable prognoses. The Tokuhashi (both original and revised), Tomita, Van der Linden, Bauer, and Sioutos scales are scoring systems (Table 1) that appear in literature, with the Tokuhashi and Tomita cited most frequently [13,24,47-52]. In the original Tokuhashi scoring system (1990), six parameters (the general condition of the patient assessed using the Karnofsky performance score, the number of vertebral metastases, the number of extraspinal bone metastases, the number of visceral metastases, the primary site of cancer, and neurological status) are each given a score between 0 and 2. Higher scores signify a better predicted survival [51]. The revised Tokuhashi system (2005) is updated to score the primary site of cancer a value between 0 and 5 [50]. The Tomita scale (2001), devised in response to improved surgical techniques, scores the tumor growth rate at the primary site, as well as the extent of visceral and bony metastases. Patients can receive a score between 2 and 10, with lower scores signifying better predicted survival [52].

Despite the frequent use of Tokuhashi and Tomita scales, there is no consensus of the superiority of these systems over others [47]. In fact, two of three literatures comparing all the aforementioned scoring scales found that the Bauer had the highest predictive value when examining heterogeneous patient samples [47,53,54].

One limitation of these prognostic scoring systems is the inability to account for the rapid development of chemotherapies, which may significantly extend survival for a given primary tumor type [57]. For example, the original Tokuhashi scale from 1990 assigns a score for renal cell carcinoma primary tumor type based on an expected survival of 4.4 months. However, current anti-VEGF agents have extended metastatic renal cell carcinoma patient survival to 19.5 months [57,58]. Therefore, it is crucial to periodically revise these scoring systems so that the best surgical option can be selected.

**The spinal instability neoplastic score (SINS)**

In 2010, the Spine Oncology Study Group established SINS in order to quantify preoperative tumor-related spinal instability [59]. This 18-point scale evaluates tumor location in the spine, mechanical pain, nature of the bone lesion (e.g. lytic, blastic, or mixed), radiographic spine alignment (i.e. subluxation of deformity), degree of vertebral collapse, and posterolateral involvement of spinal elements; 0-6 points indicates stability, 7-12 points indicates indefinite stability, while 13-18 points indicates instability and urgently requires surgical intervention (Table 1). Fourney et al. concluded that this scoring system had a near-perfect inter- and intraobserver reliability in determining the clinically relevant parameters of stability. Sensitivity and specificity were found to be 96 and 80 %, respectively, for the potentially unstable and unstable lesions [60]. Teixeira et al. found that the effectiveness of SINS was limited to experienced
Table 1: Summary of Commonly Used or Recent Prognostic Scoring Systems for Spinal Metastasis.

