The role of postoperative radiation and coordination of care in patients with metastatic bone disease of the appendicular skeleton

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Abstract

Metastatic bone disease affects approximately 300,000 people in the United States, and the burden is rising. These patients experience significant morbidity and decreased survival. The management of these patients requires coordinated care among a multidisciplinary team of physicians, including orthopaedic surgeons. This article reviews the role of radiation therapy after orthopaedic stabilization of impending or realized pathologic extremity fractures. Orthopaedic surgeons have an opportunity to benefit patients with metastatic bone disease by referring them for consideration of post-operative radiation therapy. Further research into rates of referral and the effect on clinical outcomes in this population is needed.

Introduction

Metastatic bone disease affects between 280,000-330,000 people in the United States,[1,2] accounting for $12.6 billion or 17% of the direct cost associated with cancer care in the US annualy.[3] The burden of metastatic bone disease and healthcare system cost are projected to climb with the increasing age of the population and increased survival of cancer patients. Metastatic breast, prostate and lung cancers are the most common primary diagnoses, accounting for roughly 68% of all causes, with breast metastases alone accounting for one third.[1]

The presence of bone metastases curtails survival and increases morbidity by putting patients at risk for skeletal related events (SREs). SREs are adverse events related to metastatic bone disease, and can include pathologic fracture, palliative radiation therapy for bone pain, the need for surgical intervention, spinal cord compression or malignant hypercalcemia.[4] Yong *et al.* (2011) looked at a population-based cohort of Danish patients with breast cancer between 1999-2007 with the aim of describing survival differences caused by bone metastases, and metastases with a SRE. They reported 1-year and 5-year survival rates of 59% and 8.3% for metastases with no associated SRE, while SREs reduced survival to 40.2% and 2.5% at 1-year and 5-years, respectively. Compared to breast cancer patients without metastases to bone, the 1-year mortality rate ratio for those with metastatic disease who sustained a SRE was 14.4.[5] Norgaard *et al.* (2010) similarly identified over 23,000 Danish men with prostate cancer, finding 1-year and 5-year survival to be 47.4% and 2.7% with bone metastases alone, while a SRE reduced survival to 39.9% and 0.7% at 1 and 5 years, respectively. Compared to prostate cancer patients without metastases, the 1-year mortality rate ratio for those with metastatic disease who suffer an SRE was 6.6.[6]

Metastatic lesions, especially those occurring in the femur, put patients at risk for pathologic fracture leading to subsequent decrements in mobility, quality of life (QOL), and survival.[7,8] Van der Vildt *et al.* (2017) analyzed 202 patients with metastatic bone disease and found that pathologic fracture was independently associated with diminished QOL and increased patient anxiety and depression.[8] Saad *et al.* (2007) retrospectively analyzed 3049 patients with bone metastases from breast, prostate, and lung cancers as well as multiple myeloma. Their aim was to determine the effect of pathologic fracture on survival. Pathologic fractures occurred in 10-25% of the study population during the study period, corresponding to an increased risk of death between 20-32% compared to those without fracture.[9]

Identification and management of metastases that threaten bone integrity requires a multidisciplinary team of physicians including diagnostic radiologists, radiation oncologists, medical oncologists, palliative care, and orthopaedic surgeons.[13] Mirels developed a widely reported scoring system to predict pathologic fracture risk.[14] This system takes into account the location, size, and type of lesion, as well as the amount of pain the patient is experiencing, with a score over 8 suggesting the need for prophylactic stabilization. Other models suggest that radiographic evidence of a lesion that causes cortical destruction of > 50%, measures > 2.5 cm in diameter,[15] or has >3 cm of axial cortical involvement is predictive of impending fracture.[16] Computed tomography structural rigidity analysis has also been shown to estimate fracture risk but is not yet widely available.[17] Predicting which lesions are likely to fracture continues to be an active area of research.

Recognition of and treatment for impending fracture with prophylactic stabilization preserves function and may improve mortality, with evidence of lower intraoperative risk, less blood loss, shorter hospitalizations, and reduced overall cost in comparison to surgical management of pathologic fractures.[7,18-20] When a patient is stabilized either prophylactically or for a completed pathologic fracture, it is recommended that they receive palliative radiotherapy for pain relief and disruption of the mechanisms of tumor recurrence.[18,21-27]

Radiation therapy for bone metastases

External beam radiation therapy (EBRT) can reduce tumor burden, gain local tumor control, and act protectively in the postoperative period by inducing bone mineralization and reducing recurrence risk. An important effect of EBRT in metastatic bone disease is its ability relieve pain, making it a mainstay of palliative

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treatment.[28] EBRT delivers electromagnetic radiation directly to tumor cells, damaging DNA to an extent to which the tumor cell lacks the necessary molecular machinery to repair itself, resulting in tumor cell death. While this radiation energy damages healthy cells in the same manner, non-neoplastic cells generally have more robust repair mechanisms and replicate at slower rates. Nonetheless, while bone is one of most resistant organs to radiation, care is taken to avoid unnecessary inclusion of healthy tissue in the radiation field. Methods like dose fractionation gives healthy tissue time to heal between treatments and reduces systemic side effects such as fatigue.[29]

EBRT relieves pain in 50-80% of patients with metastatic bone disease, and up to 33% achieve complete pain resolution at the radiated site.[30-33] There have been multiple randomized trials and systematic reviews describing the most effective fractionation schedule to provide optimal palliative relief to patients with metastatic bone disease. Many studies have shown that even a single dose of 8Gy provides pain relief equivalent to that of multi-fractionated schedules.[32,33] While relief from pain is equivalent for patients receiving various fractionations who respond to therapy, it is not uncommon for patients to need additional treatment.[30] In patients electing to have 8Gy single fractionation, the need for re-irradiation is approximately 20% whereas multi-fractionated schedules have re-irradiation rates of 8% with a response rate to a second round of radiation approaching 58%.[34,35]

Controlling pain is an important consideration for recommending radiation therapy, but it is only one component of improved QOL. McDonald *et al*. (2017) analyzed QOL improvement scores at 10 and 42 days in 289 patients treated with EBRT. At 10 days, 41% of patients had a reduction in overall pain, number of painful sites and pain characteristics after ERBT. They simultaneously saw increases in QOL indexes such as physical and emotional functioning, psychosocial well-being and overall QOL as measured by the EORTC [Quality of Life Questionnaire Core 15 Palliative (QLQ-C15-PAL)] and Bone Metastasis Module patient reported outcome measures compared to non-responders. The reduction in pain and metrics for QOL continued to improve at 42 days. EBRT responders reported clinically significant improvements in physical, emotional, pain, fatigue, and global domains of the QLQ-C15-PAL compared to their non-responder counterparts.[36]

The literature robustly supports radiation therapy in the management of patients with metastatic bone disease. Patients presenting to orthopaedic surgery for evaluation of fracture risk from bone metastases should be referred for consideration of radiation therapy regardless of whether surgical intervention is indicated or pursued.

Postoperative radiation therapy benefits

EBRT plays a valuable role in the multimodal management of patients who present with painful metastasis. In combination with stabilization it can drastically improve quality of life. Townsend *et al.* (1995) reported that radiotherapy after stabilization was superior to surgical intervention alone.[23] They found that patients receiving postoperative radiation had significantly reduced pain levels and reached functional status (defined as normal use of extremity with no pain or normal use with pain) at a rate of 53% compared to only 11.5% who were treated with surgery alone. In addition, 17% of the surgery group required a second operation, while postoperative radiation was protective out to one year with no patients requiring additional surgical intervention.[23] Wolanczyk *et al.* (2016) examined postoperative outcomes in patients stabilized prophylactically or for pathologic fracture that subsequently received radiation, bisphosphonates, or both. Over the 1-year follow up period, patients treated with radiation therapy or radiation and bisphosphonates had fewer SREs than those treated with bisphosphonates alone (9% and 7% *vs*. 44%). Pain flares were also lower in both the groups treated with radiotherapy (19% and 16% *vs*. 67).[24] Van Geffen *et al.* (1997) observed a reduction in postoperative bone-related complications in patients who received postoperative radiotherapy from 21% to 14% when compared with patients who did not receive additional radiotherapy. While this observation did not reach statistical significance, they postulated that the additional radiation was responsible for preventing local tumor recurrence and reducing implant failure rates.[12] Beyond the studies discussed, there is a paucity of literature quantitatively addressing outcome differences between postoperative radiotherapy *vs*. surgical intervention alone. Willeumier *et al.* (2016) reviewed this literature and cites the low quality of evidence specifically for postoperative radiation, and notes that additional studies are needed to clarify the rationale and magnitude of benefit.[37] Pending further research, it is recommended to refer these patients for consideration of postoperative radiation therapy.[21-27]

Coordinating multidisciplinary care

Coordinating multidisciplinary care for patients with metastatic disease poses challenges. Cumming *et al.* (2009) published a study highlighting the need for clear data on the multidisciplinary hand-off between departments. They found that a group of oncologists treating patients with long bone metastasis failed to refer patients to orthopaedics at a consistent rate; 16/37 patients in this study had a Mirels score of 8 or greater, 5/37 had a score equal to 8, and 16/37 had a score less than 8. Only 4 of the 16 patients at highest risk for fracture were referred, and only one of the 5 patients with a score of 8 was referred. Only 5/28 oncologists participating in the study used a scoring system to assess for pathologic fracture risk.[38] Although the study conducted by Cumming *et a*l. is limited in scope and only addresses a single regional oncology center, Risteveski *et al.* (2009) looked at the population of Ontario, Canada and found a missed opportunity for prophylactic stabilization in 60% of their study population. They described a wide variation in the rate of prophylactic stabilization amongst regions (28-82%). The authors suggested varied surveillance practices for metastatic lesions as well as differing paradigms for referral to orthopaedics were the main factors leading to the reported disparity between regions.[39]

Galasko *et al*. (2000) reviewed referral patterns for patients with breast cancer within a single region of the United Kingdom (31 hospitals). They found 963 patients with complete records, 21% (207) of whom had documented painful skeletal metastases. Orthopaedic surgery was consulted for evaluation and treatment in only 22% of the metastatic cases. Of these 207 patients, 88 had one or more skeletal complications. Of these 88, 22 suffered pathologic fracture of the femur and were subsequently referred to orthopaedics for management. With improvement in referral it is likely that some of these metastatic lesions would have been prophylactically stabilized, circumventing the morbidity of realized fracture.[40]

One metastatic bone clinic in Toronto published their experiences with 272 patient referrals between 1999-2005, highlighting their in house multidisciplinary team-based approach to care and recommendations. The initial patient consultation consisted of an evaluation by an orthopaedic surgeon, a radiation oncologist and a pain specialist, resulting in a joint recommendation for treatment. 40% of patients received recom-

mendations for palliative radiotherapy, 19% underwent surgical stabilization, further investigation and imaging was warranted in 7%, and no direct action was taken in 25%. 11% of all patients that were referred were recommended to *other support service or listed as other*. While this paper did not delineate whether these patients received pre *vs*. postoperative radiation therapy and did not report outcomes, it highlights the efficiency in definitive treatment recommendations that stem from an interconnected multidisciplinary team.[41] These examples bring to light the importance of clear communication and appropriate referral as morbidity, mortality, and cost can be reduced with prompt management of impending pathologic fracture.[7,19,20,39]

Published guidelines and recommendations

It is clear from the literature that best practice for the care of patients with metastatic bone disease is a coordinated, cooperative, and communicative multidisciplinary team. The American College of Radiology,[25] American Society for Radiation Oncology,[34] British Association of Surgical Oncology,[42] British National Institute for Health and Clinical Excellence (NICE),[43] and Japanese Orthopaedic Association,[44] in conjunction with other national societies, have published recommendations in the management of metastatic bone disease. They conclude that patients presenting with metastatic bone disease and lesions concerning for impending fracture should see an orthopaedic surgeon for evaluation and possible stabilization as well as be treated with palliative EBRT regardless of surgical indication (Table 1).

Recommendations

We recommend that all patients who present with metastases to bone should be evaluated for their individual risk of pathologic fracture. Providers may find Mirels criteria[14], as well as the other predictive models, [15-17] to be useful indicators for need to refer to a larger center for multidisciplinary care. We strongly recommend prophylactic stabilization in patients who meet surgical criteria and have impending fracture risk as evidenced by Mirels criteria or objective radiographic evidence. The orthopaedic surgeon should refer their patients for consideration of radiation therapy regardless of their treatment plan. We recommend this referral occur immediately for the postoperative patient so that radiation therapy can start promptly, ideally within two to three weeks. The referral must be coordinated with all members of the care team, including medical oncology, to reconcile any overlap in plans for chemotherapy initiation or continuation.

Conclusions

Patients who present for evaluation and management of impending or pathologic fracture secondary to metastatic bone disease represent an opportunity for the orthopaedic surgeon to play an active role in driving the appropriate care of these medically complex patients. It is abundantly clear from the literature that radiation therapy for patients with metastatic bone disease is a key component of their care, regardless of whether or not a lesion requires operative intervention. Patients with impending pathologic fracture benefit from prophylactic stabilization and should have subsequent referral to radiation oncology for postoperative EBRT.

What is not clear from the literature is how often patients who get prophylactic stabilization or those treated for a pathologic fracture actually get referred for radiation therapy. As discussed, it seems that rates of referral to orthopaedics for prophylactic stabilization varies amongst provider groups and geographical regions. The contributing factors to this discrepancy, as well as potential deficiencies in referral rates from orthopedic surgeons to radiation oncology, remain unreported. More research is needed

Table 1. Guidelines and recommendations for metastatic bone disease.

Society	Surgical management	External beam radiation therapy
American College of Radiology[25]	Patient with a symptomatic femoral metastasis and risk for fracture should be referred to an orthopaedic surgeon for assessment for prophylactic stabilization.	Patients with prophylactic stabilization should be considered for postoperative radiotherapy. Pathologic fractures should receive postoperative radiation (30Gy, 10 fractions) EBRT should be initiated immediately in patients who do not undergo surgical intervention.
American Society for Radiation Oncology[34]	Surgical decompression and stabilization in patients with spinal cord compression or instability.	Postoperative EBRT in patients with single level spinal cord compression or instability unless life expectancy is too short. The use of surgery, radionuclide, bisphosphonates, or kyphoplasty/vertebroplasty does not obviate the need for palliative EBRT for painful bone metastases.
British Association of Surgical Oncology[42]	Apparent solitary bony metastases must be discussed at a multi-disciplinary meeting prior to treatment. Orthopaedic referral is always indicated when plain films show genuine erosion of bone. >50% cortical erosion represents inevitable impending fracture.	<50% cortical erosion, radiotherapy can be considered without prophylactic fixation. EBRT is palliative and should normally be given post-stabilization once wound is healed.
Japanese Society of Medical Oncology, Japanese Orthopedic Association, Japanese Urological Association, and Japanese Society for Radiation Oncology[44]	Surgery is beneficial for pain relief and/or functional improvement. Improvement in pain, limb function, and QOL with surgical intervention for pathologic or at risk fractures. Better outcomes with surgery for at risk fracture.	EBRT is beneficial for relief of pain. Fixation of damaged cortex of femoral metastasis >3 cm in longitudinal length necessary before irradiation.
NICE Guidelines (2009)[43]	An orthopaedic surgeon should assess all patients at risk of a long bone fracture, to consider prophylactic surgery.	Use external beam radiotherapy in a single fraction of 8Gy to treat patients with bone metastases and pain.

to define rates of referral and potential barriers to routine radiation care for these patients.

Opportunities for future research include investigating national rates of referral from orthopaedics to radiation oncology for radiation therapy in patients who receive stabilization, and determining whether that rate varies regionally. The same question can be applied to other referral practices between other disciplines that care for patients with metastatic bone disease. Future research into these topics would help providers identify and implement best practices and could lead to improved interdisciplinary communication and patient care.

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