Palliative Radiotherapy for Bone Metastases: An ASTRO Evidence-Based Guideline

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This document was prepared by the Guidelines Subcommittee of the Clinical Affairs and Quality Committee of the American Society for Radiation Oncology (ASTRO) in coordination with the Third International Consensus Conference on Palliative Radiotherapy.

Before the initiation of this Guideline, all members included on the Task Force were required to complete conflict of interest statements. These statements are maintained at ASTRO Headquarters in Fairfax, VA, and pertinent conflict information is published with the report. Individuals with disqualifying conflicts have been recused from participation in this Guideline.

Adherence to this Guideline will not ensure successful treatment in every situation. Furthermore, this Guideline should not be deemed inclusive of all proper methods of care or exclusive of other methods of care reasonably directed to obtaining the same results. The ultimate judgment and propriety of any specific therapy must be made by the physician and the patient in light of all the circumstances presented by the individual patient. ASTRO assumes no liability for the information, conclusions, and findings contained in its Guidelines. In addition, this Guideline cannot be assumed to apply to the use of these interventions performed in the context of clinical trials, given that clinical studies are designed to evaluate or validate innovative approaches in a disease for which improved staging and treatment are needed or are being explored.

This Guideline was prepared on the basis of information available at the time the Task Group was conducting its research and discussions on this topic. There may be new developments that are not reflected in this Guideline, and that may, over time, be a basis for ASTRO to consider revisiting and updating the Guideline.

Conflict of interest: Arjun Sahgal and Eric Chang have served as consultants to Medtronic Kyphoplasty, though that relationship has ended and the authors did not participate in either the writing or reviewing of the kyphoplasty section of this manuscript. Lisa Kachnic serves as a consultant to Soligenics. David Howell serves as a consultant to Web MD, Medscape. Stephen Lutz has stock ownership in Tosk, Oculus, and Minerva. Charles von Gunten has received funding from Wyeth, Progenics, Baxter, and Halozyme. William Hartsell has a partnership relationship with CPTI. Peter Hoskin has received funding from Varian Medical Systems and Nucleotron. Edward Chow has received research funding and teaching honorarium from

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ABSTRACT

Purpose: To present guidance for patients and physicians regarding the use of radiation therapy in the treatment of bone metastases based upon current published evidence and complemented by expert opinion.

Methods and Materials: A systematic search of the National Library of Medicine's PubMed database between 1998 and 2009 yielded 4287 candidate original research articles potentially applicable to radiotherapy for bone metastases. A Task Force composed of all authors synthesized the published evidence and reached consensus regarding the recommendations contained herein.

Results: The Task Force concluded that external beam radiotherapy (EBRT) continues to be the mainstay for the treatment of pain and/or prevention of morbidity caused by bone metastases. Various fractionation schedules may provide significant palliation of symptoms and/or prevent the morbidity of bone metastases. The evidence for the safety and efficacy of re-treatment to previously irradiated areas of peripheral bone metastases pain is derived from both prospective studies and retrospective data, and it has been shown to be safe and effective. The use of stereotactic body radiotherapy was seen to hold theoretical promise in the treatment of new or recurrent spine lesions, though the Task Force recommended that its use be limited to selected patients preferably treated on a prospective trial. Surgical decompression and post-operative radiotherapy is recommended for spinal cord compression or spinal instability in highly selected patients with sufficient performance status and life expectancy. The use of bisphosphonates, radionuclides, vertebroplasty and kyphoplasty for the treatment or prevention of cancer related symptoms does not obviate the need for EBRT in appropriate patients.

Conclusions: Radiotherapy is a successful and time efficient means by which to palliate pain and/or prevent the morbidity of bone metastases. This Guideline reviews the available data to define its proper use and provides consensus views concerning contemporary controversies or unanswered questions that warrant prospective trial evaluation.

INTRODUCTION

Bone metastases are a common manifestation of malignancy that can cause severe and debilitating effects including pain, spinal cord compression, hypercalcemia, and pathologic fracture. The proper care of bone metastases patients requires interdisciplinary care between radiologists, radiation oncologists, medical oncologists, surgeons, pain medicine specialists, and palliative care professionals. Radiation therapy provides successful palliation of painful bone metastasis that is time efficient and associated with very few side effects. External beam radiation therapy (EBRT) provides significant palliation of painful bone metastases in 50 to 80% of patients, with up to one-third of patients achieving complete pain relief at the treated site.[1]

A widespread variation exists in worldwide practice patterns for palliative radiation dose fractionation schedules.[2] Numerous prospective randomized and retrospective trials have shown similar pain relief outcomes with single fraction radiation therapy schedules compared to longer courses of palliative radiation for previously un-irradiated bone metastases, with the main advantages to the schedules being increased convenience with a single fraction and lower re-treatment rate with a longer course.[1, 2] A wide range of radiotherapeutic options also exists for pain that recurs after radiation (EBRT or radiopharmaceuticals) is delivered for bone metastases. Among these options is a second course of EBRT to the same localized site (re-irradiation), while painful bone lesions at several anatomic sites have been treated with injectible radiopharmaceuticals or hemi-body radiotherapy, depending upon tumor histology and the distribution of metastases. Additionally, great interest has been devoted to the question of whether technological advances in radiotherapy delivery, such as stereotactic body radiotherapy (SBRT), may improve the results of the primary treatment or re-treatment of metastatic spine

lesions. Circumstances of spinal cord compression with complete or impending pathologic fracture demand a coordinated care plan between surgeons and radiation oncologists. While clinical trials with bisphosphonates initially used the need for EBRT as a failure of therapy endpoint, EBRT to the index symptomatic lesion may provide more prompt and durable symptom relief. Finally, EBRT should be used in conjunction with both kyphoplasty and vertebroplasty in patients who are treated with these interventions for spine metastases.