<table>
<thead>
<tr>
<th>Author &amp; Year</th>
<th>Scoring System Summary</th>
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| [51] Tokuhashi | 6 Prognostic Variables (each scored 0-2):
1. Karnofsky Performance Score (assigns score of 0, 1, 2 for KPS score of 10-40%, 50-70%, 80-100%, respectively)
2. Number of extra-pial bone metastasis foci (assigns score of 0, 1, 2 for ≥3, 1-2, or 0 foci, respectively)
3. Number of metastases in the vertebral body (assigns score of 0, 1, 2 for ≥3, 1-2, and 0 metastases, respectively)
4. Metastases to major internal organs (assigns score of 0, 1, 2 for unremovable, removable, and no metastases, respectively)
5. Primary site of cancer:
   1. lung/stomach: 0
   2. kidney/liver/uterus/other/unidentified: 1
   3. thyroid/prostate/breast/rectum: 2
6. Spinal cord palsy (assigns score of 0, 1, 2 for complete, incomplete, and none, respectively)
   • Total Score: 12
   • Interpretation (high score associated with better outcome):
     o Score 0-5: <3 months survival; palliative treatment
     o Score 6-8: ≤1 year survival; variable
     o Score 9-12: >1 year survival; excisional surgery
|
| [48] Bauer | 5 Prognostic Variables:
1. No visceral metastases: 1
2. No lung cancer: 1
3. Primary tumor (breast, multiple myeloma, kidney, lymphoma): 1
4. One solitary skeletal metastasis: 1
5. Absence of pathological fracture: 1
   • Total Score: 5
   • Interpretation (high score associated with better outcome):
     o Score 0-1: dead within 6 months post-op
     o Score 2-3: 25% survival 1-year post-op
     o Score 4-5: 50% survival 1-year post-op
|
| [49] Sioutos | 3 Prognostic Variables:
1. Preoperative neurological status ≤3/5 motor strength: 1
2. Multiple vertebral lesions: 1
3. Lung or colon cancer: 1
   • Total Score: 3
   • Interpretation (low score associated with better outcome):
     o Score 2-3: dead within 4.5 months, radical surgery contraindicated
|
| [52] Tomita | 3 Prognostic Variables:
1. Bone metastases (including spine) (assigns score of 1 and 2 for solitary/isolated and multiple metastases, respectively)
2. Visceral metastases (assigns score of 0, 2, 4 for no metastases, treatable, and untreatable, respectively)
3. Primary tumor:
   4. slow growth (thyroid/prostate/breast): 1
   5. moderate growth (kidney/uterus): 2
   6. rapid growth (lung/liver/stomach/colon/primary unknown): 4
   • Total Score: 10
   • Interpretation (low score associated with better outcome):
     o Score 2-3: long-term local control (50-month mean survival); wide/marginal excision
     o Score 4-5: middle-term local control (23.5-month mean survival); marginal/intralesional excision
     o Score 6-7: short-term palliation (15-month mean survival); palliative surgery
     o Score 8-10: terminal care (6 month mean survival); supportive care, no surgery
|
| [24] Van der Linden | 3 Prognostic Variables:
1. Karnofsky Performance Score (assigns score of 0, 1, 2 for KPS score of 20-40%, 50-70%, 80-100%, respectively)
2. Primary tumor:
   • Breast: 3
   • Prostate: 2
   • Lung: 1
   • Other: 0
3. Visceral metastasis:
   • Yes: 0
   • No: 1
   • Total Score: 6
   • Interpretation (high score associated with better outcome):
     o Score 0-3: 4.8-month mean survival
     o Score 4-5: 13.1-month mean survival
     o Score 6: 18.1-month mean survival
6 Prognostic Variables:
1. Karnofsky Performance Score (same as original)
2. Number of extraaxial metastases (same as original)
3. Number of metastases in the vertebral body (same as original)
4. Metastases to major internal organs (same as original)
5. Primary site of cancer (5 points max):
   - lung/osteosarcoma/stomach/bladder/esophagus/pancreas: 0
   - liver/gall bladder/unidentified: 1
   - others: 2
   - kidney/uterus: 3
   - rectum: 4
   - thyroid/breast/prostate/carcinoid tumor: 5
6. Spinal cord palsy (assign score of 0, 1, 2 for complete (Frankel A, B), incomplete (Frankel C, D), and none (Frankel E), respectively)
   - Total Score: 15
   - Interpretation (high score associated with better outcome):
     - Score 0-8: <6 months survival; conservative or palliative treatment
     - Score 9-11: ≥6 months survival; palliative treatment (typically) or excisional treatment (rarely- i.e. patient has single lesion AND no metastasis of major organ)
     - Score 12-15: ≥1 year survival; excisional surgery

4 Prognostic Variables (same as Bauer, but no pathological fracture category)
- Total Score: 4
- Interpretation (high score associated with better outcome):
  - Score 0-1: no surgery (supportive care)
  - Score 2: dorsal approach (short-term palliation)
  - Score 3-4: ventral-dorsal approach (middle-term local control)

6 Prognostic Variables:
1. Spine location (3 points max):
   - Junctional (occiput-C2, C7-T2, T11-L1, L5-S1): 3
   - Mobile spine (C3-C6, L2-L4): 2
   - Semi-rigid (T3-T10): 1
   - Rigid (L5-S5): 0
2. Mechanical or postural pain (3 points max):
   - Yes: 3
   - No (occasional pain but not mechanical): 1
   - Pain-free lesion: 0
3. Bone lesion quality (2 points max):
   - Lytic: 2
   - Lytic/blastic: 1
   - Blastic: 0
4. Vertebral body involvement (3 points max):
   - >50% collapse: 3
   - <50% collapse: 2
   - No collapse with >50% involvement: 1
   - None of the above: 0
5. Radiographic spinal alignment (4 points max):
   - Subluxation/translation present: 4
   - De novo deformity (kyphosis/scoliosis): 2
   - Normal alignment: 0
6. Posterior involvement (3 points max):
   - Bilateral: 3
   - Unilateral: 1
   - None: 0
   - Total Score: 18
   - Interpretation (low score associated with better outcome):
     - Score 0-6: stability
     - Score 7-12: indefinite instability, requires expert opinion
     - Score 13-18: unstable, requires expert opinion, urgent intervention needed

