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ASTRO GUIDELINE

PALLIATIVE RADIOTHERAPY FOR BONE METASTASES: AN ASTRO EVIDENCE-BASED GUIDELINE

Stephen Lutz, M.D.,* Lawrence Berk, M.D., Ph.D.,† Eric Chang, M.D.,‡ Edward Chow, M.B.B.S.,§ Carol Hahn, M.D.,¶ Peter Hoskin, M.D.,‖ David Howell, M.D.,# Andre Konski, M.D.,** Lisa Kachnic, M.D.,†† Simon Lo, M.B., Ch.B.,‡‡ Arjun Sahgal, M.D.,§§ Larry Silverman, M.D.,¶¶ Charles von Gunten, M.D., Ph.D., F.A.C.P.,‖‖ Ehud Mendel, M.D., F.A.C.S.,## Andrew Vassil, M.D.,*** Deborah Watkins Bruner, R.N., Ph.D.,††† and William Hartsell, M.D.‡‡‡

*Department of Radiation Oncology, Blanchard Valley Regional Cancer Center, Findlay, OH; †Department of Radiation Oncology, Moffitt Cancer Center, Tampa, FL; ‡Department of Radiation Oncology, University of Texas M.D. Anderson Cancer Center, Houston, TX; §Department of Radiation Oncology, Sunnybrook Odette Cancer Center, University of Toronto, Toronto, ON, Canada; ¶Department of Radiation Oncology, Duke University, Durham, NC; ‖Mount Vernon Centre for Cancer Treatment, Middlesex, United Kingdom; #Department of Radiation Oncology, University of Michigan, Mt. Pleasant, MI; **Department of Radiation Oncology, Wayne State University, Detroit, MI; ††Department of Radiation Oncology, Boston Medical Center, Boston, MA; ‡‡Department of Radiation Oncology, Ohio State University, Columbus, OH; §§Department of Radiation Oncology, Sunnybrook Odette Cancer Center and the Princess Margaret Hospital, University of Toronto, Toronto, ON, Canada; ¶¶21st Century Oncology, Sarasota, FL; ‖‖The Institute for Palliative Medicine, San Diego Hospice, San Diego, CA; ##Neurological Surgery, Ohio State University, Columbus, OH; ***Department of Radiation Oncology, Cleveland Clinic Foundation, Cleveland, OH; †††University of Pennsylvania School of Nursing, Philadelphia, PA; ‡‡‡Department of Radiation Oncology, Good Samaritan Cancer Center, Downers Grove, IL

Reprint requests to: Stephen Lutz, M.D., Department of Radiation Oncology, Blanchard Valley Regional Cancer Center, 15990 Medical Dr. S, Findlay, OH 45840. Tel: (419) 423-3703; Fax: (419) 427-0212; E-mail: slutz@bvha.org

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 has been published with the report. Individuals with disqualifying conflicts were recused from participation in this Guideline.

The ASTRO Guidelines present scientific, health, and safety information and might to some extent reflect scientific or medical opinion. They are made available to ASTRO members and to the public for educational and informational purposes only. Any commercial use of any content in this Guideline without the previous written consent of ASTRO is strictly prohibited.

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 might be new developments that are not reflected in this Guideline and that might, over time, be a basis for ASTRO to consider revisiting and updating the Guideline.

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A reader's note: This is an abbreviated version of the full article by Dr. Lutz *et al*. The full article, and associated appendices, can be viewed at www.redjournal.org. in the Supplemental Materials section of the publication.

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Purpose: To present guidance for patients and physicians regarding the use of radiotherapy in the treatment of bone metastases according to 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 4,287 candidate original research articles potentially applicable to radiotherapy for bone metastases. A Task Force composed of all authors synthesized the published evidence and reached a consensus regarding the recommendations contained herein.
Results: The Task Force concluded that external beam radiotherapy continues to be the mainstay for the treatment of pain and/or prevention of the morbidity caused by bone metastases. Various fractionation schedules can provide significant palliation of symptoms and/or prevent the morbidity of bone metastases. The evidence for the safety and efficacy of repeat treatment to previously irradiated areas of peripheral bone metastases for pain was derived from both prospective studies and retrospective data, and it can be safe and effective. The use of stereotactic body radiotherapy holds theoretical promise in the treatment of new or recurrent spine lesions, although the Task Force recommended that its use be limited to highly selected patients and preferably within a prospective trial. Surgical decompression and postoperative 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 external beam radiotherapy in appropriate patients.
Conclusions: Radiotherapy is a successful and time efficient method 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 provide 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 metastasis patients requires interdisciplinary care among radiologists, radiation oncologists, medical oncologists, surgeons, pain medicine specialists, and palliative care professionals. Radiotherapy (RT) provides successful palliation of painful bone metastasis that is time efficient and has been associated with very few side effects. External beam RT (EBRT) can provide significant palliation of painful bone metastases in 50–80% of patients, with up to one-third of patients achieving complete pain relief at the treated site (1).

