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Radiotherapy and Surgical Treatment of Metastatic Breast Cancer of the Spine

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Abstract

Metastatic vertebral column tumors are found in up to 20% of cancer patients, and of these, a percentage will go on to develop compression of eloquent neurological structures. Neurosurgeons often encounter these patients in an emergent situation, and decisions regarding care must be made in an expedient manner. However, many treatment paradigms depend on the histology of the causative lesion. One of the most common malignancies that metastasize to the spine in today's practice is breast cancer. Current standards of treatment revolve around utilization of radiation therapy through conventional external beam radiation therapy (cEBRT) for treatment of the pathological lesions with surgery reserved for select cases. Stereotactic radiosurgery (SRS)/ stereotactic body radiotherapy (SBRT) for spinal metastases is another exciting treatment avenue for patients with new data delineating its use on the horizon. In this review, we focus on the evolving treatment paradigms and future areas of investigation needed for spinal metastatic lesions with an emphasis on evidence for breast cancer lesions.

Keywords: Metastatic; Breast cancer; Spine; Stereotactic; Radiation

Metastatic Vertebral Column Tumors

Current estimates suggest spinal metastasis occurs in 20% of all cancer patients [1,2], with 5-20% of patients developing spinal cord compression [3-5]. However, as systemic therapies continue to improve and patient longevity increases, the incidence of spinal column metastasis will continually rise, with some suggesting the incidence as high as 40% of all cancer patients at some point during their disease course [2,6]. The most commonly encountered histologies in vertebral column metastases are breast, prostate, and lung cancer [7], with spinal lesions often found following diagnosis of a primary cancer. However, in 10% of patients with spinal metastases, it accounts for the first manifestation of an unknown primary tumor [8].

An estimated 1.4 million cases of breast cancer are newly diagnosed annually worldwide, representing the leading cause of cancer death among females in economically developing countries [9,10]. At the time of breast cancer diagnosis, roughly 5 percent of women have metastatic disease [11,12]. Of the metastatic lesions of breast cancer, bone metastases (with secondary spinal cord compression, pain, fractures, hypercalcemia) are the most common [10]. Jensen and colleagues found that among patients with bone metastases at the time of diagnosis, up to 43% develop skeletal events (pathological fracture, spinal cord compression, etc.), with subsequent surgical and radiation therapy [10,13].

In terms of location, approximately 95% of patients with spinal metastases will have epidural disease, with most pathology located in the vertebral body or pedicles, 5% will have intradural, and only 1% of patients will harbor intramedullary metastases [14,15]. Most symptomatic metastases occur in the thoracic spine, followed by cervical and lumbar, with the incidence being directly proportional to the higher number of vertebra and smaller canal diameter [16].

Survival in these patients is multifactorial, depending on primary tumor histology, systemic disease status, and comorbidities [17]. In general however, prognosis is poor with only 10-20% 2-year survival rate for all patients with spinal metastases. To this end, treatment of spinal metastases is purely palliative.

Current goals of treatment are usually related to improvement in a patient's quality of life by

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addressing pain control and preservation of neurological function, but goals may also include stabilization of the spine and local control of the disease [17].

As treatment modalities continue to improve and new technologies enter the clinical realm, the decision algorithm for management of these lesions will continue to evolve as new evidence arises. For example, advances in surgical techniques have allowed for more minimally destructive decompression and instrumentation techniques, while advances in radiotherapy has allowed once surgical diseases to be treated in a non-operative fashion.

In this paper, we will discuss the role of RT in the management of spinal metastases, with a focus on breast histology, which has for the most part become a non-surgical disease outside of a few circumstances, and to what extent do neurosurgeons play a role.

Role of Radiotherapy in the Management of Metastatic Spine Disease

The role for radiation therapy in metastatic spinal disease is a part of an emerging multidisciplinary approach to therapy with medical and surgical providers being paramount to effective treatment.

The Neurologic, Oncologic, Mechanical, and Systemic (NOMS) decision framework developed by a group at Memorial Sloan-Kettering Cancer Center (MSKCC) provides a pragmatic approach to decision making regarding therapies for metastatic spinal cord compression [17]. An extensive discussion of this framework is outside the scope of this paper, but the oncologic assessment in this system provides a valuable tool for understanding and deciding on radiation treatments for these patients.

The oncological assessment is based on the particular histologic diagnosis derived from the metastatic lesion and its response to current available therapies. Apart from conservative monitoring, radiation therapy provides the least invasive form of local tumor control and is an appealing primary treatment modality for patients unsafe for or unwilling to undergo surgical therapy, while also being utilized as adjuvant therapy after surgical debulking procedures. Primary histologies are categorized as either radiosensitive or radioresistent. This delineation is based on their responsiveness to conventional external beam radiation therapy (cEBRT) [17]. This modality is delivered in an imprecise conformal manner with one or two radiation beams to a selected target area [17]. The fraction dose that can be delivered using cEBRT is significantly limited by the spinal cord and cauda equina that are often apart of the radiation field. The toxicity limits of eloquent structures will be discussed later; however, as an attempt to circumvent this pitfall, imaged guided radiation therapy (IGRT) administration has been developed to allow high doses of radiation to be delivered in close proximity to the spinal cord, maintaining safe doses to these eloquent structures while allowing tumoricidal doses the planned oncologic targets [17]. Examples of IGRT therapy include stereotactic radiosurgery (SRS) and stereotactic body radiation therapy (SBRT). These modalities allow for the delivery of a conformal, high radiation dose to the targeted tumor volume with a steep fall-off dose gradient, which protects adjacent, often eloquent structures, delivered by a convergence of multiple beam orientations. SRS delivered in 1 fraction, and SBRT delivered in 2 to 5 fractions, provide certain benefits over cEBRT [17].

