Palliative Radiotherapy for Prostate Cancer

By Matthew J. Boyer, MD, PhD, Joseph K. Salama, MD, and W. Robert Lee, MD, MS, MEd

This review will include discussion of the role of radiation therapy for osseous metastases and metastatic spinal cord compression, as well as the use of radiopharmaceuticals for painful osseous metastases.

Introduction

Radiotherapy has been used to palliate the symptoms of advanced and metastatic prostate cancers since shortly after the discovery of x-rays and radioactivity. As early as 1909, radium bromide was shown to relieve obstructive urinary symptoms, hematuria, tenesmus, and pain from an advanced prostatic sarcoma. An early report following deep Roentgen-ray therapy for prostate cancer noted, “cessation of hemorrhage is often immediate and deep-seated pain of a very severe character...due to metastases in the spine and pelvis, generally disappears almost completely.” Radiotherapy’s palliative benefit for prostate cancer was recognized by Drs. Young and Waters of Johns Hopkins, who stated, “[Following radiotherapy] we have a great number...relieved of severe symptoms, and in many instances passed the remainder of [their] days in comparative comfort.”

Today, prostate cancer is the most commonly diagnosed noncutaneous malignancy in American men. Palliation may be required for symptomatic metastatic disease in the lymph nodes or bones or, less often, for local symptoms such as mechanical obstruction of the bladder or rectum, hematuria, and pain. Radiation remains a mainstay of palliation of these symptoms, given its effectiveness, noninvasive nature, and relative ease of administration. This review will include discussion of the role of radiation therapy for osseous metastases and metastatic spinal cord compression, as well as the use of radiopharmaceuticals for painful osseous metastases. Additionally, we will discuss the limited data on bladder outlet obstruction and hematuria, and we will present information on a newer radiation technique, stereotactic body radiation therapy (SBRT), which is being integrated into standard palliative schemes for spinal metastases and oligometastases.

External Beam Radiation Therapy (EBRT) for Osseous Metastases

The predilection of prostate cancer for spreading to bone in the form of osteoblastic metastases is well known. Approximately two-thirds of prostate cancer patients have osseous metastases at autopsy, and over 90% of patients with metastatic castration-resistant disease have evidence of osseous metastases. Recent advances in systemic therapies have resulted in a reduction of prostate cancer skeletal events, but painful skeletal metastases remain common. For more than 4 decades, EBRT in the treatment of painful metastases has been studied in prospective, and frequently randomized clinical trials. Prospective trials that include men with painful skeletal metastases from prostate cancer have studied a wide variety of fractionation schedules. The accumulated evidence from phase III studies and meta-analyses demonstrates no difference in clinical response rates between single-dose and more fractionated radiation schedules. For example, the Radiation Therapy Oncology Group (RTOG) 9714 trial randomized nearly 900 patients with osseous metastases, 50% from prostate cancer, to either 8 Gy in 1 fraction or 30 Gy in 10 fractions. No significant difference in patient-reported pain response at 3 months was observed, with 15% complete response and 50% partial response in the 8-Gy arm, vs 18% and 48% following radiation therapy to a dose of 30 Gy. When limited to patients with vertebral metastases, a common occurrence in prostate cancer, no difference in pain relief or freedom from narcotic use was seen. Similar findings with equivalent pain response were observed when a single 8-Gy fraction was compared with 24 Gy in 6 fractions, and when a single 8-Gy fraction was compared with 20 Gy in 5 fractions or 30 Gy in 10 fractions. A meta-analysis of 16 randomized trials, involving almost 5,000 patients undergoing palliative radiation for painful osseous metastases, confirms similar rates of pain control for single-fraction vs...
multi-fraction schedules.[12] Data from this analysis indicate near identical overall responses (Figure, A) and complete responses (Figure, B) in both large and small trials. Of the eight trials reporting progression to pathologic fracture or the five studies reporting progression to cord compression, there was no significant difference between single- and multiple-fraction treatment regimens. Consistent with radiobiological principles, two trials showed an increase in acute toxicity with prolonged treatments compared with single treatments.