Given the complexities of care for patients with bone metastases and the relative lack of palliative radiotherapy guidelines formulated to date, the American Society for Radiation Oncology (ASTRO) Clinical Affairs and Quality Committee convened a Task Force of experts to develop a Guideline regarding the care of patients with bone metastases.[3-6] Recommendations are based upon the results of a systematic literature review combined with the expert opinions of the Task Force members. The Guideline is presented herein.

METHODS AND MATERIALS

Process

The Guidelines Subcommittee of the Clinical Affairs and Quality Committee, in accordance with established ASTRO policy, recruited a Task Force composed of recognized experts in the fields of palliative radiotherapy for bone metastases. Those experts represent radiation oncology academic, private practice, and residency groups as well as neurosurgery and palliative medicine specialties. The Task Force was asked to provide guidance on the use of palliative radiotherapy for bone metastases to patients and physicians. The Task Force was also charged with providing

guidelines for the proper integration of radiotherapy with other available treatment options for patients with bone metastases.

In October 2009, the ASTRO Board of Directors approved a proposal to develop a Guideline regarding palliative radiotherapy for bone metastases and also authorized the membership of the Task Force. Subsequently, the Task Force participated in a series of communications by email and conference calls to compose the Guideline. The members of the Task Force divided into subgroups to address separate questions based upon their areas of particular expertise. All members of the Task Force then evaluated the responses to the questions assigned to the subgroups. After the secondary review by the Task Force as a whole, the initial draft of the Guideline was sent to external reviewers. The ASTRO Board of Directors integrated this feedback and approved the final document in July 2010.

Literature search

Whenever possible, the Guideline relies on an evidence-based approach using a formal systematic literature review. One author (S.L.) with aid from the ASTRO staff searched for English-language citations in the National Library of Medicine's PubMed database through December 22, 2009 using the Medical Subject Heading term "Radiotherapy bone metastases," limiting results to the years 1998 through 2009. Of 4287 articles originally identified, the group's specific research questions were approached by searching for combinations of the following key words: single, fraction, radiation therapy, spine, toxicity, side effects, retreatment, re-treatment, highly conformal therapy, Cyberknife, IMRT, stereotactic body, tomotherapy, spinal cord compression, surgery, kyphoplasty, vertebroplasty, meta-analysis, metaanalysis, radionuclides,

radiopharmaceuticals, or bisphosphonates. Of this sample, they identified 25 randomized clinical trials, 20 prospective single-arm studies, and 4 meta-analyses/systematic reviews.

Bibliographies of candidate studies were also reviewed to ensure that all eligible studies were evaluated, including those published prior to 1998. Some topics were defined by data that was nearly completely or exclusively retrospective in nature, though the Task Force attempted to minimize the use of retrospective data and tempered any recommendations it made based upon that data. All prospective clinical studies were reviewed by the authors addressing the questions from that subtopic, and one author (S.L.) reviewed all of the prospective studies from every topic. The prospective studies were abstracted for inclusion criteria, radiotherapy methods, clinical outcomes, and toxicity.

RESULTS

The questions and guideline statements regarding the use of palliative radiotherapy for bone metastases are listed below.

1) What fractionation schemes have been shown to be effective for the treatment of painful and/or prevention of morbidity from peripheral bone metastases?

Guideline statement. Multiple prospective randomized trials have shown pain relief equivalency for dosing schema including 30 Gy in 10 fractions, 24 Gy in 6 fractions, 20 Gy in 5 fractions, and a single 8 Gy fraction for patients with previously un-irradiated painful bone metastases. Fractionated treatment courses are associated with an 8% re-treatment to the same anatomic site

due to recurrent pain versus 20% after a single fraction, while the single fraction treatment approach optimizes patient and caregiver convenience.[1]

Narrative. An international survey showed 101 different dose schedules in common use for the treatment of painful bone metastases with EBRT.[2] Multiple trials have been performed comparing a single fraction to multiple fraction courses of EBRT for palliation of painful bone metastases.[7-33] (Table 1). The multiple fraction regimens have shown some dosing variance between studies, but the single fraction arm has typically been given as a dose of 8 Gy. The control arms have included 30 Gy in 10 fractions, 24 Gy in 6 fractions, 20 Gy in 5 fractions, and 20 Gy in 4 fractions. The endpoints for these studies always evaluated pain relief, but also evaluated narcotic relief, quality of life measures, rates of pathologic fracture and retreatment rates.