General indications
Open surgery is indicated for those who have a reasonable life expectancy (>3 months) and health status, but present with mechanical instability, medically intractable pain, tumors that do not respond to maximal doses of radiotherapy, unknown primary tumor, and/or progressive neurological deficits resulting from evaluators [61]. On the other hand, Campos et al. did not find a statistically significant difference between intraobserver intraclass correlation coefficient reliability between the orthopedic surgeons and oncologists, suggesting the reproducible nature of the test. However, prospective studies are needed to effectively evaluate SINS [62].
compliance or neural elements breast [13,28,63,64]. As such, surgical objectives include stabilization for pain relief, deformity correction, and decompression of the compressed structures [14]. A wide variety of procedures exist, ranging from basic posterior decompression to total en bloc resection with reconstruction.

As aforementioned, prognostic and stability scoring systems, such as Tokuhashi, Tomita, and SINS, may assist the surgeon in selecting the invasiveness of the operation. Ultimately, surgical procedures should be customized to the patient's needs, and the potential benefits should outweigh the risks.

**Surgical approaches**

The location of the tumor in the spine (i.e., cervical, thoracic, lumbar, sacral) and the spinal elements affected at the tumor level will dictate the approach employed. Anterior, posterior, lateral, and combination approaches can be used. Because compression is typically anterior in nature, ventral decompression yields the most successful results [3,14]. In the cervical spine, anterior or posterior approaches are utilized, though anterior cervical corpectomy offers the most direct approach [65]. Posterior approaches may be used in cases of significant instability, substantial kyphotic deformity, as well as in pathology involving the cervicothoracic junction or all three columns [65,66]. When tumor involves the craniocervical junction, transoral and transmandibular routes may be used, although these are associated with significant morbidity and are rarely used in a metastatic context. The more recently developed transnasal and transcervical approaches may also be employed, providing improved access [18]. A systematic review by Fehlings et al. revealed that posterior approaches are typically more recommended for the occiput-C2 region, while anterior approaches are better suited for C3-C6 [67]. At the cervicothoracic junction (C7-T1), the anterior or posterior approach may be used. In cases of multilevel involvement, circumferential disease, and poor bone quality, combined approaches are recommended [28,67].

In the thoracic spine, the upper elements (T1-T4) are relatively difficult to access, and anterior decompression may require an anterolateral cervical approach with sternotomy and/or thoracotomy [5]. However, there is stronger evidence that recommends the posterolateral approach as a less invasive, less technically demanding option relative to combined or anterior procedures [5,14,28,68]. The T5-T10 region is best approached via right-side thoracotomy to avoid the aortic arch and great vessels, though tumor location ultimately determines the side used [69]. Further, the thoracolumbar junction (T11-L1) is usually exposed with a combined thoracotomy and retroperitoneal approach [69]. L2-L4 levels can be accessed using via a retroperitoneal or transperitoneal and transabdominal approach [5]. Metastatic involvement limited to L5 is commonly managed using posterior decompression with stabilization, while sacral involvement may be handled using a posterior exposure, or a transperitoneal exposure to facilitate a combined approach [5].

**Expected outcomes**

While surgical outcomes vary on an individual basis, large scale systemic reviews have been conducted to generalize the statistics of the surgical benefits and risks. In 2006, Witham et al. reviewed publications for MESSC surgical outcomes spanning 1964-2005 (Table 2). With respect to laminectomy with or without conventional radiotherapy, a total of 2355 patients were reviewed; 42% of patients experienced neurological improvement, 13% experienced neurological decline, and the mortality rate was 6%. With respect to laminectomy and radiotherapy with posterior stabilization, a total of 1010 patients were reviewed; 64% of patients demonstrated motor improvement, 88% experienced pain relief, and the mortality rate was 5%. With respect to anterior decompression and stabilization, 775 patients were reviewed; 75% of patients demonstrated motor improvement, 84% experienced pain relief, and the mortality rate was 10% [45].