For prostate cancer patients with an anticipated long life expectancy, durability of treatment effect is an important concern when deciding on the appropriate radiation treatment schedule. In all of the aforementioned studies, higher retreatment rates (~20%) were observed following 8 Gy of radiotherapy. It remains unclear whether the higher retreatment rate is due to decreased durability of palliation or physician willingness to retreat following a single dose. Nevertheless, a survey of three professional radiation oncology organizations in the United States, Canada, and Australia/New Zealand showed prognosis to be the most considered factor regarding the decision between single- and multi-fraction schedules.[13] The predilection for multi-fraction schedules was much greater among practitioners in the United States. A recent Surveillance, Epidemiology and End Results (SEER) program–Medicare analysis of 3,050 patients treated for bone metastases from 2006 to 2009 showed that only 3.3% of patients (primarily those with poor prognosis) were treated with a single fraction, and 50.3% received more than 10 treatments.[14] Clinicians in Canada, Australia, and New Zealand were four to five times more likely to use a single fraction of radiation.[15]

For prostate cancer patients treated with a single fraction of radiation who experience pain recurrence, retreatment with lower doses than the commonly prescribed 8 Gy has been shown to achieve similar levels of pain control.[16] In a meta-analysis of bone metastases retreatment, a 58% response to a second course of radiation was reported, with response most common when single-fraction radiation therapy was used.[17] A recently reported randomized trial of 850 patients (27% with prostate cancer) compared retreatment of previously irradiated painful osseous metastases with either a single 8-Gy fraction or 20 Gy in 5 fractions.[18] Both the intent-to-treat analysis (8 Gy, 28%; 20 Gy, 32%) and the per-protocol analysis (8 Gy, 45%; 20 Gy, 51%) demonstrated significant overall pain relief and decreased opioid use following either retreatment schedule, even in patients who had not responded to their initial course of radiation.

In terms of pain relief, a single fraction of radiation is equivalent to more protracted schedules. This concept was recently incorporated into the American Society for Radiation Oncology (ASTRO) “Choosing Wisely” campaign for appropriate treatment, in which ASTRO advised that, “[s]tudies suggest equivalent pain relief following 30 Gy in 10 fractions, 20 Gy in 5 fractions, or a single 8-Gy fraction. A single treatment is more convenient but may be associated with a slightly higher rate of retreatment to the same site. Strong consideration should be given to a single 8-Gy fraction for patients with a limited prognosis or with transportation difficulties.”[19] For patients who need retreatment, a second course of radiation, either with another single dose or with five doses, is associated with equivalent and meaningful pain responses.

Metastatic Spinal Cord Compression

Metastatic spinal cord compression (MSCC) is a potentially debilitating consequence of cancer that affects approximately 10% of patients.[20] It is most often due to vertebral column metastases invading the epidural space. With prolonged compression, infarction of the cord can cause permanent paralysis, depending on the region of the cord involved. MSCC is more commonly seen in prostate cancer patients than in those who have cancer at other disease sites, as a result of the high percentage of prostate cancer bone metastases involving the vertebral column, purportedly from spread via the Batson plexus.[21] For many years, the mainstays of treatment were the prompt initiation of corticosteroids, to reduce edema, and EBRT (except where pathologic fracture with cord impingement necessitated surgical intervention).[22] However, in highly selected patients (such as those with limited metastases, good performance status, or < 48 hours of paraplegia) who were surgical candidates, surgery in addition to radiation improved the ability to walk, both for patients who were ambulatory prior to treatment (with 94% of those treated with surgery plus radiation able to walk vs 74% of those treated with radiation alone) and for patients who were non-ambulatory (62% vs 19%, respectively). Moreover, patients treated with upfront surgery had longer overall survival and improved continence.[20]