All of the completed studies for either a single 8 Gy fraction or multiple fractions have confirmed similar rates of pain relief varying from 50%-85% for peripheral and vertebral bone metastases. This variability in the rates of pain relief reflects differing methods of pain measurement and definition of pain relief. Despite the variation in the definitions and measurement of pain among these individual trials and meta-analyses, the two palliative radiation fractionation schedules have consistent rates of pain relief, sometimes differing by less than one percent.[34] The frequency and severity of side effects, especially in mucosal structures, are the same or less than those experienced with a multiple-fraction regimen, and are more a function of treatment planning than radiation dose fractionation.[29]

Comment: A recently completed worldwide survey of radiation oncologists suggested that differences in attitudes concerning the preferred radiotherapy fractionation for painful bone metastases relate to many factors including prognosis, risk of spinal cord compression, and performance status. Still, a statistically significant smaller proportion of radiation oncologists in the United States employed a single fraction of palliative radiation for bone metastases in peripheral bones and in the spine when compared to their counterparts in other countries. This lower utilization of single fraction palliative radiation in the United States occurs even in cases where patients fit the eligibility criteria for those previously completed randomized trials. The authors concluded that there has been a delay in the incorporation of evidence into practice for the choice of fractionation for painful bone metastases, and the Task Force suggests that those results be translated to changes in patterns of care.[1, 2]

2) When is single fraction radiotherapy appropriate for the treatment of painful and/or prevention of morbidity from uncomplicated bone metastasis involving the spine or other critical structures?

Guideline statement. Though many of the studies presented in Table 1 did not delineate treatment relief by spine versus non-spine metastases, the Task Force could find no evidence from reviewing the data to suggest that a single 8 Gy fraction provides inferior pain relief to a more prolonged course of treatment in painful spine sites, though single fractionation is associated with a 20% incidence of re-treatment versus 8% with fractionated therapy.[17, 20, 22, 27, 29, 30, 32, 33] The set-up and prescription points for treatment should follow those outlined by the International Consensus on Palliative Radiotherapy Endpoints for future clinical trials in bone metastases to minimize risk and to allow for consistent reporting of treatment results.[35] The Task

Force does not feel that any additional trials are needed to confirm the use of single fraction therapy in these circumstances.

Narrative. Spine metastases are defined in this Guideline as metastatic lesions involving the vertebral bones, with or without extraosseous extension, located anywhere from the first cervical level through the sacrum. There is no evidence that painful bone metastases in the spine have a different response to single fraction therapy compared to other sites in the body. A subset analysis from RTOG 97-14 showed no difference in pain or narcotic relief in spine sites compared to extremity sites and no difference in response between cervical spine, thoracic spine or lumbar spine sites.[29]

As acute radiation reactions are generally greater and are more prolonged during multi-fraction radiation (smaller radiation dose per fraction over many weeks) versus a single large fraction of radiation over a single treatment day, single fraction radiation has an advantage over multi-fraction radiation.[29] Additionally, the resolution of acute radiation reactions begins upon completion of the course of radiation, making the overall time spent with acute radiation reactions shorter with single fraction radiation. The incidence of a temporary flare of bone pain may be higher with single fraction treatment, but anti-inflammatory medications are helpful to minimize this symptom.[36] Treatment to large fields including the stomach (for example, over the lower thoracic spine) may be associated with nausea with either single fraction or multiple fraction treatment. Prophylactic anti-emetics typically will prevent or minimize this symptom whether administered after a single fraction of radiation, or over two to three weeks of multi-fraction palliative radiation.

Although studies have reported fewer acute side effects with a single 8 Gy fraction, single fraction radiation is associated with a 2.0 to 2.5 times higher incidence of re-treatment due to persistent or recurrent pain. There are some situations in which alternative treatment schedules should be considered: 1) in patients where the need for retreatment would be problematic, 2) in patients with previous treatment to the spine, 3) in those with femoral axial cortical involvement greater than 3 cm in length, 4) in those who have undergone a surgical stabilization procedure, and 5) in those patients with spinal cord compression, cauda equina compression or radicular nerve pain.[1, 3, 4, 37] One prospective randomized study suggested that patients with radicular pain who received 8 Gy in a single fraction had slightly worse response rates compared to those who received 20 Gy in 5 fractions, although the difference was not statistically significant.[27]

Treatments to the spinal bones should be prescribed to the mid-vertebral body, with inclusion of at least one vertebral body above and below the painful vertebral body level or levels. Other sites should be prescribed as an applied dose for single incident fields and a mid-plane dose for opposed fields, taking into account the normal tissue tolerance of those structures included in the treated volume. Long bone lesions should be treated with at least a 2 cm margin proximal and distal to the radiographically evident abnormality. Simulation and verification films should be completed in all cases to document target localization.[35] The treatment techniques for patients receiving SBRT should be those described in the protocol offered to the patient.

3) Are there long term side effect risks that should limit the use of single fraction therapy?