Current radiation therapy (RT) dosing, based on randomized, controlled trials, along with meta-analyses, have shown excellent pain control and minimal side effects with a number of fractionation schemes (30 Gy in 10 fractions, 24 Gy in 6 fractions, 20 Gy in 5 fractions, or 8 Gy in one fraction [18-21]. In fact, the recently published American Society for Therapeutic Radiation Oncology Task Force Guidelines found no evidence that a single fraction of 8 Gy was inferior to more prolonged RT course for pain relief, though single fraction dosing is associated with a 20% repeat treatment incidence compared to 8% with fractionated RT [22]. As stated above, cEBRT is limited by the tolerance of surrounding structures, which leads can lead to sub therapeutic dose delivery in terms of tumor control probability [23]. In patients with poorly anticipated length of survival from their systemic disease, this may not be problematic. But for disease states with a prolonged survival, cEBRT becomes less appealing due to the decreased probability of long-term tumor control for more resistant histologies. Other benefits of SBRT/SRS include minimizing the volume of bone marrow irradiated to include only the affected areas, allowing the continuation of systemic therapies and decreasing risk of affecting blood counts compared to cEBRT, convenience of patients due to smaller number and shorter duration of outpatient visits for dosing, minimal radiation to the adjacent normal tissue while maximizing target dose, and decreased fusion/instrumentation failure compared to cEBRT in post-operative RT [24].

Prior to initiating therapy, the patient is immobilized for high-resolution CT and non-contrasted magnetic resonance imaging (MRI) for treatment planning. The CT allows visualization of the sclerotic and lytic components of the pathology, while the MRI provides delineation of soft tissue structures and the extent of disease beyond the bony vertebral segment. These images are then fused for treatment planning with the following parameters defined. Gross tumor volume (GTV) is the radiographically visible tumor based on the fused imaging, encompassing the sclerotic and lytic pathology of the CT scan with the additional soft tissue extension and any signal change visualized on the MRI. The clinical target volume (CTV) includes the areas that have the potential for harboring microscopic disease not seen on imaging. The exact definition and application of CTV may vary from institution to institution. Practices may include no additional volume added for CTV such that CTV=GTV, others may add an anatomically based CTV (i.e. encompass part or the entirety of an involved vertebral body or posterior elements based on local disease) to the GTV, increasing the treatment field [25]. Planning target volume (PTV) is a 2 to 3 mm geometric expansion beyond the CTV, which accounts for potential errors in patient set-up, organ motion, and mechanical limitations of the image guidance and treatment delivery systems. It also allows for safer dosing limits to the spinal cord and cauda equina, minimizing the risk of long term radiation myelopathy while providing doses adequate to alleviate pain and control the disease locally [23]. In the post-operative setting, treatment planning can range from the entirety of the tumor bed and any area concerning for residual disease while others include the entire vertebral body and any adjacent areas of tumor extension or the postoperative levels of vertebrectomy and any residual tumor in the target volumes [26].

The critical structures which are contoured above and below the target volume (TV; the planned area to be treated with radiation) prior to therapy include the spinal cord, cauda equina and the cal sac by using CT [27], CT-MRI fusion [28], or CT-myelogram [28,29], with some authors advocating an organ at risk volume that includes a 1 to 2 mm expansion applied to the spinal cord/cauda equina [26,30].

Additionally, dose constraints are applied to these structures at risk to account for set-up errors, patient motion, and mechanical motion limitations of the system [31,32]. The dose to other surrounding organs (bowel, liver, kidneys) re also kept to safe levels [33].

Radiosensitivity varies among solid tumors, of which breast cancer has routinely been shown to have favorable responses to radiation response with the use of conventional external beam radiation treatment (cEBRT) and other radiotherapy options[1,20,34-40]. Regardless of the level of epidural spinal cord compression (ESCC), radiation therapy to radiosensitive tumors such as breast has led to improved local tumor control, ambulatory status, and pain relief for patients [17]. Favorable tumor histology such as breast (along with myeloma, lymphoma, prostate) are associated with a better survival prognosis, as well as better ambulatory function following treatment [38,41-43]. Maranzano and Latini [42] determined that metastatic breast cancer patients have a response duration of 12 months, with 67% patients regaining ambulation from a non-ambulatory state. Rades et al. [44] recently published a new scoring system to estimate survival in patients that underwent radiation therapy for metastatic spinal cord compression from breast cancer, finding scores correlated significantly with the presence of visceral metastases, time developing motor deficits, ambulatory status, involved vertebrae and Eastern Cooperative Oncology Group (ECOG) score [44].

Gerszten and colleagues conducted a systematic literature review suggesting that SRS is safe and effective, provides an incremental benefit over conventional radiotherapy in terms of durable symptomatic response and local control independent of histology, especially for radiosensitive histology [24]. The NOMS framework achieves durable tumor control by emphasizing use of cEBRT for radiosensitive tumors in both low-grade ESCC (with no myelopathy) as well as high-grade ESCC (+/- myelopathy) [17]. This defines radiation as the primary treatment for spinal metastases, while delineating surgical intervention for separation of the tumor from the critical neurological structures to create a margin to allow radiation therapy rather than gross total resection [17].