For men with MSCC from prostate cancer who are not surgical candidates, 30 Gy in 10 fractions remains a standard therapy. Limited extraspinal metastases, better performance status, and longer interval from initial diagnosis to MSCC have been associated with improved survival.[23] Grouping...
prostate cancer patients based on five factors, including ambulatory status (ambulatory or not), Eastern Cooperative Oncology Group (ECOG) performance status (1/2 vs 3/4), other bone metastases (yes vs no), visceral metastases (yes vs no), and interval from cancer diagnosis to radiotherapy (< 15 months or > 15 months), has provided robust prognostic information. The 6-month survival rate divided by 10 was used as the score for each individual factor; the sum of the scores for the 5 prognostic factors was shown to correlate with overall survival and was used to divide patients into 3 groups. Men who were nonambulatory, had other sites of metastatic disease, and had shorter intervals from diagnosis—Group I—had poorer survival (median, 6.5 months), while men with some (Group II) or none of these characteristics (Group III) had significantly longer survival (medians of 44.6 months vs 95.8 months, respectively). This grouping may be useful to clinicians when selecting appropriate radiation doses to manage spinal cord compression, providing support for the use of shorter radiation courses (8 Gy × 1 and 4 Gy × 5) for men categorized as Group I, while reserving longer fractionation schedules (3 Gy × 10, 2 Gy × 20, 2.5 Gy × 15)—which have been associated with improved local control—and neurosurgical intervention for men in groups II and III.[24,25]

Re-irradiation for recurrent MSCC is increasingly considered as a treatment option, given the improved understanding of both spinal cord recovery from radiation injury[26] and the impact of second courses of radiation on the potential for myelopathy.[27] Following re-irradiation for prostate cancer MSCC, a response rate of 84% was seen; 42% of patients had improvement in neurologic symptoms, while symptom progression halted in an additional 42%. [24] Despite these data, many practitioners are reluctant to offer a second course of radiotherapy for fear of causing permanent radiation-induced spinal cord injury.

**Hemibody Irradiation**

Men with prostate cancer often present with multiple sites of painful osseous metastasis. The randomized trials described above for palliation of painful osseous metastases consisted of patients with one to three sites of disease[28] or disease that could be treated within one radiation field.[10] Hemibody irradiation, which involves the delivery of radiation to large treatment volumes and encompasses multiple individual metastases, remains a treatment option for men with more diffuse painful osseous metastases.[29] Application of larger-field radiation has been associated with earlier responses than smaller-field radiotherapy, with 80% of patients who did respond showing improvement at 1 week and 50% of this group doing so at 2 days.[30] However, given the large volume of normal tissues irradiated, toxicity has been a concern. Phase I studies have demonstrated that a single fraction of 6 Gy to the upper body and 8 Gy to the lower body could be safely administered.[30] When local-field irradiation was combined with hemibody irradiation in 499 patients (33% with a prostate cancer primary), the combination therapy was associated with a longer median time to new disease (12.6 months vs 6.3 months).[31] However, this came at the price of significantly more grade 3/4 hematologic and grade 2/3 gastrointestinal toxicity.

In an attempt to reduce the toxicity of hemibody irradiation, particularly in prostate cancer patients who live long enough for toxicities to manifest, studies have focused on approaches to further optimize the radiation dose by fractionating the hemibody course. The International Atomic Energy Agency conducted a phase III study in developing countries comparing a standard hemibody regimen—5 fractions of 3 Gy[32]—with 2 experimental arms: 2 fractions of 4 Gy on the same day, or 4 fractions of 3 Gy delivered twice daily on 2 consecutive days. Ninety-one percent experienced pain relief. The median time to any pain relief in all arms was quite rapid—3 days—and time to maximum pain relief was 9 days. Grade 3/4 toxicity was seen in 12%. Men with prostate cancer fared best in the control arm, where they even exhibited a significantly improved survival compared with the other two arms ($P = .006$).