Guideline statement. The Task Force did not find any suggestions from the available data that single fraction therapy produces unacceptable rates of long term side effects which might limit this fractionation scheme for patients with painful bone metastases. Numerous prospective,

randomized trials have failed to show any significant difference in long-term toxicity between a single 8 Gy fraction and more prolonged therapy courses for uncomplicated, painful bone metastases. No additional studies are suggested to confirm this recommendation at this time.

Narrative. The long term side effects of radiotherapy for bone metastases may include delayed bone remodeling and rare cases of radiation myelopathy. The most recently completed trials that compare single- to multi-fraction radiotherapy schedules suggest either a statistically insignificant or clinically insignificant difference in the rates of late fractures of the treated bones, with incidences ranging from 2-11%.[17, 21, 22, 27, 29, 30, 32, 33] Though few of the trials included radiation myelitis as one of the primary endpoints of the study, none of these trials documented a difference in the incidence of radiation myelitis by fractionation schedule. A recent re-evaluation of the Radiation Therapy and Oncology Group 97-14 data showed the risk for spinal cord myelopathy to be zero and equivalent in patients who were treated with either a single 8 Gy fraction or 30 Gy in 10 fractions for painful lesions of the spine.[38] The Task Force found that there were no additional significant risks in long term side effects from a single 8 Gy fraction to recommend limiting its use for patients with painful bone metastases.

4) When should patients receive re-treatment with radiation to peripheral bone metastases?

Guideline statement. Although no specific trial has been completed to define criteria for the re-treatment of patients with recurrent symptoms of metastatic disease, most trials have included the option of re-treatment. Rates of re-treatment have been 20% with single fraction palliative radiation schedules compared 8%with lengthier courses of treatment. The Task Force recommends that, whenever possible, patients should be placed on prospective randomized trials

to further define the appropriate use of radiotherapy in the setting of recurrent symptoms of cancer.

Narrative. None of the completed retrospective analyses of re-treatment for recurrent metastatic bone pain separated their findings into spine and non-spine sites. Additionally, the data either make no mention of side effects from the cumulative treatment to one site or simply describe the toxicity to be acceptable. The risks of re-treatment obviously depend upon the normal tissue tolerance of the tissues contained in the treatment volume, and that assessment might be made more difficult by a limited understanding of the amount of long term repair of radiation effects in any of those structures. The available data would suggest that a failure to achieve pain relief following the initial radiation course does not preclude the potential for palliative relief after re-treatment.[13, 39-41] Randomized trials of single- versus multi-fraction radiotherapy reveal a re-irradiation rate of 11-42% and 0-24%, respectively.[8, 11, 19, 21, 27, 29] It is unclear whether the higher rate of re-treatment following single fraction radiotherapy results in part from the radiation oncologist's belief that the combined total dose will not exceed the normal tissue tolerance of the adjacent organs included in the treatment volume when compared to the risks of re-treatment following a multi-fractionated course to a higher total dose. These studies did not specify criterion for re-treatment or a fractionation schedule for re-treatment radiation dosing. Additionally, many of the studies did not describe whether patients required re-treatment for persistent pain or for pain that recurred after an initial response.

Though no prospective trials have been completed to report results of re-treatment for painful bone metastases, several smaller retrospective analyses have suggested that re-treatment may

provide reasonable rates of palliation. The initial fractionation schema and re-treatment doses in these studies are heterogeneous, which may partially explain a wide range of pain relief from re-treatment of 33-84%. [13, 28, 39, 40-45] (Table 2). Two studies examined the feasibility of a second re-treatment dose, though the patient numbers in these studies are too small to arrive at any conclusions.[41, 42] The presence of persistent pain in weight bearing or long bones would necessitate a re-assessment of pathologic fracture risk as part of the ongoing work-up when considering re-irradiation. Clinical trials that include specific criteria for re-irradiation should be considered to further define the appropriate use of radiotherapy in the setting of recurrent symptoms of cancer.

5) When should patients receive re-treatment with radiation to spine lesions causing recurrent pain?

Guideline statement. Sites of recurrent pain in spine bones can be successfully palliated with EBRT re-treatment, though the available data do not allow for conclusive statements regarding dosing and fractionation. Care must be taken when the re-irradiated volume contains the spinal cord, and it may be appropriate to sum the biologically effective doses from the initial and re-treatment regimens to estimate the risk of radiation myelopathy. The Task Force recommends that these patients be treated on the available clinical trial.

Narrative. While few of the available retrospective studies separated patients by whether their retreatment was delivered to fields containing the spinal cord, the results do suggest reasonable rates of pain control with a limited risk of side effects following re-irradiation of spine sites initially treated with single fractions between 4 Gy and 8 Gy.[13, 28, 40, 42-45] A small number of

retrospective studies have also suggested that spine metastases treated to longer initial courses and higher total doses may be safely retreated with additional radiotherapy. [28, 39, 46-48] One report pooled published and single-institutional data to calculate a biologically effective dose (BED) according to the linear quadratic model with an alpha/beta ratio of 2 Gy for the spinal cord. The results suggested that the risk of radiation myelopathy was 3% when the combined BED of two courses was less than 135.5 Gy(2), the interval between the courses was no less than 6 months, and neither single course delivered a BED of greater than 98 Gy(2). [48]

An ongoing prospective randomized trial will investigate pain relief from re-irradiation with either 8 Gy in a single fraction or 20 Gy in 5 fractions to previously radiated painful sites of bone metastases. Patients are eligible for the study whether their initial therapy was delivered in single or multiple fractions, but those who received initial doses of 24 Gy in 6 fractions, 27 Gy in 8 fractions, or 30 Gy in 10 fractions to the spine or any part of the pelvis encompassing small or large bowel and/or the rectum are not eligible for re-treatment. The results of this study will therefore confirm or deny whether these recognized re-treatment fractionation schema are safe and effective.[49]

6) What promise does highly conformal radiotherapy hold for the primary treatment of painful bone metastasis?