Toxicity and Shortcomings of Radiotherapy

One major complication from radiotherapy is the development or progression of vertebral compression fractures. These fractures can occur after SBRT and after single fraction SRS to spinal metastasis [45]. Investigators from MSKCC reported that following single-fraction SRS to vertebral metastases, there is a nearly 40% incidence of new or progressive vertebral compression fractures [46]. Risk factors for these compression fractures included lytic tumors, location below T10, and >41% of the vertebrae involved by the tumor. One study showed that a pre-existing vertebral compression fractures were more likely to progress, become symptomatic (i.e. pain), and require surgery than *de novo* fractures [47]. This highlights the need for careful patient planning and selection for radiation therapy, because in the face of impending mechanical instability secondary to a compression fracture, a surgical approach followed by radiation treatment would likely represent a better option than radiation alone.

Furthermore, evidence supports a limit in the amount of SBRT that the spinal cord can tolerate, which invariably limits the total amount of radiation applied [23,48]. For example, for fractionated radiation given at 2 Gy per fraction, a homogenous dose of 45 Gy results in a <0.5% risk of radiation-induced myelopathy [49]. The spinal cord is estimated to be able to tolerate 8-10 Gy of homogenous exposure if given a single fraction [50,51]. Based on the treatment of 177 patients with radiosurgery for spine metastases with single fraction of 8–18 Gy, Ryu and colleagues recommended limiting the volume of the spinal cord that received a dose of >10 Gy to 10% of the spinal cord volume contour [52]. Nevertheless, there may be an anatomical difference (i.e., cervical, thoracic, lumbar) in the tolerance of the spinal cord to radiation. For instance, the cauda equina may be more resistant than the rest of the spinal cord, although this finding has not been consistently shown across studies [52]. Sahgal et al. [53] based on dosimetric data from their cohort of patients who developed radiation-induced myelopathy after SBRT, suggested that 10 Gy in a single fraction is safe and proposed that a normalized 2 Gy equivalent biologically effective dose of 35 Gy [54] given in up to 5 fractions is low-risk, although additional considerations may be necessary if the spinal cord has been previously irradiated [48,54]. Another review published by the Quantitative Analysis of North Tissue Effects in the Clinic concluded that for partial cord irradiation, a maximum cord dose of 13 Gy in a single fraction or 20 Gy in 3 fractions was associated with a <1% risk of injury [55]. With regard to the radiation dose experienced other organs such as a the lungs, small bowel, esophagus, and kidneys, high-grade toxicities have not been reported after SBRT [25]. This is not to say that patients do not experience complications from the radiation delivered to those structures. Toxicities reported after spine radiosurgery include dysphagia, esophagitis, nausea, vomiting, lethargy, paresthesia, pain flare, vasculitis, skin hyper pigmentation, transient laryngitis and radiculitis, and wound complications [23,26-28,56-58]. There is some evidence that prophylactic dexamethasone use can reduce pain flares [59,60]. More work is needed to identify other supportive and prophylactic adjuncts that can reduce these side effects of radiation therapy that greatly impair the quality of life of the patients suffering from them.

Given the principle of SBRT is treating the tumor volume while minimizing the dose at the vertebral-segment-spinal cord interface, treating the involved vertebral bodies is generally regarded as safe and effective with low rates of treatment failure reported [34,61,62]. However, epidural failure or failure at the thecal sac-vertebral body interface is more common given the relative under dosing of microscopic epidural tumor with sub therapeutic radiation doses, with some authors suggesting that the proximity of the target volume (TV) to the thecal sac is a significant risk for this type of failure (e.g. TV within 1mm of epidural space) [26,34,30,63]. The consequence of treatment failure at the interface can be significant, particularly if tumor growth results in malignant epidural cord compression. Intentionally excluded areas within the TV and in intentional avoided areas beyond the tumor margin have also been reported [26,63]. Currently, it remains unclear if the practice of treating only the visible tumor is superior to treating the anatomical margin beyond the tumor itself by encompassing the entire vertebral body and adjacent pedicles, lamina, and spinous process. Although to date reports from major academic institutions that typically target the tumor alone have been similar to those sites that target the anatomical margins [34,64]. Finally, the practice of applying no margin into the adjacent soft tissues for paravertebral disease may increase the risk of margin failure, as paraspinal muscles do not provide a barrier to tumor spread/growth. As such, Sahgal et al. [65] state that a small margin of 0.5cm along the paraspinal muscles may be responsible if the disease extends beyond the vertebral body on MRI [65].

One final consideration regarding the limitations and

shortcomings for SBRT is its significant cost. Given a single fraction of SBRT can cost >$70,000, while a single fraction course of palliative radiotherapy is approximately $18,000 and a 10 fraction course of palliative radiotherapy is approximately $57,000, prospective trials exploring the differences in disease control, pain relief, quality of life, and survival are needed to determine if the cost differential is clinically justified [66].