Widespread variation exists in the 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 RT schedules compared with longer courses of palliative RT for previously unirradiated bone metastases, with the main advantages to the schedules being the increased convenience with a single fraction and the lower repeat treatment rate with a longer course (1, 2). A wide range of radiotherapeutic options also exists for pain that has recurred after RT (EBRT or radiopharmaceutical agents) has been given for bone metastases. Among these options is a second course of EBRT to the same localized site (repeat RT). Also, painful bone lesions at several anatomic sites have been treated with injectable radiopharmaceutical agents or hemibody RT, depending on the tumor histologic features and the distribution of the metastases. Additionally, great interest has been devoted to the question of whether technological advances in RT delivery, such as stereotactic body RT (SBRT), could improve the results of the primary treatment or repeat treatment of metastatic spinal lesions. The circumstances of spinal cord compression with complete or impending pathologic fracture demand a coordinated care plan between surgeons and radiation oncologists. Although clinical trials with bisphosphonates initially considered the need for EBRT as a failure of therapy endpoint, EBRT to the index symptomatic lesion might provide more prompt and durable symptom relief. Finally, EBRT should be used in conjunction with both kyphoplasty and vertebroplasty in patients who have been treated with these interventions for spinal metastases.

Given the complexities of care for patients with bone metastases and the relative lack of palliative RT 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). The recommendations have been based on the results of a systematic data 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 RT for bone metastases. These experts represented 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 RT for bone metastases to patients and physicians. The Task Force was also charged with providing guidelines for the proper integration of RT 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 RT for bone metastases and also authorized the membership of the Task Force. Subsequently, the Task Force participated in a series of communications by electronic mail and conference telephone calls to

Table 1. Prospective randomized trials comparing single- vs. multiple-fraction radiotherapy regimens for painful, uncomplicated bone metastases

Study	Patients (*n*), tumor histologic type	Fractionation	Overall pain relief (%)	Complete response (%)	Acute toxicity (%)	Late toxicity (%)	Repeat treatment rate (%)	Investigator	Year	Reference
Prospective randomized Phase III trials										
8-Gy single fraction RT for metastatic skeletal pain: randomized comparison with multifraction schedule	775, various histologic types	8 Gy/1 Fx	78	57	30	2	23	Bone Pain Trial Working Party	1999	9
		20 Gy/5 Fx or 30 Gy/10 Fx	78	58	32	1	10			
Randomized clinical trial with 2 palliative RT regimens in Spain	160, various histologic types	8 Gy/1 Fx	75	15	13	NR	28	Foro	2008	13
		30 Gy/10 Fx	86	13	18	NR	2			
Radiation Therapy and Oncology Group 97-14	898, breast or prostate cancer	8 Gy/1 Fx	66	15	10	4	18	Hartsell	2005	11
		30 Gy/10 Fx	66	18	17	4	9			
Randomized trial of 3 single-dose RT regimens for metastatic bone pain	327, various histologic types	4 Gy/1 Fx	59	21	32	6	42	Jeremic	1998	7
		6 Gy/1 Fx	73	27	29	7	44			
		8 Gy/1 Fx	78	32	37	7	38			
Prospective randomised multicenter trial of single-fraction RT (8 Gy × 1) vs. multiple fractions (3 Gy × 10)	376, various histologic types	8 Gy/1 Fx	Equivalent	NR	NR	4	15	Kaasa	2006	12
		30 Gy/10 Fx	Equivalent	NR	NR	11	4			
Randomized trial of single-dose vs. fractionated palliative RT for bone metastases	241, various histologic types	8 Gy/1 Fx	62	15	35	5	21	Nielsen	1998	15
		20 Gy/4 Fx	71	15	35	5	12			
Trans-Tasman Radiation Oncology Group 96-05 (neuropathic pain)	272, various histologic types	8 Gy/1 Fx	53	26	5	5	29	Roos	2005	10
		20 Gy/5 Fx	61	27	11	4	24			
Long-term follow-up of cancer patients receiving RT for bone metastases: results from randomized multicenter trial—Norway	188, various histologic types	8 Gy/1 Fx	PR	PR	PR	5	27	Sande	2009	14
		30 Gy/10 Fx	PR	PR	PR	5	5			
Global analysis of Dutch Bone Metastasis Study	1,171, various histologic types	8 Gy/1 Fx	72	37	Equivalent	4	25	Steenland	1999	16
		24 Gy/6 Fx	69	33	Equivalent	2	7			