Guideline statement. Stereotactic body radiation therapy (SBRT) is a technology that delivers high doses to metastatic spine disease with a steep dose gradient that may allow superior sparing of the adjacent neural structures including the spinal cord and cauda equina. The published

efficacy and safety data for SBRT are mostly from retrospective single-institution studies, and some of the measured endpoints in these studies are different from those used to evaluate other treatment types. Given that the complexities of dosing and target delineation for SBRT have yet to be fully defined, the Task Force strongly suggests that these patients be treated only on available clinical trials and that SBRT should not be the primary treatment of vertebral bone lesions causing spinal cord compression.

Narrative. Stereotactic body radiation therapy has emerged as an innovative treatment modality for the management of bony metastasis in the spinal bones. It provides an attractive means to deliver a higher BED to the vertebral bones and surrounding paraspinal areas with relative sparing of the adjacent neural structures such as the spinal cord and the cauda equina. Given the heterogeneity of prognosis for patients with bone metastases, there is interest to define a subset of patients with a limited number of bone metastases who may achieve more durable pain relief or overall failure-free survival with SBRT. Similar to SBRT for the treatment of oligometastasis in lungs and liver, patients considered for this modality should fulfill certain inclusion and exclusion criteria based on evidence obtained from the review of the literature, and such patients should be considered for clinical trials.[50-58] (Table 3)

The data summarized in Table 4 represents only those studies that report on spine metastases exclusively, or break out spine metastases outcomes separately, and specify the follow-up duration.[51, 56, 57, 59-68] Those reports that include primary spine tumors in their analysis are excluded as it confounds any ability to make conclusions on the outcome of patients treated for osseous metastatic disease. In serial reports of successive experiences from the same institution, only the most recent or relevant studies were included. Those studies focused on post-operative

adjuvant SBRT are also excluded as this represents a distinct group of patients as compared to patients treated with intact spine metastases.

The current state of evidence, shown in Table 4, is limited to efficacy data after administration of SBRT for spine metastases. Only one study represents a true Phase 1/2 study where defined stopping rules for toxicity are instituted in the original clinical trial methodology.[51] Highly conformal therapies may exclude subclinical disease, increasing a risk for clinically relevant re-growth of tumor. Additionally, none of the delivered radiotherapy doses have been proven to eradicate gross disease, so even those areas within the SBRT target volume are subject to tumor regrowth. Only a randomized trial will determine if there is any benefit of high biologically effective doses for vertebral body metastases to warrant the risk of spinal toxicity associated with this treatment.

Based on the data in Table 5, promising rates of local and pain control across different tumor histologies are reported.[57, 69] Most studies do not provide actuarial data, and the definition of local control has also been modified in the spine SBRT literature to comprise mainly the radiologic response of the treated tumor. In contrast, the trials for efficacy of conventionally planned EBRT define local control on the basis of pain relief or need for analgesics rather than radiographic control. Given its impact on overall quality of life, pain control is considered to be the clinically relevant outcome for patients treated with palliative intent.

Late toxicities

The treatment of spinal metastases with SBRT is not without risk to the patient, especially when considering that the risk of clinically significant late toxicities with conventional palliative radiotherapy regimens is negligible. There have been five cases of radiation myelopathy reported following spine SBRT in patients with no prior radiotherapy, and five cases of radiation myelopathy in patients treated with spine SBRT as re-irradiation.[59, 60] Radiation myelopathy represents an unacceptable outcome for the palliative patient, as patients are rendered permanently neurologically impaired. The use of high dose single fraction SBRT has also resulted in a significant rate of new or progressive vertebral compression fractures. An uncommon complication with conventional EBRT regimens, one report documented fracture progression in 27/71 (38%) of vertebrae treated with SBRT.[61] Although low grade esophageal and pulmonary side-effects may occur with EBRT, severe complications are rare. However, following spine SBRT in 119 patients, one case of fatal esophageal necrosis and one case of bronchial stenosis requiring dilatation was reported.[62]

These toxicities largely arose due to the lack of knowledge of normal tissue tolerance with high dose per fraction radiation. As we learn more, the incidence of significant adverse effects should diminish. The incidence of radiation myelopathy after SBRT has already dramatically declined as a result of published reports that have provided guidance for safe spinal cord radiation dose limits.[59, 60] However, strict adherence to methods to prevent intra-fractional motion is critical to prevent the previously observed significant late morbidities of SBRT, as even small positional uncertainties in the millimeter range can result in marked overdosing of adjacent organs at risk.

7) When should highly conformal radiotherapy be considered for re-treatment of spine lesions causing recurrent pain?

Guideline statement. While there are no definitive data to specify the proper patient selection criteria or radiotherapy dose for recurrent painful lesions of the spine, some early data suggests that re-treatment to spine lesions with SBRT may be feasible, effective, and safe, though the Task Force believes that the use of this approach should be limited to the setting of clinical trial participation.

Narrative. It is feasible to deliver re-treatment to sites of recurrent metastatic spine pain with stereotactic body radiotherapy.[51, 57, 63, 65-67] The research into the use of SBRT for re-treatment is limited, though with fastidious patient positioning SBRT may allow for greater sparing of previously treated spinal cord than would conventional EBRT treatment delivery. However, the specifics of SBRT re-treatment dosing and target delineation are insufficiently defined to allow for SBRT re-treatment outside of the clinical trial setting, and there is no evidence of superiority of SBRT over conventional EBRT with respect to pain control. Some authors caution that the steep dose gradients produced by SBRT may lead to unexpected side effect risks, and that re-irradiation utilizing SBRT should be further evaluated by prospective evaluation.[48, 59-62]

8) Does the use of surgery, radionuclides, bisphosphonates or kyphoplasty/vertebroplasty obviate the need for palliative radiotherapy for painful bone metastasis?

A) Surgery and external beam radiotherapy for spinal cord compression

Guideline statement. The available data suggests that surgery does not obviate the need for post-operative external beam radiotherapy in patients with spinal cord compression. The choice for

surgical decompression should be made by an interdisciplinary team including a neurosurgeon, with performance status, primary tumor site, extent and distribution of metastases and expected survival taken into account. The optimal dosing of post-operative external beam radiotherapy cannot be determined from the available data, though longer schedules, like 30 Gy in 10 fractions, is most commonly used since the intent is to eradicate microscopic residual disease rather than relieve symptoms through partial tumor regression with palliative radiation schedules. No reports exist regarding the use of single fraction palliative EBRT in the postoperative setting. Eligible patients with spinal cord compression should be considered for available radiotherapy dose fractionation trials.[70, 71]

Narrative. Up to 40% of cancer patients suffer metastases to the spine with 2.5% experiencing symptoms of spinal cord compression which can cause sensory and motor deficits as well as bowel and bladder incontinence. Treatment options include corticosteroids and external beam radiotherapy, with spinal decompressive surgery reserved for specific clinical conditions in which patients have adequate performance status to tolerate surgery, and a sufficient life expectancy to warrant the necessary post-operative healing and rehabilitation.[72]

The Task Force was also unable to conclusively recommend any specific radiotherapy fractionation scheme for patients with spinal cord compression based upon outcomes including ambulation and survival, though progression-free survival and local control may be improved with a lengthier course when surgery is not feasible.[73-76] However, one study did show that a single 8 Gy fraction was equally as effective in this setting as a course of 16 Gy in two fractions given one week apart for patients with poor performance status.[74] Selection of a radiation schedule can be facilitated by a scoring system, which is based on the relevant prognostic

factors, that accurately predicts both ambulation rates and survival following radiotherapy for spinal cord compression.[77, 78]

Surgical decompression with stabilization plus radiotherapy for selected single level spinal cord compression patients may increase the chances for maintaining or regaining ambulation when compared to radiotherapy alone in appropriately selected patients. Prospective randomized data from one trial showed that there was a statistically significant improvement in overall ambulation rates (84% versus 57%), duration of ambulation (122 days versus 13 days), regaining lost ambulation (62% versus 19%), and survival (126 days versus 100 days) with surgery plus post-operative radiotherapy compared to radiotherapy alone.[79] (Table 6)

The choice for surgical decompression should be carried out by an interdisciplinary team that accounts for prognostic factors which include a slow progression of neurologic symptoms, ambulation that is maintained or has only been lost in the previous 48 hours, a single level of compression, the absence of visceral or brain metastases, an estimated survival of at least three months, a lengthy interval between the initial diagnosis and spinal cord compression, age less than 65 years, spine instability, retropulsed bone fragments, and tumors that arise in the prostate, breast, or kidney.[73, 79-85] (Table 7). If a neurosurgeon is not available for a patient who would potentially benefit from resection, every effort should be made to transfer them to a center with a spine surgeon.

B) Radiopharmaceuticals and external beam radiotherapy

Guideline statement. The Task Force recognized that radiopharmaceuticals are an important, and often underutilized, palliative care option for multifocal bone metastases. The available data do not suggest that the use of systemic radiopharmaceuticals obviates the need for palliative external beam radiotherapy for bone metastases, though radiopharmaceutical use has most commonly been limited to both circumstances of osteoblastic metastases documented by a Technetium-99 bone scan, for certain malignant histologies, and where the number of anatomic sites of pain is too great to reasonably be treated with standard external beam radiotherapy. Further prospective studies should address the prophylactic use of systemic radiopharmaceuticals in patients with limited bone metastases as well as the possible combination of radiopharmaceuticals with other systemic agents such as bisphosphonates or chemotherapy.

Narrative. Prospective randomized data have shown that the addition of systemic radiopharmaceuticals to EBRT for patients with hormone refractory prostate cancer decreases the need for further treatment of bone metastases and improves quality of life.[86] Radiopharmaceuticals have most commonly been used in the setting of multiple sites of painful bone metastases, greater in number than would be reasonably treated with localized EBRT, such as circumstances where those sites occur on both sides of the diaphragm. Radiopharmaceuticals are taken up most actively in areas of bone growth present in osteoblastic metastases, mirroring uptake seen in technetium-99 bone scans. Strontium-89 acts as an analogue that is incorporated directly in the hydroxyapatite of bone, while Samarium-153 forms insoluble salts with remodeling bone. Radiopharmaceuticals are therefore systemic agents that act locally at sites of metastatic bone disease by virtue of their delivery of radiotherapy to only a depth of 0.2 to 3.0 mm from their sites of deposition. Though the surrounding normal tissues are relatively spared by these two agents, both can cause myelosuppression, a potentially serious side effect in this

population of patients.[87] In practice, the incidence of myelosuppression is low. Patients at highest risk for myelosuppression following administration of systemic radionuclides have widespread tumor infiltration of bone marrow and significant prior myelosuppressive therapy such as chemotherapy.

Strontium-89 and samarium-153 have a similar time until pain relief, overall efficacy, and risk of toxicity. Prospective studies suggest that these radiopharmaceuticals have a pain relief onset of 2- 3 weeks, partial response rates of 55-95%, complete response rates of 5-20%, and a mean duration of pain relief of 3-6 months. Side effects may include a pain flare in 10-40% of those treated as well as a self-limiting myelosuppression with a nadir in blood counts 6-7 weeks after treatment and recovery by 8-12 weeks following the injection.[88-96] (Table 8)

One trial that randomized patients with prostate or breast cancer to either Strontium-89 or Samarium-153 for treatment of multiple areas of painful metastases showed no significant difference in response rates or side effects.[97] Strontium-89 and Samarium-153 have both been tested with concurrent chemotherapy with promising results, but the data are not sufficient to make broad recommendations about their combined use.[98, 99] Samarium-153 has been combined with kyphoplasty in one small study that also allows no definitive conclusions.[100] Strontium-89 plus the bisphosphonate zoledronic acid showed promising results in one small randomized study and is currently being studied in a large prospective trial.[101, 102] Data does suggest that hemi-body EBRT may be used with equal success in patients with multiple sites of painful bone metastases in geographic areas where access to radionuclides is limited or in cases where their use is contraindicated.[103, 104]

C) Does the use of bisphosphonates obviate the need for external beam radiotherapy for painful bone metastasis?

Guideline statement. The Task Force believes that the use of bisphosphonates does not obviate the need for external beam radiotherapy in those patients with painful, uncomplicated bone metastases. Several prospective studies suggest that the concurrent delivery of external beam radiotherapy and bisphosphonates successfully palliates bone pain and promotes re-ossification of the damaged bone with an acceptable risk of toxicity, though it has not been shown that the combination is better than EBRT alone when pain relief is the measured variable.[105-110] The Task Force strongly recommends that large prospective, randomized trials be undertaken to more fully delineate the optimum radiotherapy fractionation and mode of delivery (EBRT versus radiopharmaceuticals), dose and duration of bisphosphonate therapy, and scheduling of this treatment combination.

Narrative. The use of bisphosphonates in patients with bone metastases associated with certain malignant histologies has increased in the past decade, and their use has been shown to both decrease bone pain scores and to reduce skeletal related events such as pathologic fracture, spinal cord compression, need for local radiotherapy, and hypercalcemia.[111-116] Drawbacks to the delivery of bisphosphonates can include renal impairment and osteonecrosis of the jaw.[117-119]

At present, bisphosphonates are limited in indication to osteoblastic or mixed osteoblastic/osteolytic bone metastases. Once injected, bisphosphonates are internalized by osteoclasts, causing a decrease in both their activity and viability. In addition to causing tumor

cell death, radiotherapy is also thought to influence the activity of osteoclasts by reducing tumor produced osteoclast activating factors (OAF's), suggesting that the two modalities may act synergistically to diminish the deleterious effects of these cells in the setting of bone metastases. EBRT and bisphosphonates have a theoretic ability to act in a complementary fashion because of their local versus systemic spatial cooperation and also because their toxicity profiles do not significantly overlap. Bisphosphonates appear safe and effective when combined with either single or multiple fraction radiotherapy.[120, 121] (Table 9). The Task Force could not find data to recommend one bisphosphonate or fractionation scheme combination as having greater efficacy than another.

To date, no randomized phase III study has compared monotherapy to the combination of EBRT and bisphosphonates. As most bone metastases have both an osteoblastic and an osteolytic component, the theoretic advantage of adding EBRT, especially single fraction radiation, is the treatment of the osteolytic component by EBRT, and EBRT acting in synergy with bisphosphonates to treat the osteoblastic component of the bone metastases. Similar to bisphosphonates, radiopharmaceuticals take advantage of systemic delivery and may act synergistically to improve pain control.[122, 123] The addition of radiopharmaceuticals to bisphosphonate therapy is under investigation in a phase III multi-institutional trial.[124]

D) Kyphoplasty or vertebroplasty and external beam radiotherapy

Guideline statement. There are no prospective data to suggest that the use of either kyphoplasty or vertebroplasty obviates the need for EBRT in the management of painful bone metastases. Kyphoplasty and vertebroplasty theoretically show the most promise in patients with metastatic

spine disease causing instability of the vertebral body, though the lack of completed prospective studies should limit their standard use. Small series of patients have been treated with kyphoplasty or vertebroplasty plus external beam radiotherapy, stereotactic radiosurgery, or interstitial Samarium-153, yet the results do not allow for definitive statements regarding the use of these combined regimens. Future prospective trials of vertebroplasty and kyphoplasty should address questions including proper patient selection, efficacy, toxicity, and timing in relation to radiotherapeutic interventions.

Narrative. Percutaneous vertebroplasty involves the radiologically guided injection of polymethylmethacrylate surgical cement into a vertebral bone with the goals of pain relief and stabilization of pathologic vertebral compression fractures. The procedure has most commonly been performed in the setting of osteolytic lesions and is contraindicated in those with spinal cord compression or significant extraosseous tumor extension. Side effects may include extravasation of cement outside of the vertebral bone as well as traumatic fracture, pneumothorax, pulmonary embolism, fat emboli, dural tears, and death. The prospective studies that have been reported suffer from small patient numbers, heterogeneity of tumor type, non-uniform reporting of pain relief, and inconsistent documentation of toxicities. The reports from those studies do suggest the potential for good pain relief in patients with osteolytic metastases.[125-130] (Table 10).

Kyphoplasty is a variant of vertebroplasty that involves insertion of a balloon into an affected vertebral body following which the balloon is inflated and filled with viscous polymethylmethacrylate cement in an effort to provide pain relief and stability. Kyphoplasty has

theoretical advantages over vertebroplasty including a greater increase of vertebral body height and lower risk of cement extravasation. The disadvantages of kyphoplasty compared to vertebroplasty include the need for general anesthesia and both a lengthier procedure time and period of monitoring after completing the procedure. As is true for vertebroplasty, there are currently no available data from prospective randomized trials to determine appropriate patient selection, rates of success, specific side effect risks, and coordination with other treatments such as external beam radiotherapy. The small amount of comparison that is feasible from the prospective data shows little difference in pain outcomes between the two types of procedures.[131-135] (Table 10)

CONCLUSIONS

External beam radiotherapy has been and continues to be the mainstay for the treatment of painful, uncomplicated bone metastases. Although various fractionation schemes may provide good rates of palliation, numerous prospective randomized trials have shown that either 8 Gy in one fraction, 20 Gy in 4 fractions, 24 Gy in 6 fractions, or 30 Gy in 10 fractions can provide excellent pain control and minimal side effects. The longer course has the advantage of a lower incidence of re-treatment to the same site while the single fraction proves more convenient for patients and caregivers. Re-irradiation with EBRT may be safe, effective, and less commonly necessary in patients with a short life expectancy. Bisphosphonates do not obviate the need for external beam radiotherapy for painful sites of metastases and may indeed act effectively in combination with EBRT. Stereotactic body radiotherapy may be useful for patients with newly discovered or recurrent tumor in the spinal column or paraspinal areas, but the Task Force

suggests that SBRT be reserved for patients who fit specific inclusion and exclusion criteria, who are treated in centers with sufficient training and experience, and preferably within the confines of a therapeutic trial.

The use of radionuclides seems most appropriate in circumstances in which patients have several sites of painful osteoblastic metastases in an anatomic distribution greater than that which would conveniently or safely be treated with external beam radiotherapy. Hemibody radiotherapy is an option for these patients who reside in geographic areas where radionuclides are not readily available or when they are medically contraindicated.

Surgical decompression and stabilization plus post-operative radiotherapy should be considered for selected patients with single level spinal cord compression or spinal instability, unless the patients have too short of an anticipated life expectancy. Kyphoplasty and vertebroplasty may be useful for the treatment of lytic osteoclastic spine metastases or in cases of spinal instability where surgery is not feasible or indicated; they do not obviate the need for external beam radiotherapy, and there are no data to suggest that the addition of vertebroplasty or kyphoplasty further improve symptoms or have a greater impact on clinically significant endpoints than EBRT alone. There is a need for additional prospective trials to better define if there is a patient population that would benefit from treatment with kyphoplasty or vertebroplasty, and, if so, how those procedures should best be sequenced with EBRT.

Finally, all future trials should measure consistent variables as defined by the International Consensus on Palliative Radiotherapy Endpoints, as well as assessing functional domains and quality of life with validated instruments such as the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire for patients with bone metastases.[36, 136] The

proper management of painful osseous metastases demands prompt discovery, appropriate pharmacologic management, and the data-driven use of palliative external beam radiotherapy.

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