For men with diffuse painful prostate cancer metastases, hemibody irradiation is an effective tool for rapid pain relief, especially when radiopharmaceuticals are not appropriate or available. A hemibody irradiation schedule of 5 fractions of 3 Gy is associated with good pain control, while minimizing the risk of toxicity.

**Radiopharmaceuticals**

For patients with diffuse painful osteoblastic metastases, an alternative to hemibody radiotherapy is systemically delivered bone-seeking radiopharmaceuticals. Based on their chemical properties, these medicines localize to bone, delivering short-path-length beta or alpha radiation, which has been shown to have a significant positive impact on patients’ quality and quantity of life. By avoiding the entrance and exit dose of external radiation, toxicity is usually limited to the nearby marrow. The
effects of beta-emitters (strontium-89, samarium-153, and rhenium-186) have been reviewed previously and will not be considered here further.[33]

Radium-223 is an alpha-emitter. It is a bone-seeking calcium mimetic that preferentially targets regions of high bone turnover, emitting high-energy alpha particles and inducing primarily double-strand DNA breaks. Its short range (< 100 μm) limits damage to surrounding marrow and other normal tissues. Compared to beta-emitting radiopharmaceuticals, alpha particles have a higher relative biologic effectiveness. In a phase II study, use of radium-223 in men with castration-resistant prostate cancer (CRPC) significantly reduced levels of bone alkaline phosphatase (the primary endpoint), and was associated with strong trends for reduced skeletal events ($P = .065$) and improved survival ($P = .066$, log-rank).[34]

These findings were confirmed by a recently published phase III trial that included men with CRPC without visceral metastases but with at least two symptomatic osseous metastases.[6] Enrolled men had either progressed on, or were not candidates for, docetaxel. Additional requirements included a minimum prostate-specific antigen (PSA) level of 5, an ECOG performance status of 0–2, and a life expectancy of 6 months. Patients were randomized to 6 intravenous injections of 50 kBq/kg of radium-223 every 4 weeks or placebo. This study was stopped early when a planned interim analysis showed that patients treated with radium-223 had improved median survival compared with those who received placebo (14.9 months vs 11.3 months, respectively; $P < .001$) and a 30% reduction in the risk of death (hazard ratio = 0.7; 95% confidence interval, 0.58–0.83; $P < .001$). Furthermore, the group treated with radium-223 had an improved time to first skeletal-related event (as indicated by use of EBRT, new symptomatic pathologic fractures, spinal cord compression, or tumor-related orthopedic surgical intervention) (15.6 months vs 9.8 months; $P < .001$) and objective improvements in quality of life as measured by a > 10-point increase in scores on the Functional Assessment of Cancer Therapy–Prostate (FACT-P) tool. These results were achieved without significantly more grade 3/4 toxicity compared with placebo, and with similar rates of hematologic toxicity, despite the fact that 57% of patients had been previously treated.

**SBRT for Palliation**

Recently, SBRT—a combination of advanced immobilization, planning, imaging, and treatment delivery techniques—has enabled delivery of fewer, more focused doses of ablative radiation to tumor(s) while reducing the radiation exposure of normal tissues.[35] SBRT has been adopted as standard therapy for medically inoperable early-stage non–small-cell lung cancer,[36] and is being actively investigated to treat primary tumors of the prostate, pancreas, kidney, and liver.[37-40] SBRT is also under active investigation for treatment of vertebral metastases, including those in men with prostate cancer. Because retreatment rates following standard palliative radiotherapy average 20%,[12] and because there are increasing lines of systemic therapies available for prostate cancer,[41] men are living longer and experiencing progressive spinal metastases that can be quite morbid. Following conventional radiation for spinal metastases in men with recurrent tumors > 5 mm from the spinal cord, SBRT has been shown to result in high rates (67%-87%) of control of the treated tumor, as well as freedom from neurologic progression, with limited toxicity.[42-44] Additional investigations have evaluated SBRT using single[42] or multiple[45] fractions as the initial treatment for spinal metastases. Although a small percentage of patients in one such study had prostate cancer,[46] high rates of treated-tumor control (72.4%-91%) were seen. Additionally, following SBRT, the percentage of pain-free patients in the study increased from 26% to 54%, and opioid use decreased significantly. Evidence is emerging, however, that vertebral body fracture within the first 6 months after SBRT is a significant complication, occurring in ~14% of patients following spinal SBRT.[47] Vertebral compression was particularly high for men treated with doses > 20 Gy, as well as for those with lytic metastases, prior vertebral body compression fracture, or spinal deformity.