In 2013, Kalooostian et al. provided a similar analysis of surgical outcomes, though studies published in 2006 or later were also included. With respect to laminectomy with or without conventional radiotherapy, a total of 2098 patients were reviewed; 46% of patients experienced neurological improvement, 14% experienced neurological decline, and the mortality rate was 4%. With respect to laminectomy and radiotherapy with posterior stabilization, a total of 1164 patients were reviewed; 62% demonstrated motor improvement, 84% experienced pain relief, and the mortality rate was 7%. With respect to anterior decompression and stabilization, 832 patients were reviewed; 68% of patients demonstrated motor improvement, 86% experienced pain relief, and the mortality rate was 6% [13] (Table 2). The trend in improved surgical outcomes over the years was associated increasingly aggressive surgical strategies [45].

**Minimally invasive surgery (MIS)**

MIS is a field that has developed significantly over the past decade, and currently encompasses a variety of techniques such as video-assisted thoracoscopic surgery (VATS) [70], mini-open decompression [71], minimal access spine surgery (MASS) [72], and percutaneous pedicle screw fixation [73]. The overall objective is to provide the postoperative benefits associated with open surgery, but with a lower morbidity rate. This is accomplished by reducing soft tissue (i.e. paraspinal muscles, ligaments, fascia, skin, etc.) trauma using smaller incisions and muscle-splitting retractor technology. The advantages of reduced trauma include decreased blood loss, shorter hospitalization stay, and earlier mobilization. The potential for MIS to yield superior wound healing rates is particularly significant in the context of metastatic spine disease because it results in a shorter period between surgery and adjuvant therapies [74-76]. Because MIS causes less tissue damage, it is suitable for a broader range of patients with metastatic spine disease, especially those with high systemic tumor burden, aggressive tumor pathology, shorter expected survival (less than 6-12 months), and old age, who would otherwise be excluded from traditional surgery [74,77-79]. Furthermore, there is some studies report that with an experienced surgical team, the operating time of MIS can compare favorably to that of open surgery [79,80]. Low-class evidence also suggests that when compared to traditional open techniques, new MIS techniques significantly lower acute and subacute costs due to potentially decreased complication rates, length of stay, and blood loss, as well as fewer discharges to rehab.
### Table 2: Summary of Expected Outcomes for Various Spinal Metastasis Therapies.