Role for Surgeons

Historically, surgery in the form of posterior decompression (i.e. laminectomy) was used as a sole treatment for spinal metastases [67]. With the development of radiotherapy however, such surgeries were eventually abandoned in part due to a randomized trial in which laminectomy plus radiotherapy did not provide any additional benefit to radiotherapy alone [68,69]. However, performing a laminectomy often did not address the anterior location of a metastatic lesion and could cause destabilization in patients already with a component of anterior instability. It is therefore important to reconsider surgeries role in the treatment of breast cancer spinal metastases.

Typical goals of surgery in a patient with a spinal metastasis are to relieve medically refractory pain, restore or preserve neurological function, maintain structural stability of the spine, or correct a significant spinal deformity due to the lesion. As spinal metastases may be the first manifestation of cancer in up to 20% of individuals [70], another goal may include obtaining tissue for a histological diagnosis in patients with an unknown primary tumor. It is also essential to consider what the patient's goals of care are. For some, a focus may be maintaining the ability to walk and their prior independence while for others pain relief may be the main focus [53].

Although no definitive guidelines exist, proposed indications for surgical resection of a lesion include relapse after or progression while undergoing radiotherapy and chemotherapy, spinal instability or a pathological fracture, and in patients who meet the entry criteria defined by Patchell et al. [68,71] (i.e. patient with a radio-insensitive primary tumor, true displacement of spinal cord seen on MRI, single area of cord compression, and no total paraplegia for longer than 48h). The choice of whether or not to undergo surgical management should be tailored to each individual patient and formulated by a multidisciplinary team in conjunction with the patient's own desires. Factors that may influence the choice of therapy include the timing of neurological symptom onset, life expectancy of the patient, mechanism of cord compression, prior treatment modalities, and the number of compressing spinal metastases. For example, it is important to address signs of acute cord compression immediately while symptoms may still be reversible, which usually requires emergent decompression in order to avoid neurological sequelae.

Although posterior decompression alone has fallen out of favor in the management of spinal metastases, surgeons are now treating spinal metastases with a more anterior approach with the goal of resecting as much of the lesion as possible along with circumferential decompression of the spinal cord. A major study demonstrating the benefit of this approach came from Patchell and colleagues who conducted a prospective randomized study in which patients with spinal cord compression caused by a single metastatic lesion were assigned to receive either surgery followed by radiotherapy (30 Gy in ten fractions) or radiotherapy alone. Patients needed to have an expected survival of at least 3 months, MRI evidence of metastatic epidural spinal cord compression restricted to a single contiguous area, a cancer origin other than CNS or spinal column, no prior history of cord compression or preexisting neurological disease, and at least 1 neurological symptom. Exclusion criteria included patients with very radiosensitive tumors (lymphomas, leukemia, multiple myeloma, and germ-cell tumors), multiple areas of spinal cord compression, or total paraplegia for longer than 48 hours. Fifty patients were randomized to initial surgery, and of these, all but 3 patients received post-operative radiotherapy. The goal of surgery was to remove as much tumor as possible, provide immediate decompression, and provide intraoperative spinal stabilization when needed. Fifty-one patients were randomized to initial radiotherapy, and of these, one required surgery because of deterioration of strength during radiotherapy. Primary endpoints were ability to walk and ambulatory time after treatment. The study was discontinued on interim analysis due to the superior response of the group randomized to surgery plus radiotherapy. The percentage of patients retaining ability to walk after treatment was 84% in the surgery arm compared to 57% in radiation alone arm. Patients treated with surgery were also able to walk for a significantly longer period of time than those treated with radiation alone (median 122 d vs. 13 d). In the surgery arm, 10 out of 16 paraplegic patients regained ability to walk compared to 3 out of 16 patients in radiation alone arm. Surgery did not increase hospital stay length and actually decreased the use of morphine and steroids. 30-day morbidity was worse in RT only group. Median survival was also improved in the surgery arm (126 days) compared to the radiation alone arm (100 days) which the authors attributed to the higher ambulatory rates in the surgery group [71]. These results have also been supported by a meta-analysis by Klimo et al. [72] comparing surgery (with or without preoperative or post-operative adjunctive radiotherapy) with radiation alone in patients with symptomatic spinal cord compression, which found that patients were 1.3 times more likely to be ambulatory after treatment and twice as likely to regain ambulatory function.

Data specifically examining more extensive surgical decompression in breast cancer spinal metastases is limited. In the randomized study by Patchell et al. [71], breast cancer accounted for 11% of patients in both arms of the study but results were not stratified by tumor type. Shehadi et al. [73] reported a retrospective review of 87 patients with metastatic breast cancer spinal disease treated with resection and aggressive decompression. Of the 76 patients who were ambulatory pre-operatively, 98% were still ambulatory post-operatively. Of the 11 patients who were non-ambulatory pre-operatively, four patients were alive at 3 months postoperatively, three of which regained ambulation. Pain was also significantly reduced in these patients. Tancioni et al. [74] reported a retrospective study of 23 breast cancer patients treated with decompressive surgery followed by radiotherapy. Complete remission of pain that lasted until death or progression of disease in another skeletal site was obtained in 96.1%. Remarkably, all patients had complete recovery of neurologic deficit. While such results are promising, they do not examine differences that may exist between different subtypes of breast cancer, indicating a future area of study.

The above reports demonstrate the revitalization of surgical care for patients with spinal metastases. The exact surgical approach however depends on the tumor location, degree of infiltration, and whether reconstruction is required or not. Although a complete detailing of surgical approaches to the spine is outside the scope of this review, surgeons have used anterior (e.g. transthoracic, retroperitoneal, transoral, transmandibular, transnasal, and transcervical) and

posterolateral approaches (e.g. costotransversectomy, lateral extracavitary) including newer minimally invasive approaches for removing spinal metastases and achieving decompression [75,76]. Kaloostian et al. [76] performed various meta-analyses for different surgical approaches for metastatic spinal cord disease. 832 patients who had undergone vertebral body resection and stabilization for anteriorly located metastatic processes were reviewed. Percent motor improvement ranged from 32–100%, percent pain improvement ranged from 60–100%, and mortality ranged from 0–30%. Molina et al. [77] completed a retrospective study of 11 outcome reports examining endoscopic video-assisted thoracoscopic surgery (VATS) and mini-open minimal access spine surgery (MASS) approaches in cases of metastatic spine disease. Both procedures showed efficacy in treating neurological dysfunction and pain with complication rates, operative blood loss, and median length of stay being lower in the minimally invasive cohort of patients.

As an additional procedural approach to improving quality of life in these patients, vertebroplasty and kyphoplasty have been used to reinforce involved vertebral bodies. For vertebroplasty, a needle is fluoroscopically guided into the diseased bone, and PMMA cement is injected into the malignant bone cavity. Kyphoplasty differs in that a balloon is inflated within the vertebral body to create a low-pressure space to inject the cement. Lee and colleagues provided vertebroplasty for patients with solitary metastases. Of 19 patients, the 8 that had breast cancer all experienced immediate pain improvement and reduction in analgesic requirement [78]. Kaloostian et al. [76] performed a meta-analysis of vertebroplasty and kyphoplasty for metastatic spine disease. 864 patients who underwent vertebroplasty were included in the analysis, and percent mobility improvement ranged from 52-70%, percent pain improvement ranged from 73-100%, and percent pain increase ranged from 0-13%. 277 patients who underwent kyphoplasty were included in the analysis, and percent mobility improvement ranged from 65-91%, percent pain improvement ranged from 80-100%, and percent pain increase was 0%. In 2011, Berenson and colleagues reported the Cancer Patient Fracture Evaluation (CAFE) study, a randomized controlled trial comparing balloon kyphoplasty with non-surgical management for patients with painful vertebral body compression fractures. The primary endpoint was back-specific functional status measured by the Roland-Morris disability questionnaire (RDQ) score at 1 month. Patients needed to be at least 21 years old, one to three compression fractures from T5-L5 secondary to cancer, and RDQ score of at least 10. Patients were excluded if they had osteoblastic tumors or primary bone tumors, substantial clinical morbidities, VCF morphology deemed unsuitable for kyphoplasty by the treating physician, requirement of additional surgical treatment for the fracture, or needed treatment with high-dose steroids or intravenous pain medication. 65 of the 70 patients assigned to the kyphoplasty arm and 52 of the 64 patients to the non-surgical management arm were analyzed. While there was no change in the RDQ score in the non-surgical group, the mean RDQ score in the kyphoplasty group decreased from 17.6 to 9.1 at 1 month [79].

As suggested in the original study by Patchell et al. [71], a critical component of choosing particular patients for surgical management is to consider the life expectancy of a patient. In their study, only patients with a life-expectancy greater than 3 months were included. To address this, several scoring systems have been developed to help predict prognosis of patients with metastatic spinal disease. Tokuhashi et al. [80] first proposed a 12-point scoring system aimed to estimate patient prognosis based on 6 parameters including: the general condition of the patient, the number of extra spinal bone metastases, the number of metastases in the vertebral body, metastases to the major internal organs, the primary site of cancer, and the severity of spinal cord palsy. In a later report, the group developed a revised 15-point scoring system based on the same parameters in order to improve the consistency between predicted and actual survival. This revised scoring system had a consistency rate between predicted prognosis based on the criteria and the actual survival period of 86.4% in patients prospectively analyzed and 82.5% in patients evaluated retrospectively. Total scores of 0 to 8, 9 to 11, and 12 to 15 predicted a life expectancy of less than 6 months, 6 months or more, and 1 year or more, respectively. These prognostic criteria were useful for predicting the prognosis irrespective of treatment modality. Patients with a life expectancy predicted to be less than 6 months were recommended to undergo conservative treatment while those with more favorable score could undergo some form of surgery [81]. Tomita and colleagues developed another 10-point scoring system based on grade of malignancy, presence of visceral metastases, and number of bone metastases. Based on these scores, wide or marginal excision for long-term local control was recommended for a score of 2–3 points, marginal or intralesional excision for middle-term local control for a score of 4 –5 points, palliative surgery for short-term palliation for a score of 6-7, and non-operative management for a score of 8-10 [82]. The revised Tokuhashi scoring system has been shown to provide prognosis for patients with breast cancer [83]. However, Wang and colleagues reported that in patients with breast cancer spinal metastases with ER/HR negative status, surgery was associated with a higher mortality risk and shorter median survival. The authors suggested that the Tokuhashi and Tomita scoring systems should be modified in these subtypes [84]. Another scoring system called the spinal instability neoplastic score (SINS) reported by Fourney and colleagues in the Spine Oncology Study Group has been used to quantify preoperative tumor-related spinal instability as an indication for surgery. Scoring was based on location, pain, bone lesion, radiographic spinal alignment, vertebral body collapse, and posterolateral involvement of spinal elements. The sensitivity and specificity of SINS for potentially unstable or unstable lesions were 95.7% and 79.5%, respectively, and the κ statistic for predictive validity was 0.712 (95% CI, 0.676 to 0.766) [85]. As we continue to improve our ability to predict which subgroups of patients will benefit most from surgical management, its role and the best surgical approaches in patients with spinal metastases are likely to be better defined.

Future Directions

The management of breast cancer spinal metastases is likely to evolve over the coming decade given the development of new chemotherapy, further characterization of tumor pathophysiology, and better delineation of the roles of radiotherapy and surgery. For example, several clinical trials are aimed at comparing external beam radiation with stereotactic radiosurgery for relief of pain symptoms and local tumor control. RTOG 0631 is a randomized phase II/III trial designed to compare stereotactic body radiation therapy (1x16 Gy) with external-beam radiation therapy (1x8 Gy) in treating patients with 1-3 spine metastases, with the goal of assessing successful delivery of radiation and pain improvement (NCT00922974). Ryu et al. [86] reported the phase II results demonstrating the feasibility of providing this form of radiation for spinal metastases, and phase III results are pending. Investigators at Radboud University and others in the Netherlands are conducting a phase III trial also comparing conventional radiotherapy (1x 8Gy) with stereotactic radiotherapy

Table 1: Recruiting and ongoing therapeutic clinical trials related to treatment of spinal metastases.

ClinicalTrials.gov Identifier	Primary Sponsor	Status	Summary	Intervention Groups	Primary Outcome
NCT00922974	RTOG	Recruiting	Randomized phase III trial comparing SBRT and EBRT for spine metastases	Experimental: IGRT/SRS/SBRT (1x16Gy) Comparison: EBRT (1x8 Gy)	Complete or partial pain response at 3 months as measured by the Numerical Rating Pain Scale
NCT02407795	Radboud University	Recruiting	Randomized phase III trial comparing conventional RT with SRS for spinal metastases without cord compression	Experimental:SRS (1x20Gy) Comparison: CRT (1x8Gy)	Pain reduction measured by the Dutch Brief Pain Inventory questionnaire at 6 weeks since baseline
NCT02364115	UMC Utrecht	Recruiting	Randomized controlled trial comparing CRT with SBRT in patients with	Experimental: SBRT (1x18 Gy to visible metastasis and 8Gy on bony compartment containing metastasis) Comparison: CRT (1x8 Gy)	Pain response within 3 months according to the International Bone Metastases Consensus Endpoints for Clinical Trials
NCT02512965	NCIC Clinical Trials Group	Recruiting	Randomized phase II feasibility study comparing SBRT with CRT for spinal metastases without symptomatic MSCC	Experimental: SBRT (2x12 Gy) Comparison: CRT (5x4 Gy)	Ability to randomize 54 patients with spinal metastases over 18 months to SBRT or CRT within a Canadian multicenter setting
NCT01290562	University Health Network, Toronto	Ongoing but not recruiting	Phase II study to evaluate the efficacy of SBRT as an alternative to CRT in patients with spinal metastases with no prior RT, prior RT, or in post-operative period	Experimental: SRS (1x20-24 Gy or 2x10-12 Gy or 3x7-8 Gy)	Efficacy of spine SBRT using image and symptom based local control criteria at 5 years
NCT01254903	M.D. Anderson Cancer Center	Ongoing but not recruiting	Phase I study of the feasibility of single fraction SRS as primary management of inoperable, non-irradiated MSCC	Target dose of 1x18 Gy	Number of occurrences of paralysis caused by radiation myelitis up to 12 months post-RT
NCT00573872	University of Alabama at Birmingham	Ongoing but not recruiting	Phase I/II study to determine define quality assurance procedures and to estimate palliative response and local control for single fraction SRS for spinal metastases without acute cord compression	Phase I: 20-25 Gy in 5 fractions Phase II: 9-24 Gy in 1 fraction	To determine intrafraction target motion and define quality assurance procedures for single fraction spinal SRS
NCT01347307	St. John's Mercy Research Institute, St. Louis	Ongoing but not recruiting	Phase IV trial evaluating use of SRS for treatment of spine metastases and primary spine tumors	Metastases: SRS (1x14-25 Gy or 3x7-9 Gy or 5x5-6 Gy)	Symptom control at 6 weeks post-RT and local tumor recurrence rate at 5 years
NCT02616887	IstitutoClinicoHumanitas	Recruiting	Phase II study examining SBRT andVMAT for spinal metastasis with minimal epidural compression	Experimental: SBRT and VMAT (1x18 Gy)	Toxicity of RT and local control of treated lesion within 1 year
NCT01654068	University of Kentucky	Recruiting	Non-randomized phase II study to determine if Conformal high dose Intensity modulated RT is an appropriate option for spinal metastases	Experimental: Conformal high dose Intensity modulated RT (1x14Gy) for either a solitary lesion or 2-3 lesions	Time to any skeletal related event up to 24 months
NCT00853528	Boston Medical Center	Ongoing but not recruiting	Phase I trial to study side effects and best dose of hypofractionated SRS for spinal metastases without acute cord compression	Experimental: Maximum tolerated dose of hypofractionated SRS	Determine maximum tolerated dose
NCT02608866	National Taiwan University Hospital	Recruiting	Randomized phase II study comparing single fraction and hypofractionated SRS for non-operative spinal metastases	Experimental Arm 1: SRS (1x16 Gy) Experimental Arm 2: SRS (3x8 Gy)	Adverse events within 4 months
NCT01826058	Samsung Medical Center	Recruiting	Non-randomized phase II trial examining single and hypofractionated SBRT for MSCC	Experimental: SBRT in one to four fractions: 1x16-24 Gy 2x20-26 Gy 3x21-30 Gy 4x24-36 Gy	Neurologic motor response at 1 month
NCT01223248	Memorial Sloan Kettering Cancer Center	Recruiting	Randomized phase III trial comparing single versus hypofractionated doses of IGRT for spinal metastases without cord compression	Experimental Arm 1: IGRT using single dose of 24 Gy Experimental Arm 2: IGRT of 3x9 Gy	Local/regional control rates over 2 years

NCT02320825	Memorial Sloan Kettering Cancer Center	Recruiting	Randomized phase III trial comparing post-operative single and hypofractionated SRS for MSCC	Experimental Arm 1: single-fraction SRS (1x24 Gy) Experimental Arm 2: high-dose hypofractionated SRS (3x9 Gy, total dose of 27 Gy)	Local tumor control using MRI or CT over 2 years
NCT01594892	Wuerzburg University Hospital	Ongoing but not recruiting	Non-randomized phase II study examining hypofractionated SRS for spinal metastases without acute MSCC	Experimental Arm 1: For long life expectancy – 10x4.85 Gy to involved areas and 3 Gy to non-involved areas of the vertebrae Experimental Arm 2: For intermediate life expectancy - 5x7 Gy to involved areas and 4 Gy to non-involved areas of the vertebrae	Pain response within 3 months
NCT01752036	Sidney Kimmel Comprehensive Cancer Center	Recruiting	Phase II study evaluating post-operative SRS for local control of spine metastases	Experimental: SRS (5x6 Gy)	Recurrence rate at 12 months
NCT01849510	University of Erlangen-Nürnberg Medical School	Recruiting	Randomized phase II trial to compare standard hypofractionated RT with or without simultaneous, integrated boost (IGRT & SRS) for spinal metastases	Experimental: dose intensified hypofractionated 12x3 Gy plus integrated boost 12x4 Gy (IGRT & SRS) Comparison: hypofractionated 10x3Gy	Time to progression over 5 years
NCT02527304	Albert Einstein College of Medicine of Yeshiva University	Recruiting	Single arm interventional study examining feasibility of adaptive staged SBRT in treating patients with non-operable spinal metastases	Experimental: Adaptive staged SBRT in which additional doses are given within 14-21 days after the full initial dose at the discretion of the treating physician	Radiographic response as measured by a reduction in the epidural tumor volume, a reduction in thecal sac compression, or the distance between the gross disease and spinal cord on imaging scans (MRI or CT myelogram) within 10 weeks of treatment
NCT02622841	UMC Utrecht	Recruiting	Phase I/II study to assess the feasibility and safety of combining SBRT and surgical stabilization for painful unstable spine metastases	Experimental treatment: Combination of SBRT and pedicle screw fixation within 48 hours	Occurrence of adverse events within 90 days post-treatment
NCT02167633	Rigshospitalet, Denmark	Recruiting	Randomized trial comparing SRS with decompressive surgery followed by EBRT for MSCC	Experimental: SRS (1x16Gy) Comparison: posterior decompression/laminectomy plus postoperative EBRT (10x3Gy)	Ability to walk at 6 weeks
NCT02480036	Loyola University	Recruiting	Phase I study examining IORT with kyphoplasty for patients with a spinal metastasis and loss of vertebrae height	Experimental: IORT with kyphoplasty	Pain assessment up to 52 weeks
NCT00855803	University of Texas Southwestern Medical Center	Recruiting	Non-randomized phase II trial examining SBRT with vertebroplasty for patients with spinal metastases	Experimental Arm 1: With prior RT -undergo 5 fractions of SBRT Experimental Arm 2: No prior RT – single fraction of SBRT	Pain response at 3 months
NCT02367378	Icahn School of Medicine at Mount Sinai	Recruiting	Prospective case control study designed to assess minimally invasive spine tumor decompression with comparison with historical controls.	Experimental: Minimally invasive surgical procedures Comparison: historical controls of patients treated with surgical resection, chemotherapy, and RT	Survival time up to 2 years
NCT01077154	Amgen	Ongoing but not recruiting	Randomized phase III trial comparing Denosumab versus placebo to prevent disease recurrence in bone or other parts of the body	Experimental: Denosumab 120mg subcutaneously once monthly for 6 months. 120mg SC every 3 months for the next 4.5 years. Plus daily calcium and Vitamin D supplementation for 5 years. Placebo: Placebo subcutaneous injection plus daily calcium and Vitamin D supplementation for 5 years	Bone metastasis-free survival up to 7 years 5 months