Based on these preliminary data demonstrating high rates of pain control in patients with spinal metastases initially treated with SBRT, the RTOG 0631 trial (ClinicalTrials.gov ID number NCT00922974) is randomizing patients with spinal metastases (including men with prostate cancer) to either a single conventionally delivered 8-Gy dose or a single SBRT dose of 16–18 Gy. The investigators hypothesize that image-guided radiosurgery/SBRT will result in a 40% improvement (from 51% to 70%) in the proportion of patients experiencing pain relief at 3 months compared with EBRT. The randomized phase II portion of the study has been completed and the phase III study is ongoing.
SBRT for Limited Metastatic Disease

Not all men with metastatic prostate cancer present with diffuse disease. Autopsy\cite{48} and longitudinal studies\cite{49} suggest that the majority of men have fewer than 5 metastases present more than 10 years after diagnosis. Therefore, there may be a subgroup of patients in the clinical state of oligometastasis, in whom metastasis-directed therapy for all known disease may render them disease-free for long periods of time.\cite{50} Small single-institution series have shown that SBRT delivered to osseous metastases\cite{51,52} and pathologic lymph nodes\cite{52-54} results in high rates of treated-metastasis control, as summarized in Table 2. Prospective studies are underway to determine the utility of SBRT as a means of deferring initiation of androgen suppression therapy in men with hormone-sensitive prostate cancer.

Bladder Outlet Obstruction

Local progression of the primary tumor accounts for 15% to 20% of cases of CRPC.\cite{55} Because of the proximity of the prostate to the bladder and rectum, local progression may present clinically with symptoms of bladder outlet obstruction, hematuria, and rectal obstruction. Although no large prospective trials have evaluated the role of radiation to palliate locoregionally advanced prostate cancer, a number of retrospective, single-institution studies have shown a benefit. One of the most recent and largest reports detailed outcomes of 58 patients treated for locally advanced prostate cancer from 2003 to 2007 with 20 Gy in 5 fractions.\cite{56} Six weeks following treatment, 81% had improvement in hematuria, 88% had improvement in rectal obstruction, and 75% had improved urinary outlet obstruction. A review of nine studies, which were published between 1972 and 2009 and included 104 patients, demonstrated symptom improvement in 75% of treated patients, with response rates ranging from 62% experiencing symptom improvement for ureteric obstruction to 80% experiencing improved pain symptoms.\cite{55}

Conclusions

Radiotherapy is an effective tool for palliation of symptoms commonly caused by prostate cancer. The majority of painful bone metastases respond equally well to single or multiple fractions of external radiotherapy. Retreatment with a second course of radiation induces pain responses in approximately 50% of patients. For more diffuse metastases, either hemibody radiation or systemic radiopharmaceuticals can reduce pain, and radium-223 is associated with improved survival in men with CRPC. Hematuria, bladder outlet obstruction, and rectal compression are all improved with palliative radiotherapy. The ability of SBRT to reduce pain compared with standard EBRT is being investigated, as is the role of SBRT in treating patients with limited metastatic disease.

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Table 1: Summary of Prospective Randomized Studies Identified by Chow ...
Table 2: Summary of Studies Reporting Outcomes of Oligometastatic Prostate Cancer

References:


