Radiotherapy for Primary and Metastatic Spinal Tumors

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Primary and metastatic spinal tumors as a group represent a heterogeneous mixture of benign and malignant processes. In general, primary tumors of the spine remain relatively uncommon, and the majority of spinal tumors that are treated annually represent systemic spread of extraosseous primary malignancy. The management of spinal tumors requires meticulous yet expedient attention as the consequences of failed or inappropriate treatment can be devastating. Radiotherapy has proven beneficial in many tumors of the spine, particularly metastatic lesions, Ewing’s sarcoma, and myeloid malignancies. A review of the use of radiotherapy for the more common primary spinal malignancies and metastasis is presented.

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Although relatively uncommon, primary spinal tumors represent a heterogeneous mixture of benign and malignant processes. These result in a broad spectrum of symptoms ranging from a minor backache to severe weakness that prevents one from walking (due to neurologic structure impingement). Common benign tumors that develop in the spine include aneurysmal bone cysts, hemangiomas, giant cell tumors of bone, osteoid osteomas, meningiomas, and osteoblastomas. There are many primary malignant processes that can also develop in the spine, including chordomas, chondrosarcomas, osteosarcomas, Ewing’s sarcomas, plasmacytomas, multiple myeloma, and lymphoma. Although the differential diagnosis for a spinal tumor may appear lengthy, these primary disease processes only account for a minority of all spinal tumors diagnosed annually.1-6

The majority of spinal tumors treated annually represent systemic spread of an extraosseous primary malignancy. Skeletal metastases represent one of the most common manifestations of metastatic malignancy, and vertebral column involvement is the most common site for bony metastases to be located.7 Although difficult to quantify, estimates suggest that over 100,000 patients develop osseous metastasis in the USA annually. In these patients, it is estimated that 20% have spinal column involvement.8,9 Most spine metastases derive from breast, prostate, lung, kidney, and hematopoietic cancers.10-18

No matter the etiology, the management of spinal tumors requires meticulous but expedient attention as the consequences of failed or inappropriate or careless treatment can be neurologically devastating and potentially irreversible. Surgical intervention has been established as a beneficial treatment with durable results in the setting of primary and secondary tumors of the spine.13,16,19-22 The application of radiotherapy (RT) can serve as an adjunct to surgery or at times might be used in place of surgery or as a preparative regimen to make a tumor more readily resectable. RT is used extensively in tumors of the spine, both in primary and in metastatic lesions, and this review addresses options, techniques, and results of modern-day RT applications.

Radiotherapy for Primary Tumors

As mentioned previously, there are a variety of primary malignant tumors of the spine. The most recognized and treated malignancies typically derive from 1 of 2 tissue types, soft tissues (sarcomas) or hematopoietic cells (hematopoietic cancers). The frequency of use and effectiveness of primary and adjuvant RT approaches vary greatly among these primary cancers even within tumors of similar cell-level progenitors.

Chordoma

These rare, slow-growing tumors often arise in the sacrum or base of skull.23 Men are more commonly affected than
women and are more commonly identified in the fifth to seventh decades. Surgical resection is the mainstay of treatment but can be fraught with difficulty due to the complexity of removing tumors that commonly are intimately associated with nerve roots. Recurrence, although typically indolent in its course, can be common. RT has been found to be useful in the adjuvant and primary setting because of the difficulty of achieving a complete resection. The most favorable reported results with RT combine high-dose proton beam therapy (PT) with an aggressive surgical approach. There are multiple potential reasons for the improved outcomes with PT, but it is likely that the greatest component of success derives from the ability to optimize the therapeutic ratio with PT to a higher degree than traditional RT with photons (see below for further explanation).

Osteosarcoma
Osteosarcoma is a highly malignant tumor that commonly develops in young males. In osteosarcoma of the extremity, neoadjuvant chemotherapy followed by complete surgical resection represents the gold standard. Investigations into adequate therapy without surgery using contemporary chemotherapy are controversial and uncommon. RT as a single modality has not been shown to be particularly effective in the primary management of osteosarcoma. RT combined with systemic agents have been infrequently investigated but have shown potential for improving local control and limb preservation following induction with chemotherapy. Typically, RT is not administered in the primary management of osteosarcoma (including in spinal presentations) but could be considered in the palliative setting.

Chondrosarcoma
Chondrosarcomas were first described in 1943 by Lichtenstein and Jaffe. Although relatively uncommon, they represent the second most common primary bone tumor. Opposite of osteosarcomas, chondrosarcomas typically develop in adulthood (commonly in the fourth to seventh decades). Further, chondrosarcoma is a slow-growing tumor that can develop in any portion of the bony spine. The gold standard of therapy for these indolent tumors remains surgical resection and this alone results in a relatively favorable prognosis for patients with newly diagnosed, resectable disease. However, a complete resection can be hampered by the size, location, and extent of the tumor. Historically, it has been believed that chondrosarcomas are typically resistant to both chemotherapy and RT. Studies investigating the administration of RT during a course of care for a patient with chondrosarcoma indicate that statistically significant improvements in local control can be achieved with 3-dimensional (3D) conformal photon or proton therapy either as a primary or as an adjuvant modality. Nevertheless, wide-surgical resection remains the preferred definitive management option.

Plasmacytoma/Multiple Myeloma
Two other common malignant tumors that can develop in the spinal column include solitary plasmacytoma and multiple myeloma. Both of these hematologic malignancies are more common in men. Although multiple myeloma is more common in the sixth and seventh decades of life, solitary plasmacytoma typically presents at a younger age. Solitary plasmacytoma is a rare entity and by definition is a single tumor involving a specific area of the spine or bone. In a good proportion of patients, they are thought to predispose the individual to the subsequent development of multiple myeloma regardless of local therapy. Multiple myeloma represents systemic involvement of the marrow space with likely diffuse involvement of the spinal column. Both malignancies are exquisitely sensitive to RT. Plasmacytoma is commonly treated with a 4- to 6-week course of tumor-directed RT with excellent results in local control. However, evidence indicates a high, albeit variable, risk of progression to myeloma with 10-year rates commonly reported as greater than 50%. RT is commonly used in multiple myeloma as a palliative tool to help improve patients’ quality of life, decrease pain, and prevent pathologic fracture. Palliative RT in this situation is commonly delivered with a shorter 2- to 3-week course with good results.

Lymphoma
Lymphoma is described as a “small round blue-cell malignancy” that can develop primarily in the bones of the spine. Resection is not typically required or recommended (unless necessary for prophylactic measures in stabilizing or reinforcing the vertebrae). Various subtypes of lymphoma can involve the bone primarily. Although generally rare, best evidence reveals that primary lymphoma of the spine should be treated with induction chemotherapy tailored to the lymphoma cell type, followed by consolidative RT. Several randomized studies have demonstrated a significantly improved disease-free survival with the combination of chemotherapy and radiation compared to chemotherapy alone or RT alone in the primary management of intermediate grade non-Hodgkin’s lymphoma. Although little data regarding RT dose for spinal lymphoma are available, it is reasonable to extrapolate information from the doses implemented in the above trials for bony primary sites.

Ewing’s Sarcoma
Another “small round blue-cell tumor,” Ewing’s sarcoma is the second most common primary tumor of bone in children (behind osteosarcoma). Ewing’s class of tumor has a characteristic age distribution with presentations uncommon in children younger than 8 years of age and in adults older than 25 years. Although primary disease in the spine occurs in a relative minority of patients, it historically has represented a relatively more aggressive subtype of disease based on control and survival rates compared to other sites. The marked improvement in survival realized contemporarily with advanced chemotherapy has created a controversy in balancing long-term local disease control with long-term function.