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Author &amp; Year</th>
<th>Study Description</th>
<th>Outcomes</th>
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<tbody>
<tr>
<td><strong>External Beam Radiation Therapy (EBRT)</strong></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>[97]</td>
<td>Systematic review and meta-analysis of 11 randomized trials involving 3487 bony metastatic sites</td>
<td>Single-fraction therapy:  • 60% pain relief rate  • 34% complete pain relief rate  • 21.5% retreatment rate*  • 3% pathological fracture rate* Multi-fraction therapy:  • 59% pain relief rate  • 32% complete pain relief rate  • 7.4% retreatment rate*  • 1.6% pathological fracture rate* *indicates statistically significant difference between two modalities</td>
</tr>
<tr>
<td></td>
<td>[45]</td>
<td>Systematic review and meta-analysis of 1396 MESCC patients</td>
<td>• Overall rate of motor improvement: 36%  • Overall rate of motor decline: 17%</td>
</tr>
<tr>
<td></td>
<td>[98]</td>
<td>Systematic review and meta-analysis of 25 randomized trials involving 2818 single-fraction and 2799 multi-fraction patients with bone metastases</td>
<td>Single-fraction therapy:  • 60% pain relief rate  • 23% complete pain relief rate Multi-fraction therapy:  • 61% pain relief rate  • 24% complete pain relief rate* Significantly higher retreatment rate for single-fraction therapy</td>
</tr>
<tr>
<td></td>
<td>[13]</td>
<td>Systematic review and meta-analysis of 2251 MESCC patients</td>
<td>• Overall rate of motor improvement: 40%  • Overall rate of motor decline: 13%</td>
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<tr>
<td><strong>Stereotactic Radiosurgery (SRS)</strong></td>
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<td></td>
<td>[106]</td>
<td>Series of 336 patients (500 metastases) treated with single-fraction (12.5-25Gy)</td>
<td>• Pain relief rate: 86%  • Local control rate: 90-95%  • Neurological improvement rate: 84%  • No major complications</td>
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<tr>
<td></td>
<td>[13]</td>
<td>Systematic review and meta-analysis of 1028 patients</td>
<td>• Overall local tumor control rate: 92%  • Overall pain relief rate: 83%  • Overall rate of pain increase: 4%</td>
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<td><strong>Surgery</strong></td>
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<td></td>
<td>[45]</td>
<td>Systematic review and meta-analysis of 2355 MESCC patients</td>
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</tr>
<tr>
<td></td>
<td>[13]</td>
<td>Systematic review and meta-analysis of 2098 MESCC patients</td>
<td>• Overall rate of motor improvement: 46%  • Overall rate of motor decline: 14%  • Overall rate of motor decline: 4%</td>
</tr>
<tr>
<td></td>
<td>[45]</td>
<td>Systematic review and meta-analysis of 1010 MESCC patients</td>
<td>• Overall rate of motor improvement: 64%  • Overall rate of pain relief: 88%  • Overall mortality rate: 5%</td>
</tr>
<tr>
<td></td>
<td>[13]</td>
<td>Systematic review and meta-analysis of 1164 MESCC patients</td>
<td>• Overall rate of motor improvement: 62%  • Overall rate of pain relief: 84%  • Overall mortality rate: 7%</td>
</tr>
<tr>
<td></td>
<td>[45]</td>
<td>Systematic review and meta-analysis of 775 MESCC patients</td>
<td>• Overall rate of motor improvement: 75%  • Overall rate of pain relief: 84%  • Overall mortality rate: 10%</td>
</tr>
<tr>
<td></td>
<td>[13]</td>
<td>Systematic review and meta-analysis of 832 MESCC patients</td>
<td>• Overall rate of motor improvement: 68%  • Overall rate of pain relief: 86%  • Overall mortality rate: 6%</td>
</tr>
<tr>
<td><strong>Minimally Invasive Surgery (MIS)</strong></td>
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<td>[83]</td>
<td>1 patient treated with MI corpectomy</td>
<td>Pain and neurological improvement</td>
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<td>[79]</td>
<td>8 patient treated with MI transpedicular vertebrectomy</td>
<td>5/8 patients experienced improvements in pain and neurological deficit</td>
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<td>[77]</td>
<td>1 patient treated with MIS circumferential decompression</td>
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Studies of MIS using minimally invasive retractors and/or the mini-open technique published in 2000 or later revealed an overall recurrence rate of 8%, complication rate of 22%, 88% rate of neurological improvement, and 94.7% rate of pain improvement [71,77-80,82-87] (Table 2).

In the current absence of high-class evidence that definitively demonstrates advantages of MIS over open surgery; the latter option remains the prevalent method of operating [88]. One concern with MIS is the rate of local recurrence, which may necessitate reoperation [71]. In addition, MIS techniques are generally associated with a steeper learning curve and may not be suitable for multi-level lesions and kyphotic deformities [79]. Moreover, for thoracoscopic or laparoscopic MIS procedures, equipment can be costly [71].

**Embolization**

Embolization is an important procedure in the context of metastatic spinal tumors because it significantly reduces intraoperative blood loss, especially for hypervascular tumors (e.g. renal cell, thyroid, choriocarcinoma) [5,89]. Thus, it potentially reduces overall operating time, and decreases the chance of postoperative hematomas, which can lead to further complications such as neurological deficits, wound breakdown, and the need for reoperation [5,90]. The window between embolization and surgery should not exceed 48 hours.
Emboli 2014. Embolization can be performed using particles, coils, or ONYX. [6,91,92]. Further, the degree of embolization (partial vs. complete) does not significantly affect intraoperative blood loss [93]. When patients experience emergent neurological decline, embolization may be skipped in order to quickly initiate surgery [13].

**RADIOTHERAPY**

**External beam radiation therapy (EBRT)**

EBRT has long been the staple treatment for metastatic disease [94], offering both non-mechanical pain relief and neurological improvement. Reduction of tumor size and inflammation, as well as the reosification of lytic lesions, are thought to be the underlying mechanisms for pain relief [95]. In cases of lytic metastases, EBRT should follow surgery in order to decrease the need for reoperation [95,96]. An analysis of 3487 randomized painful metastatic sites revealed a 60% rate of analgesic success for single fraction radiotherapy and a 59% rate for multifraction therapy [97] (Table 2). A more recent systematic review and meta-analysis 25 randomized controlled trials reported 60% and 61% rates of pain relief for single and multi-fraction radiotherapy, respectively, as well as 23% and 24% rates of complete pain relief for single and multi-fraction radiotherapy, respectively [98]. Other smaller scale studies estimate pain palliation in a range from 57-77% [17,99,100].

Neurological deficits should ideally be treated with decompressive surgery followed by EBRT [44]. In one literature review of 1396 MESCC patients treated with radiation therapy alone, overall rate of motor improvement was 36% and overall rate of motor decline was 17% [45]. In another review of 2,251 MESCC patients treated with radiation therapy alone, overall rate of motor improvement was 40% and overall rate of motor decline was 13% [13] (Table 2).

Common dosing schedules include a 8 Gy in a single-fraction, 20 Gy in 5 fractions, 30 Gy in 10 fractions, 37.5 Gy in 15 fractions, and 40 Gy in 20 fractions. The most frequently used is 30 Gy in 10 fractions over 2 weeks. Postoperatively, EBRT is employed 2-4 weeks after surgery and applied to a field that includes both tumor and the entire instrument, with a typical margin of 1-5 cm, or 2 levels above and below the metastatic site [95]. Unfortunately, EBRT is limited by its imprecise nature. Thus, high single-dose exposure is not recommended, as it can cause significant harm to neighboring neural structures [5]. Moreover, single fraction radiotherapy is associated with higher retreatment and pathological fracture rates, as well as inferior long-term pain control [97,101,102]. EBRT alone is indicated in cases of diffuse spread of metastases, an expected survival of <3 months, radiosensitive tumor, total neurological deficit duration that exceeds 24-48 hours, and/or an inability to undergo surgery [17].

**Stereotactic radiotherapy**

Stereotactic body radiotherapy (SBRT) and stereotactic radiosurgery (SRS) are interchangeable terms in the context of spinal metastases that refer to high dose, image-guided administration of radiation, typically between 1-5 fractions [6,17,95]. Fractionated therapy is more appropriate for large tumor volumes or situations in which a single-fraction treatment risks delivering unacceptable levels of radiation to the spinal cord [95]. Currently, SBRT is used in cases of small-volume metastasis, limited metastatic tumor burden (1-3 metastases), no more than 2 contiguous diseased levels, good performance status, and expected survival of >3 months [95,103]. This treatment is administered in an outpatient facility and is able to conformally deliver 2-7 times the standard palliative daily dose of 3 Gy due to its steep dose gradient between cancerous and healthy tissue. Image-guided localization can conservatively provide accuracy within a 2-3mm window [17,104], though deviations of 1-2 mm can result in substantial damage to the spinal cord [95]. Stereotactic technologies such as Cyberknife technology can yield accuracy within a sub-millimeter range and a precision window of 0.11mm [95,105].

Patients undergoing SRS experience marked pain relief (85% relief rate), especially in comparison to conventional radiotherapy [17,99]. Additionally, studies suggest a control rate and radiographic response in the approximate range of 80-90% [6,17,106]. Gerszten et al., in a study consisting of 336 patients, demonstrated a local control rate of 88-90%, a pain relief rate of 86%, and a neurological improvement rate of 84% in patients with prior deficits [106]. In a recent large-scale meta-analysis of 1,028 patients who underwent SRS specifically for metastatic spine disease, overall local tumor control rate was 92%, overall percent pain improvement rate was 83%, and overall rate of pain increase was 4% [13] (Table 2).

In contrast to EBRT, stereotactic radiotherapy is effective against tumors that are classically determined to be radioresistant, does not irradiate excess bone marrow, does not interfere with chemotherapies, and can be administered in one day at an outpatient center. Additionally, it has been shown to be an effective salvage treatment for previously irradiated regions [95]. Evidence also suggests that it may provide patients with more immediate and durable pain control. Its ability to deliver greater magnitude of engenders a superior rate of local tumor control [17,107]. Though an optimal dosing regimen has yet to be established, data suggest that a single fraction dose 24Gy yields higher rates of tumor control [108,109], while single fraction treatment <15 Gy to some region of the target volume results in treatment failure [110,111]. With respect to cost-effectiveness, stereotactic radiotherapy is cheaper than surgery [112], but significantly more expensive than EBRT [113].

**Separation surgery**

“Separation surgery” is a recently developed technique to treat high-grade MESCC involving radioresistant tumor, with the goals of providing superior tumor control relative to EBRT and reducing the risk of surgical morbidity. Unlike traditional surgery, this operation avoids aggressive tumor resection so that patients rarely require anterior reconstruction [110].

Briefly, separation surgery begins with a posterolateral laminectomy, in addition to a unilateral or bilateral facetectomy. Upon exposure, the thecal sac is decompressed as epidural tumor is circumferentially resected beginning at the normal dural planes. The posterior longitudinal ligament is resected to form a margin with respect to the anterior dura and facilitate
spinal cord decompression. Uniquely, tumor is dissected away from the spinal cord in order to create a 2-3 cm gap. This allows administration of high-dose postoperative SRS without risking damage to delicate neural structures. Vertebral body resection occurs to a limited degree. Afterwards, posterior segmental instrumentation is placed accordingly [114, 115].

Within 2-4 weeks of the operation, a single fraction or hypofractionated dose is delivered [114]. Because this procedure is a significant paradigm shift, some authors now suggest that the goal of modern surgery is to provide a separation of the tumor from the spinal cord in order to optimize the radiation dose that can be safely delivered to the lesion, as opposed to achieving maximal resection [110].

Moulding et al. reviewed 21 patients undergoing separation surgery and SRS (18-24 Gy). Overall 1-year local progression risk was 9.5%. Patients receiving high-dose single fraction SRS (24 Gy) had a low progression risk of 6.3%, while patients receiving low-dose single fraction SRS (18-21 Gy) had an elevated progression risk of 20% [108]. More recently, Laufer et al. retrospectively analyzed the results of 186 patients treated with this paradigm. Notably, local tumor control was dependent on postoperative radiation dose; the 1-year local progression rates of high-dose hypofractionated therapy (median total dose 27 Gy; 3 fractions of 8-10 Gy), low-dose hypofractionated therapy (median total dose 30 Gy; 5-6 fractions, total dose range 18-36 Gy), and single fraction therapy (24 Gy) were 4.1%, 9.0%, and 22.6%, respectively [114]. Both studies demonstrated that separation surgery provides durable local tumor control regardless of tumor radiosensitivity (Table 2).

### PERCUTANEOUS VERTEBROPLASTY & KYPHOPLASTY

Vertebroplasty and kyphoplasty are minimally invasive procedures that can offer significant pain relief for patients with pathological vertebral fractures. Vertebral augmentation is indicated in the presence of intractable pain caused by vertebral body collapse while absolute contraindications include tumor mass involving the spinal canal (i.e. causing neurological deficit), asymptomatic vertebral fracture, unmanageable bleeding disorder, allergy to bone cement, and localized or generalized infection [18, 116-119].

Percutaneous vertebroplasty involves fluoroscopically-guided needle insertion into the vertebral body using a transcapedicular, parapedicular or costopedicular approach. Polymethylmethacrylate (PMMA) bone cement is then used to solidify the fractured level, strengthening the site of the lesion and thus improving the stability. Patients are then subjected to bed rest for 2 hours before mobilization. Typically, a CT scan is conducted before discharge to assess cement distribution in the vertebral body and extravasation [120].

Kyphoplasty involves a similar procedure, although a cavity is first created using a balloon-like device prior to cement injection. This procedure offers the potential advantage of restoring vertebral height. A systematic review by Hulme et al. suggests that the analgesic outcomes of these procedures are similar and that kyphoplasty results in a reduced rate of cement leakage (this is not very significant, however, because both procedures exhibit low rates of leakage) [121]. Notably, the overall cost of kyphoplasty is 5-10 times that of vertebroplasty because of equipment and anesthesia expenses [119].

SKyphoplasty is a newer variant of kyphoplasty that differs with respect to the method used to create the cavity. In this technique, a stiff plastic tube is passed through a cannula and then expanded [120]. The purported benefits of this technique over its predecessor include no chance of balloon rupture as well as better directional control during the expansion of the device [122]. Unfortunately, there is not enough evidence to support it in the context of metastatic spine disease, though it is cheaper than kyphoplasty [123].

### Analgesic mechanism

The analgesic effects of these vertebral augmentation procedures were once thought to be a result of cytotoxic antitumor effects, thermoablation of nociceptive nerve endings, and ischemia; however, recent evidence suggests that pain relief is achieved primarily via mechanical stabilization [124, 125].

### Expected outcomes

In a meta-analysis of 864 patients who underwent vertebroplasty, overall rate of pain improvement was 91%, overall rate of pain increase was 1%, and overall rate of improved mobility was 62%. In the same study, 277 kyphoplasty patients were reviewed; overall rate of mobility improvement was 69, overall rate of pain improvement was 93%, and no patients experienced increased pain (Table 2). Uniquely, this literature review included those with metastatic disease and a small fraction of patients with multiple myeloma [13].

### SYSTEMIC THERAPIES

#### Chemotherapies

Chemotherapy is an integral part of long-term control of spinal metastases, and greatly depends on the tumor histology (i.e. chemosensitivity and receptor status) [6]. This form of therapy can either serve to directly act on the tumor or minimize the secondary effects of the tumor [126]. Drugs which target hormone receptors are especially relevant to breast and prostate cancers. In breast cancer, agents which bind to estrogen receptors include tamoxifen, as well as aromatase inhibitors, such as anastrozole, exemestane, and letrozole [12, 127]. In prostate cancer, gonadotropin-releasing hormone agonists and antiandrogens are typically administered [128]; a recent study recommended the use of intermittent androgen deprivation over continuous androgen deprivation [129]. For cancers that are not associated with hormonal receptors, cytotoxic agents are used [6].

#### Bisphosphonates

Bisphosphonates are a class of drugs that inhibit osteoclast activity, thereby reducing tumor-induced osteolysis and bone resorption. They reduce the risk of pathological fracture, as well as the incidence of local lytic pain and hypercalcemia [130, 131]. There is inconclusive data regarding the antitumor effects of bisphosphonates [132]. Recently, a phase III trial comparing the novel agent, denosumab, to zoledronic acid was conducted, with
the former drug exhibiting superior results with respect to the number of skeletal events patients experienced [133].

Corticosteroids

Corticosteroids are an established therapy in addressing pain secondary to metastatic tumor growth by reducing inflammation. As a short-term measure, they may also improve neurological deficits by decreasing the extent of spinal cord compression [5]. In cases of lymphoma, myeloma, and breast cancer, corticosteroids have demonstrated antitumor effects [46,134].

FUTURE DIRECTIONS

Currently, the treatment of metastatic spine disease remains palliative, and involves a combination of radiotherapy, chemotherapy, and surgery. Image-guided radiotherapies are able to deliver high, conformal doses to the desired target while sparing adjacent tissues. Improved surgical techniques and instrumentation are able to reduce morbidity and mortality, while latest generation chemotherapies exhibit greater receptor specificity and potency. In a general sense, progress in all three fields will continue. Surgery will likely become increasingly minimally invasive in order to avoid perioperative complications. In addition, instrumentation and bone cements will likely become increasingly biomimetic and may be formulated with anti-tumor agents.

As higher class studies are conducted, the roles of various treatment options (e.g. separation surgery vs. minimally invasive surgery vs. open surgery) will be better understood. Relatively new treatment paradigms such as kyphoplasty followed by SRS [135] or transpedicular coblation corpectomy followed by kyphoplasty and SRS [136] have yet to be compared to more established palliative techniques. Further, a number of ablative technologies, including plasma-mediated radiofrequency and cryotherapy have emerged, providing effective tumor debulking and significant pain improvement [137-140]. The available treatments and combination therapies will continue to expand. Only by determining the niche of each therapy can physicians provide the optimal regimen for patients with metastatic spine disease.

REFERENCES


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