NCT00566618	M.D. Anderson Cancer Center	Ongoing but not recruiting	Phase I/II trial of Dasatinib with zoledronic acid for the treatment of breast cancer with bone metastasis	Experimental: Dasatinib Phase I first cohort – 100 mg PO daily for 28 days; Zoledronic acid Phase I first cohort – 4 mg IV every 4 weeks	Maximum tolerated dose for Dasatinib in combination with zoledronic acid
NCT01586273	Philips Healthcare	Recruiting	Single arm interventional study to evaluate high intensity focused ultrasound for treating painful bone metastases	Experimental: MRI-guided high intensity focused ultrasound with the Philips Sonalleve device	Pain response 30 days after treatment
NCT01091883	InSightec	Recruiting	Randomized phase III study comparing MRI-guided focused ultrasound and EBRT for treatment of metastasis bone tumors	Experimental: MRI-guided focused ultrasound with Exablate device Comparison: EBRT	Adverse events over 6 months
NCT02464761	Sunnybrook Health Sciences Centre	Recruiting	Phase I study examining photodynamic therapy for the treatment of spinal metastases	Experimental: IV Visudyne with light delivery through fiber optic cables using diode laser	Intraoperative dosimetry during surgery
NCT01637766	Weill Medical College of Cornell University	Recruiting	Phase I study examining intra-arterial chemotherapy for spinal metastases with grade 1 or 2 cord compression not candidates for RT or surgery	Experimental: selective intra-arterial delivery of Melphalan at max dose of 16 mg/m^2	Percentage of patients in whom intra-arterial chemotherapy is performed without severe complication within 30 days

SRS: Stereotatic radiosurgery; SBRT: stereotactic body radiotherapy; IGRT: Image guided radiotherapy; VMAT: volumetric modulated arc therapy; IORT: intraoperative radiotherapy; RT: radiotherapy; EBRT: external beam radiotherapy; CRT: conventional radiotherapy; MSCC: metastatic spinal cord compression.

(1x20 Gy), assessing impact on pain control (NCT02407795).

The optimal dose regimen of stereotactic radiosurgery to maximize local control while prevent adverse events also still needs to be determined. Investigators at MSKCC in conjunction with other centers are examining single fraction (24 Gy) or hypofractionated (3x9 Gy) stereotactic radiosurgery's role in the post-operative setting (NCT02320825). Although hypofractionated doses may decrease the incidence of complications such as vertebral compression fractures, recent results in previously non-irradiated renal cell carcinoma spinal metastases show better 1- and 2-year local control rates with single rather than multifractionated stereotactic radiosurgery [87]. The applicability of this finding to breast cancer has yet to be determined. Alternatively, other investigators at the Albert Einstein College of Medicine in collaboration with the National Cancer Institute are examining the efficacy of adaptive staged stereotactic body radiotherapy where single-fraction treatment can be provided with an additional dose 14-21 days later depending on diagnostic interval imaging and spinal cord dose constraints, with the aim of assessing radiographic response (NCT02527304).

Lastly, it is important to consider instances in which new surgical techniques may be used. Investigators at UMC Utrecht are assessing stereotactic body radiotherapy followed by surgical stabilization in patients with unstable spine metastases in a phase I/II study (NCT02622841). Others are comparing survival outcomes between minimally invasive surgery with current standard treatments of spinal metastases including surgical resection, chemotherapy, and radiotherapy (NCT02367378). It is important to note that while many of these trials will likely accrue a substantial number of patients with breast cancer spinal metastases, there is still a lack of data delineating outcome with different breast cancer subtypes.

It is also important to consider new forms of medical management for spinal metastases. Denosumab and bisphosphonates (e.g. zoledronic acid) have been used for the treatment of skeletal-related events and pain in women with boney metastases from breast cancer [88-91]. However, new TGF-β and Src tyrosine kinase inhibitors are other classes of agents that show promise in targeting bone metastases [88,92]. In addition to preventing bone-related pain and fractures, there is an interest in whether these agents can actually prevent formation of bone lesions. For example, there is some evidence that zoledronic acid, when added to chemotherapy, increases the elimination of disseminated tumors cells from the bone marrow [93]. Such findings warrant further investigation to determine if this or similar agents may prevent formation of spinal metastases. A current clinical trial by Amgen is assessing denosumab's ability to prevent bone metastases with the primary end-point of bone metastasis-free survival (NCT01077154).

Although some trials have looked at breast cancer patients as a group, most do not distinguish between the various subtypes based on hormone receptor and HER2 status. The subtype of breast cancer can significantly impact overall survival and outcomes in patients with breast cancer spinal metastases. Triple negative and ER/HR negative status breast cancer spinal metastases are correlated with worse overall survival after treatment and may thus warrant different considerations in the treatment of these patients [84,94]. These markers may also relate to characteristics of a lesions such as whether these lesions are blastic versus lytic [95]. As more biomarkers of breast cancer are revealed, it is likely that treatment strategies will need to be tailored to the specific subtype of breast cancer (Table 1).

Conclusion

As new information from randomized trials comes to light, the role of neurosurgeons in the treatment of metastatic spinal disease from breast cancer will continue to evolve. Currently, the disease burden of the spine itself is managed through the utilization of SBRT/SRS, with indications for surgery following a more supportive rather than curative role. With further improvements of radiation dosing regimens and adjuvant hormonal therapies, it will be interesting to see what the future holds for these patients. Ideally, we would move from a palliative philosophy to a curative philosophy. However, at the present, we have yet to arrive at this destination.

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