It is still not clear what represents the optimal modality for local control in combination with chemotherapy—surgery, RT, or some combination. Many of the available data for RT
alone are biased because historically many of the patients undergoing primary RT represented an unfavorable population of tumors. More recent data, however, with modern RT techniques, demonstrate comparable rates of local control and survival with primary RT compared to historical surgical controls in patients with complex nonoperable tumors, such as those in the spine or pelvis. Recent and current Cooperative Group studies recommend using primary RT alone in patients with bulky tumors and in surgically difficult sites (including the spine, skull, and pelvis), as well as for those patients with poor response to induction chemotherapy and in which surgery would result in unacceptable functional results (Fig. 1). RT would be indicated in conjunction with surgery in those patients who have inadequate margins. RT typically consists of 5 to 7 weeks of treatment in the primary setting.

Radiotherapy for Metastatic Disease

The spine represents the most common site of skeletal metastases with over 18,000 new cases of spinal metastases recognized annually. Although surgery represents a mainstay in the management of spinal metastases, RT maintains a tried-and-true role in palliating patients with metastatic disease. RT techniques can be employed in a broad range of circumstances, including as a prophylactic measure against future pathologic fracture, palliation of bone pain, and palliation of severe symptoms related to cord compression and impending neurologic compromise.

Noncomplicated Spinal Metastasis

The beneficial role of achieving analgesia of bone metastases with RT is well documented and has been recognized since the early use of photons in medical treatment. Although the response to RT has been quantified and qualified by many different criteria and instruments over the decades, the preponderance of evidence reveals that 70%-90% of patients will achieve a beneficial response from analgesic-directed RT with complete responses observed in up to 40% of patients. Further, the palliative role of RT cannot be overstated in the patient with multiple sites of pain and tenderness, as RT commonly represents the least morbid approach to achieving broad-spectrum, prompt symptom relief relative to other medical and surgical options.

Specific dose-fractionation schedules for palliative treatment of bone metastases can be variable and are based on the particular clinical situation for each patient. There is no standard treatment approach insofar as there are many dose fractionation schedules for uncomplicated spinal skeletal metastasis. Two large meta-analyses and an additional update (in addition to hundreds of single institution and collaborative group studies) have consistently revealed no significant differences in complete and partial pain response rates following single-fraction (8 Gy) vs. multifraction regimens in many randomized trials. The most recent published update reported no observable differences in overall and complete response rates in both intention-to-treat and assessable patients. However, the likelihood of re-treatment was 2.5-fold higher in those undergoing single fraction vs. multifraction therapy. Further analyses have shown a statistically significant increase in the risk of subsequent pathologic fracture in patients undergoing single-fraction palliative RT. Nevertheless, re-treatment following recrudescence of pain following single- or multifraction palliative RT is feasible, well-tolerated, and without evidence of increased spinal cord toxicity in certain situations.

Malignant Spinal Cord Compression

The RT approach for patients with more severe spinal involvement resulting in cord compression should not be confused with that already described for uncomplicated, painful metastases. The symptoms of cord compression are not easily
mistaken as 90% of patients will have pain and up to 50% will have difficulty walking and experience sensory, bowel, or bladder dysfunction.74,76

Malignant spinal cord compression is best visualized with magnetic resonance imaging and is identified as compression of the dural sac and its contents by an extradural tumor mass. The minimum radiologic evidence for cord compression is indentation of the theca at the level corresponding to the clinical features.77

Although only a minority of patients who present with malignant cord compression will be surgical candidates, the role of surgical decompression followed by postoperative RT was established by a randomized controlled trial reported by Patchell et al.78 One hundred patients with cord compression were randomized to RT alone or surgical decompression followed by RT. Significantly more patients in the surgery group were able to walk after the treatment, retained the ability to walk for a longer duration after treatment, and regained the ability to walk relative to those in the RT alone group.

However, many patients presenting with malignant cord compression are not candidates for surgery for various reasons, including multiple levels of spinal involvement, limited life expectancy, or concurrent morbidities that prevent a surgical procedure. RT represents a mainstay of therapy in those patients and is typically supplemented with high-dose corticosteroids.79,80 RT in both the complicated and the uncomplicated spinal metastasis setting is commonly prescribed to the posterior wall of the vertebral body (or anterior aspect of the spinal cord proper). Typically, most practitioners prefer a more protracted course of RT in the cord compression setting and courses vary from 5 daily fractions of 4 Gy to 23 daily fractions of 2 Gy.81 The most common schema used in the USA is 10 daily fractions of 3 Gy. However, the available retrospective and prospective data would indicate no substantial benefit of one fractionation schedule over another when analyzing for functional outcomes.81,84 Additionally, some of those series included patients treated with a single 8-Gy fraction course (among other more protracted regimens) and no substantial difference in clinical outcomes or increase in acute or late toxicity were reported.81,84

Radiotherapy Techniques

Modern advances in computer technology and the delivery of RT have led to the development of treatment techniques, such as 3D conformal, intensity-modulated, and proton beam therapy. However, recognizing that most spinal tumors are metastases, much of spinal RT is delivered using conventional 2-dimensional (2D) techniques or 3D conformal techniques. Techniques involved with each approach, including advantages and disadvantages, are discussed.

2D Radiotherapy

2D RT is a simple and convenient approach to treating spinal tumors, particularly in the metastatic disease setting (Fig. 2). Typically, a radiation oncologist would elect to use a single unopposed field directed anteriorly from the posterior aspect of the patient while covering the involved spine. Alternatively, if the patient diameter in the treated region is larger, the area of treatment interest is deep to the skin (generally >7–8 cm), or if the lower portions of the spine are being targeted, 2 directly opposed beams would be employed for therapy with the goal of improved target coverage. When treating the upper cervical spine, opposed lateral beams are commonly used to spare the anterior portion of the neck and throat and to limit treatment of the esophagus and other radiosensitive soft tissues.

Commonly, a patient who has consented to undergo RT to the spine will have a computed tomographic (CT) simulation before treatment. During the simulation, the patient is positioned either supine or prone (rarely in a decubitus position) and axial CT images are obtained of the body area of interest. Using a computer interface, the radiation target area can be specifically defined and a common safety margin of one uninvolved vertebral body above and below the affected area is incorporated (eg, if a metastatic lesion is present at T5, radiation treatment is commonly directed at vertebral levels T4 through T6). A treatment field can then be designated directly on the computer or on printed digital reconstructed radiographs that are reconstructed from the CT data. The field is then digitally applied to the CT data, and tissue compensators may be applied. A dose is prescribed and the specific treatment time is then calculated. Verification films of the patient in the treatment position, on the treatment machine, using mV or kV imaging devices immediately before the first dose delivery are standard. Depending on the clinical situation and technology/equipment available, the simulation, calculation, and treatment process can now be performed entirely on the treatment machine.

Alternatively, a physician may decide to use a multiple-beam arrangement in completing a radiation treatment for a spinal tumor. This technique, when employing 2 opposing lateral beams and a single posterior beam, for example, can optimize dose to the targeted area with the benefit of decreasing entrance and exit dose to the contents of the anterior abdomen, thereby reducing the risks of treatment-related toxicity. Ideally, each treatment approach will be patient-specific in an effort to curtail the risks of therapy and maximize target access and thus dose to the designated target area.

3D Conformal Radiotherapy and Intensity-Modulation

Contemporary imaging technologies allow the practicing radiation oncologist to better define, in 3 dimensions, cancer anatomy and normal tissue anatomy. Magnetic resonance imaging, CT, and positron emission tomography offer an invaluable resource for clearer target delineation and treatment design. The combination of advances and access in imaging technologies with the technical growth of RT, particularly with the advent of computer-controlled multileaf collimators, has allowed for the development and refinement of 3D treatment approaches that serve to maximize tumor dose and minimize normal tissue exposure.
The development of 3D conformal RT plans is approached in a similar manner as outlined in the 2D RT section. The difference, however, is that the 3D conformal approach often employs an increased number of beams that are shaped to conform to the target. Technological advances, including multileaf collimators, beam’s eye view, and forward or inverse treatment planning, are actively used to create and deliver a 3D plan. Further individual modulation of beams and beamlets within each beam can achieve even greater conformity and in conjunction with inverse treatment planning is better known as intensity-modulated radiation therapy (IMRT). 3D and IMRT techniques can be used to obtain greater dose conformity to targets and sharp dose fall off beyond the target and to decrease dose to adjacent normal tissues (Fig. 3). Although not particularly necessary in the palliative setting where lower doses are commonly applied, IMRT and 3D conformal RT have a particularly important role in achieving significant total doses to primary malignant lesions of the spinal column that otherwise would be unachievable owing to the potential for substantial toxicity to the nearby normal tissues.

**Stereotactic Body Radiotherapy**

By design, stereotactic body radiotherapy (SBRT) is best applied to small treatment volumes, using fewer but significantly higher dose fractions, and steep dose gradients—all of which act in concert to maximize cell kill and minimize the risk of damage to normal tissues. Extracranial techniques for stereotactic RT have been investigated since the early 1990s and results from the treatment of medically inoperable, early-stage nonsmall cell lung cancer would indicate substantially improved local control compared to traditional external beam techniques. Preliminary data in lung cancer suggest that in addition to high levels of control, SBRT typically results in low rates of treatment-related toxicity.

Many institutions have investigated and reported clinical outcomes with SBRT in treating metastatic spinal tumors, both primarily and as re-treatment following clinical failure of previous radiation by standard dose-fractionation schema. Results indicate a high potential for prompt symptom relief and excellent rates of local control with minimal toxicity. An extensive discussion of SBRT is beyond the limits of this
review; please refer to the article on Stereotactic Radiosurgery by Levine in this issue.

**Proton Beam Therapy**

The use of protons in RT has received increased attention as a modality that is equally as effective as photons but with improved dose distributions. Proponents highlight the benefit of PT in the therapeutic ratio, as PT has the capacity to deliver similar or higher doses to malignant tissues while decreasing doses to the adjacent normal tissues. Although PT has not been extensively investigated clinically in spine applications, in principle this technique could prove beneficial in treating patients with larger tumor volumes, in compromised adjacent organ function, or in disease or symptom progression involving areas that were previously irradiated. Optimally, PT would be delivered to tumors that are more superficial than deep because of their physical properties.

PT takes advantage of delivering a particle, or proton, rather than an energy, which because of its significantly larger mass has a finite range in tissue. Clinically, this translates into a beam of “energy” derived from the proton’s interactions with tissue that generate full dose at the depth or level of the target with little to no exiting energy beyond the target. This technique substantially lowers the dose to nontargeted adjacent and downstream organs or structures, thereby reducing the risk of tissue injury and toxicity. The use of PT in spinal tumors is most notable in chordomas. Owing to the limited number of proton facilities and the generally well-tolerated use of other RT modalities, PT is not commonly used in the metastatic tumor setting currently.

**Conclusion**

RT has been used extensively in tumors of the spine, both primary and metastatic, for several decades. While used most commonly with palliative intent for metastatic lesions, further development of 3D conformal, intensity-modulated, stereotactic, and particle therapy techniques (such as proton beam) have changed the role of RT in several primary disease and metastatic disease settings. In specific tumor types, such as Ewing’s sarcoma, myeloid malignancies, or other primary sarcomas of bone, technical advances and results from past clinical trials have allowed for the expansion of RT’s application with improved local tumor control and patient outcomes primarily or as an adjuvant treatment following surgery. The future evolution of radiation therapy and its specific role in the treatment of both benign and malignant spinal tumors will be dependent on further clinical studies in a heterogeneous group of patients.

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