Abbreviations: Fx = radiotherapy fractions; NR = not reported; Equivalent = reports described as equivalent between treatment arms; PR = previously reported in trial first authored by Kaasa *et al.* (12).

compose the Guideline. The members of the Task Force divided into subgroups to address the separate questions according to 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 relied on an evidence-based approach using a formal systematic literature review. One investigator (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 the results to 1998 through 2009. Of the 4,287 articles originally identified, the group's

Table 2. Data describing repeat treatment of painful spinal metastases

Study	Patients (*n*), tumor histologic type	Initial dose	Retreatment fractionation	Pain relief	Comments	Investigator	Year	Reference
Local repeat RT	30, various histologic types	Mostly 30 Gy/10 Fx	10 Gy/5 Fx to 26 Gy/13 Fx	50%	Better pain relief for those with initial CR vs. PR	Hayashi	2002	39
Prospective randomised trial of 4 or 8-Gy single doses for metastatic bone pain	40, various histologic types	4 Gy/1 Fx 8 Gy/1 Fx	Most received 8 Gy/1 Fx; some received 20 Gy/5 Fx	71% 44%	No difference in response by histologic type	Hoskin	1992	13
Single 4-Gy repeat RT for painful bone metastases after single-fraction RT	109 initial responders, 26 nonresponders, various histologic types	4 Gy/1 Fx 6 Gy/1 Fx 8 Gy/1 Fx	4 Gy/1 Fx	74% initial responders; 46% nonresponders	31% CR	Jeremic	1999	40
Second single 4-Gy repeat RT for painful bone metastases	25, various histologic types	4 Gy/1 Fx, plus repeat RT, 4 Gy/1 Fx 6 Gy/1 Fx plus repeat treatment; 4 Gy/1 Fx 8 Gy/1 Fx plus repeat treatment 4 Gy/1 Fx	4 Gy/1 Fx (second re-RT)	80%	No pain control difference in initial responders vs. nonresponders	Jeremic	2002	41
Repeat RT for painful bone metastases	57, various histologic types	Single fraction therapy to 41%, fractionated treatment to 59%	8 or 10 Gy/1 Fx, 26 Gy/6 Fx, 28 Gy/7 Fx, 30 Gy/10 Fx	87%	Patients treated were initial nonresponders	Mithal	1994	42
Low-dose, single-fraction RT for metastatic bone pain	11, various histologic types	4 Gy/1 Fx	4 Gy/1 Fx to initial responders, multifraction or 8 Gy/1 Fx to nonresponders	100%, initial responders; 0%, nonresponders	2 patients underwent re-RT second time	Price	1988	43
Single-dose RT (6 Gy): palliation of painful bone metastases	18, various histologic types	6 Gy/1 Fx	6 Gy/1 Fx	72%	Long intervals between primary and repeat treatment	Uppelschoten	1995	45
Repeat treatment and Dutch Bone Metastasis Study	173, various histologic types	8 Gy/1 Fx 24 Gy/6 Fx	8 Gy/1 Fx, 46 patients Multifractions, 91 patients 8 Gy/1 Fx, 27 patients Multifractions in 9 patients	66% 46%	Single fraction therapy effective initial treatment or repeat treatment	van der Linden	2004	28

Abbreviations: RT = radiotherapy; Fx = radiotherapy fractions; CR = complete response; PR = partial response.
The references listed in Table 2 correspond to those cited in the full manuscript published online and contained in the Supplemental Materials section.

specific research questions were approached by searching for combinations of the following key words: single, fraction, radiotherapy, spine, toxicity, side effects, retreatment, re-treatment, highly conformal therapy, Cyberknife, IMRT [intensity-modulated radiotherapy], stereotactic body, tomotherapy, spinal cord compression, surgery, kyphoplasty, vertebroplasty, meta-analysis, metaanalysis, radionuclides, radiopharmaceuticals, and bisphosphonates. Of this sample, they identified 25 randomized clinical trials, 20 prospective single-arm studies, and 4 meta-analyses/systematic reviews.

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

Table 3. Suggested inclusion and exclusion criteria for patients enrolled in trials to evaluate stereotactic body radiotherapy for spinal bone metastases

Characteristic	Inclusion	Exclusion
Radiographic	1) Spinal or paraspinal metastasis by MRI (50, 51) 2) No more than 2 consecutive or 3 noncontiguous spine segments involved (50–53)	1) Spinal MRI cannot be completed for any reason (50, 51) 2) Epidural compression of spinal cord or cauda equina 3) Spinal canal compromise >25% (58) 4) Unstable spine requiring surgical stabilization (50, 51, 54, 57) 5) Tumor location within 5 mm of spinal cord or cauda equina (50, 51) (relative*)
Patient	1) Age ≥18 y (50, 54) 2) KPS of ≥40–50 (50, 51, 54, 55) 3) Medically inoperable (or patient refused surgery) (50, 51)	1) Active connective tissue disease (50) 2) Worsening or progressive neurologic deficit (50–52, 57) 3) Inability to lie flat on table for SBRT (50–52) 4) Patient in hospice or with <3-month life expectancy
Tumor	1) Histologic proof of malignancy (50, 51, 56) 2) Biopsy of spine lesion if first suspected metastasis 3) Oligometastatic or bone only metastatic disease (50)	1) Radiosensitive histology such as MM[50-52] 2) Extraspinal disease not eligible for further treatment[51]
Previous treatment	Any of the following: 1) Previous EBRT <45-Gy total dose 2) Failure of previous surgery to that spinal level (50–52) 3) Presence of gross residual disease after surgery	1) Previous SBRT to same level 2) Systemic radionuclide delivery within 30 days before SBRT (50–52) 3) EBRT within 90 days before SBRT (50–52) 4) Chemotherapy within 30 days of SBRT (50–53)

Abbreviations: MRI = magnetic resonance imaging; KPS = Karnofsky performance status; SBRT = stereotactic body radiotherapy; MM = multiple myeloma; EBRT = external beam radiotherapy.

* Relative indicates that optimally tumor >5 mm from spinal cord; if this distance is closer, case-by-case discussion required because published data suggest risk of failure is greater (50, 63).

The references listed in Table 3 correspond to those cited in the full manuscript published online and contained in the Supplemental Materials section.

RESULTS

The questions and Guideline statements regarding the use of palliative RT 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 unirradiated painful bone metastases. Fractionated RT courses have been associated with an 8% repeat treatment rate to the same anatomic site because of recurrent pain vs. 20% after a single fraction; however, the single fraction treatment approach optimizes patient and caregiver convenience (1).

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

Guideline statement

Although many of the studies presented in Table 1 did not delineate treatment relief by spinal vs. nonspinal metastases, the Task Force could find no evidence from reviewing the data to suggest that a single 8-Gy fraction provided inferior pain relief compared with a more prolonged RT course in painful spinal sites, although single fractionation has been associated with a 20% incidence of repeat treatment vs. 8% with fractionated RT (7–14). 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 the risk and allow for consistent reporting of treatment results (17). The Task Force does not believe that any additional trials are needed to confirm the use of single-fraction RT in these circumstances.

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 that 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 RT courses for uncomplicated, painful bone metastases. No additional studies are suggested to confirm this recommendation at this time.

4) When should patients receive repeat treatment with RT for peripheral bone metastases?

Guideline statement

Although no specific trial has been completed to define the criteria for the repeat treatment of patients with recurrent symptoms of metastatic disease, most trials have included the option of repeat treatment (Table 2). The rates of repeat treatment have been 20% with single-fraction palliative RT schedules compared with 8% with lengthier RT courses. The Task Force recommends that, whenever possible, patients should be included in prospective randomized trials to further define the appropriate use of RT in the setting of recurrent cancer symptoms.

Table 4. Summary of current data for spinal SBRT for spinal metastases

Study	Patients (*n*), tumors (*n*), histologic type	Fractionation	Repeat RT	Pain relief	Complete response	Local control/ definition	Investigator	Year	Reference
Cohort study	69, 127, various histologic types	Mean: 15.5 Gy/2 Fx	15 patients	61/69	NR	96.8% FFP at 10 mo; 123/127 (97%)/ imaging	Tsai	2009	63
Cohort study	38, 60, various histologic types	Median: 24 Gy/3 Fx	37 tumors	31/46	NR	Repeat RT: 34/37 (92%); no previous treatment: 18/23 (78%); entire cohort: 85%, 1-y FFP*/ imaging and pain	Sahgal	2009	64
Cohort study	93, 103, various histologic types	Median: 24 Gy/ 1 Fx	0	NR	NR	90% FFP at 15 mo	Yamada	2008	65
Cohort study	32, 33, various histologic types	Median 18 Gy/3 Fx	22 patients	30/32	13/32 at 1 mo	28/32/imaging and/or pain	Nelson	2008	66
Phase I-II study with defined stopping rules	63, 74, various histologic types	30 Gy/5 Fx (32/ 63) or 27 Gy/ 3 Fx (31/63)	35 patients	Narcotic use declined from 60% to 36% at 6 mo	NR	57/74; 1-y FFP: 84%/imaging	Chang	2007	51
Cohort study	393, 500, various histologic types	Mean 20 Gy/1 Fx	344 tumors	290/336 improvement	NR	440/500/ imaging	Gerszten	2007	57
Cohort study	49, 61, various histologic types	10–16 Gy/1 Fx	0	52/61	NR	57/61/imaging and pain	Ryu	2005	56
Cohort study	21, 21	Median 20 Gy/5 Fx	20 patients	NR	NR	19/21/imaging	Yamada	2005	67
Cohort study	5, 5	10 Gy/1 Fx	5 patients	NR	NR	5/5/imaging and/or pain	Hamilton	1995	68

Abbreviations: SBRT = stereotactic body radiotherapy; NR = not reported; FFP = freedom from progression; other abbreviations as in Table 2.

* Nonrandomized comparison indicated no significant difference between repeat treatment and no previous treatment tumor groups.

The references listed in Table 4 correspond to those cited in the full manuscript published online and contained in the Supplemental Materials section.

5) When should patients receive repeat treatment with RT to spinal lesions causing recurrent pain?

Guideline statement

Sites of recurrent pain in spinal bones can be successfully palliated with EBRT repeat treatment, although 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 might be appropriate to sum the biologically effective doses from the initial and repeat treatment regimens to estimate the risk of radiation myelopathy. The Task Force recommends that these patients be treated within the available clinical trial.

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

Guideline statement

Stereotactic body RT is a technology that delivers high doses to metastatic spinal disease with a steep dose gradient that might allow superior sparing of the adjacent neural structures, including the spinal cord and cauda equina. The published efficacy and safety data for SBRT have mostly been from retrospective single-institution studies, and some of the measured endpoints in these studies were different from those used to evaluate other treatment types (Tables 3, 4 and 5). 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 within available clinical trials and that SBRT should not be the primary treatment of vertebral bone lesions causing spinal cord compression.

Table 5. Summary of current data for spinal SBRT for spinal metastases reporting on specific histologic types

Study	Patients (*n*), tumors (*n*), histologic type	Fractionation	Repeat treatment	Pain relief	CR	Local control/ definition	Investigator	Year	Reference
Cohort study	48, 55, renal cell	30 Gy/5 Fx; 24 Gy/3 Fx; 24 Gy/1 Fx	22 patients	52% of patients had durable response and were pain free at 12 mo	52% of patients had durable response and were pain free at 12 mo	43/55, 1-y FFP 82%/imaging	Nguyen	2009	69
Cohort study	NR, 93, renal cell	Mean maximum intratumor dose 20 Gy/1 Fx*	NR	94%	NR	87%/imaging	Gerszten	2007	57
Cohort study	NR, 83, breast	Mean maximum intratumor dose 20 Gy/1 Fx*	NR	96%	NR	100%/imaging	Gerszten	2007	57
Cohort study	NR, 80, lung	Mean maximum intratumor dose 20 Gy/1 Fx*	NR	93%	NR	100%/imaging	Gerszten	2007	57
Cohort study	NR, 38, melanoma	Mean maximum intratumor dose 20 Gy/1 Fx*	NR	96%	NR	75%/imaging	Gerszten	2007	57

Abbreviations as in Table 2 and Table 4.
* Data represent subanalysis from larger cohort study; therefore, this dose represented that for large mixed cohort of patients and not specifically this group of patients with histologic type specified.
The references listed in Table 5 correspond to those cited in the full manuscript published online and contained in the Supplemental Materials section.

7) When should highly conformal RT be considered for repeat treatment of spinal lesions causing recurrent pain?

Guideline statement

Although no definitive data are yet available to specify the proper patient selection criteria or radiation dose for recurrent painful lesions of the spine, some early data have suggested that repeat treatment to spinal lesions with SBRT might be feasible, effective, and safe, although the Task Force believes that the use of this approach should be limited to the setting of clinical trial participation.

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

Surgery and EBRT for spinal cord compression

Guideline statement

The available data have suggested that surgery does not obviate the need for postoperative EBRT for patients with spinal cord compression (Table 6). The choice of surgical decompression should be made by an interdisciplinary team that includes a neurosurgeon, with the performance status, primary tumor site, extent and distribution of metastases, and expected survival taken into account (Table 7). The optimal dosing of postoperative EBRT could not be determined from the available data. However, longer schedules, such as 30 Gy in 10 fractions, have been the most commonly used because the intent will be to eradicate microscopic residual disease rather than relieve symptoms through partial tumor regression with palliative radiation schedules. No reports have been published regarding the use of single-fraction palliative EBRT in the postoperative setting. Eligible patients with spinal cord compression should be considered for available RT dose fractionation trials.

Radiopharmaceuticals and EBRT

Guideline statement

The Task Force recognized that radiopharmaceuticals are an important, and often underused, palliative care option for multifocal bone metastases. The available data do not suggest that the use of systemic radiopharmaceuticals obviates the need for palliative EBRT for bone metastases. However, radiopharmaceutical use has most commonly been limited to circumstances of osteoblastic metastases documented by a technetium-99 bone scan, for certain malignant histologic types, and in cases in which the number of anatomic sites of pain is too great to reasonably be treated with standard EBRT (Table 8). Additional 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.

Does the use of bisphosphonates obviate the need for EBRT for painful bone metastasis?

Guideline statement

The Task Force believes that the use of bisphosphonates does not obviate the need for EBRT for those patients with painful, uncomplicated bone metastases. Several prospective studies have suggested that the concurrent delivery of EBRT and bisphosphonates successfully palliates bone pain and

Table 6. Studies investigating surgery and radiotherapy for spinal cord compression

Study	Patients (*n*), histologic type	Treatment regimen	Overall ambulation rate after treatment (%)	Duration of ability to ambulate	Survival	Regained ambulation after treatment (%)	Investigator	Year	Reference
Short-course vs. split-course RT for metastatic spinal cord compression: randomized trial	184, various histologic types	16 Gy/2 Fx, Days 1 and 7	68	3.5 mo	4 mo	29	Marazano	2005	73
		30 Gy/8 Fx (15 Gy/3 Fx then 15 Gy/5 Fx)	71	3.5 mo	4 mo	28			
8-Gy single-dose RT effective for metastatic spinal cord compression: results of Phase III randomized multicenter Italian trial	327, various histologic types	8 Gy/1 Fx	62	5 mo	4 mo	21	Marazano	2009	74
		16 Gy/2 Fx	69	5 mo	4 mo	32			
Surgery and RT vs. RT alone: randomized trial	101, various histologic types	Steroid, surgery, postoperative RT to 30 Gy/10 Fx	84	122 d	126 d	62	Patchell	2005	79
		Steroid, RT to 30 Gy/10 Fx	57	13 d	100 d	19			
Prospective evaluation of 2 RT schedules with 10 Fx vs. 20 Fx for metastatic spinal cord compression	214, various histologic types	30 Gy/10 Fx	60	NR	NR	29	Rades	2004	84
		40 Gy/20 Fx	64	NR	NR	30			

Abbreviations as in Table 2.
The references listed in Table 6 correspond to those cited in the full manuscript published online and contained in the Supplemental Materials section.

promotes re-ossification of the damaged bone, with an acceptable risk of toxicity (Table 9). However, it has not been shown that the combination is better than EBRT alone when pain relief has been the measured variable. The Task Force strongly recommends that large prospective, randomized trials be undertaken to more fully delineate the optimum RT fractionation and mode of delivery (EBRT vs. radiopharmaceuticals), the dose and duration of bisphosphonate therapy, and the scheduling of this treatment combination.

Kyphoplasty or vertebroplasty and EBRT

Guideline statement

No prospective data are available to suggest that the use of either kyphoplasty or vertebroplasty obviates the need for EBRT in the management of painful bone metastases.

Table 7. Suggested inclusion and exclusion criteria for patients considered for surgical intervention for spinal cord decompression

Characteristic	Factors favoring surgical decompression plus postoperative RT
Radiographic	1) Solitary site of tumor progression
	2) Absence of visceral or brain metastases
	3) Spinal instability
Patient	1) Age <65 y
	2) KPS ≥70
	3) Projected survival of >3 mo
	4) Slow progression of neurologic symptoms
	5) Maintained ambulation
	6) Nonambulatory for <48 h
Tumor	1) Relatively radioresistant tumor histologic type (*i.e.,* melanoma)
	2) Site of origin suggesting relatively indolent course (*i.e.,* prostate, breast, kidney)
Treatment	1) Previous EBRT failed

Abbreviations as in Table 3.
The references listed in Table 7 correspond to those cited in the full manuscript published online and contained in the Supplemental Materials section.

Table 8. Studies investigating use of radionuclides for bone metastases

Study	Patients (*n*), histologic type	Radionuclide	Pain response rate (%)	Maximum response rate (%)	Acute toxicity (%)	Subsequent EBRT required (%)	Survival	Investigator	Year	Reference
Studies using strontium-89										
Results of a double blind study of 89-strontium therapy of skeletal metastases	49, prostate cancer	Sr-89 3 × 75 MBq	36	NR	50	NR	46% at 2 y	Buchali	1988	89
		Saline placebo	50		23		2% at 2 y			
Prospective, randomised double-blind study of strontium for prostate cancer	32, prostate cancer	Sr-89	85	21	83	NR	NR	Lewington	1991	90
		Nonradioactive strontium	80	7	40					
Strontium-89 vs. local field RT for prostate cancer: Phase III EORTC	203, prostate cancer	Sr-89 150 MBq	35	NR	28	60	7.2 mo	Oosterhof	2003	91
		EBRT	33		20	56	11 mo			
Phase III trial of strontium-89 to EBRT for prostate cancer	126, prostate cancer	EBRT plus Sr-89 10.8 mCi	83	45	45	NR	27 wk	Porter	1993	86
		EBRT plus placebo	50	30	3		34 wk			
Strontium-89 as adjuvant to EBRT: randomized study	95	EBRT plus Sr-89	30	NR	52	NR	NR	Smeland	2003	92
		EBRT plus placebo	20		18					
Studies using samarium-153										
Dose-controlled study of 153-Sm for painful bone metastases	114	153-Sm 0.5 mCi/kg	55	NR	20	NR	82% at 16 wk	Resche	1997	93
		153-Sm 1.0 mCi/kg	70		13		83% at 16 wk			
Samarium-153 for bone metastases in prostate cancer: Phase III randomized trial	152, prostate cancer	153-Sm	45	38	25	NR	7 mo	Sartor	2004	94
		152-Sm nonradioactive	65	18	17		7 mo			
Palliation of pain associated with metastatic bone cancer using samarium-153	118, various histologic types	153-Sm 0.5 mCi/kg	70	28	8	NR	NR	Serafini	1998	95
		153-Sm 1.0 mCi/kg	72	31	23					
		Placebo	44	14	3					
Samarium-153 for hormone-refractory prostate cancer	32, prostate cancer	153-Sm 40 MBq/kg	72	38	6	NR	NR	Dolezal	2007	96
Studies comparing strontium-89 and samarium-153										
Strontium-89 vs. Samarium-153 EDTMP: comparison of treatment of prostate and breast carcinoma	100, breast or prostate cancer	Strontium-89 150 MBq	74	30	32	NR	NR	Baczyk	2007	97
		Samarium-153 37 MBq/kg	80	40	38					
Studies that combined strontium-89 or samarium-153 with other interventions										
Samarium-153 and kyphoplasty	19	153-Sm (3 mCi) mixed in cement for kyphoplasty	100	NR	0	NR	NR	Cardoso	2009	100
Strontium-89 and zoledronic acid	25, breast cancer	Zoledronic acid plus Sr-89 150 MBq	96	68	60–72	NR	NR	Storto	2006	101
		Zoledronic acid with sequential Sr-89 150 MBq	85	15	23–69					
		Zoledronic acid without Sr-89 150 MBq	82	9	NR					
Samarium-153 and docetaxel	12, prostate cancer	153-Sm 37 MBq/kg plus docetaxel	58	50	17	NR	11.5 mo	Suttman	2008	99

Abbreviations: EBRT = external beam radiotherapy; Sr-89 = Strontium-89; 153-Sm = Samarium-153; EORTC = European Organization for Research and Treatment of Cancer; EDTMP = ethylene diamine tetramethylene phosphonate; other abbreviations as in Table 4.

The references listed in Table 8 correspond to those cited in the full manuscript published online and contained in the Supplemental Materials section.

Table 9. Studies investigating combined bisphosphonates and radiotherapy for bone metastases

Study	Patients (*n*), histologic type	Bisphosphonate	EBRT	Pain relief	Mild acute toxicity (%)	Repeat treatment rate	Investigator	Year	Reference
Prospective trials that compared treatment regimens									
Zoledronic acid with high- or reduced dose RT	100, breast cancer	Zoledronic acid, 4 mg monthly	30 Gy/10 Fx	95%	ND	ND	Atahan	2009	105
			15 Gy/5 Fx	92%					
Zoledronic acid plus single-dose 6- or 8-Gy RT	139, various histologic types	Zolendronic acid, 4 mg every 4–5 wk	8 Gy/1 Fx	ND (all patients improved)	22	NR	Manas	2008	107
			6 Gy/1 Fx		14				
Dose escalation of pamidronate with concurrent RT	42, various histologic types	Pamidronate, 90–180 mg monthly	30 Gy/10 Fx	100%	23	None	Kouloulias	2003	106
		Pamidronate, 180 mg monthly			75	None			
		None			NR	NR			
Prospective studies									
RT with concurrent zoledronic acid	18, renal cell cancer	Zoledronic acid, 4 mg monthly	NR	100% (44% CR, 56% PR)	NR	NR	Vassiliou	2009	121
Combination ibandronate and RT	45, various histologic types	Ibandronate, 6 mg monthly	30–40 Gy	100% at 3 mo; 85% at 6 mo	13	None	Vassiliou	2007	108
RT plus disodium pamidronate	33, breast cancer	Pamidronate, 180 mg monthly	30 Gy/10 Fx	100% (88% CR, 12% PR)	39	NR	Kouloulias	2002	109
Image assessment of combined RT and bisphosphonates	18, breast cancer	Pamidronate, 180 mg monthly	30 Gy/10 Fx	100% (77% CR, 23% PR)	39	NR	Kouloulias	2002	110

Abbreviations: EBRT = external beam radiotherapy; ND = no difference; other abbreviations as in Table 2.
The references listed in Table 9 correspond to those cited in the full manuscript published online and contained in the Supplemental Materials section.

Kyphoplasty and vertebroplasty have theoretically shown the most promise in patients with metastatic spinal disease causing instability of the vertebral body, although the lack of completed prospective studies should limit their standard use (Table 10). Small series of patients have been treated with kyphoplasty or vertebroplasty plus EBRT, stereotactic radiosurgery, or interstitial samarium-153. However, 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 such as proper patient selection, efficacy, toxicity, and timing in relation to radiotherapeutic interventions.

CONCLUSIONS

External beam radiotherapy has been, and continues to be, the mainstay for the treatment of painful, uncomplicated bone metastases. Although various fractionation schemes can provide good rates of palliation, numerous prospective randomized trials have shown that 30 Gy in 10 fractions, 24 Gy in 6 fractions, 20 Gy in 5 fractions, or 8 Gy in a single fraction can provide excellent pain control and minimal side effects. The longer course has the advantage of a lower incidence of repeat treatment to the same site, and the single fraction has proved more convenient for patients and caregivers. Repeat irradiation with EBRT might be safe, effective, and less commonly necessary in patients with a short life expectancy. Bisphosphonates do not obviate the need for EBRT for painful sites of metastases and might, indeed, act effectively when combined with EBRT. SBRT might be useful for patients with newly discovered or recurrent tumor in the spinal column or paraspinal areas; however, the Task Force suggests that SBRT be reserved for patients who fit specific inclusion and exclusion criteria, who undergo treatment at centers with sufficient training and experience, and should preferably be treated 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 could conveniently or safely be treated with EBRT. Hemibody RT is an option for these patients who reside in geographic areas where radionuclides are not readily available or when they are medically contraindicated.

Table 10. Studies investigating vertebroplasty/kyphoplasty and bone metastases

Study	Patients (*n*)/ levels (*n*)	Diagnoses	Pain scale	Mean preprocedure score	Mean postprocedure score	Symptomatic extravasation rate (%)	Neurologic toxicity	Investigator	Year	Reference
Prospective studies using vertebroplasty										
Percutaneous vertebroplasty and bone cement leakage	14/42	Various histologic types, MM, H	Visual analog scale (0–10)	8	1	0	0	Anselmetti	2008	125
Percutaneous vertebroplasty in octogenarians: results and follow-up	22/48	Various histologic types, MM	Verbal rating scale (0–5)	5	2	0	0	Cahana	2005	126
Percutaneous vertebroplasty in patients with intractable pain from osteoporotic or metastatic fractures	13	Various histologic types	Site-specific pain score (0–10)	NR	NR	8	8	Cheung	2006	127
Percutaneous vertebroplasty for osteolytic metastases and myeloma	37/40	Various histologic types, MM	McGillMelzack (0–5)	Pain relief*	Pain relief*	2	8	Cotton/ Cortet	1996/ 1997	128, 129
Medium-term results of percutaneous vertebroplasty in MM	12/19	MM	Visual analog scale (0–10)	8	3	0	0	Ramos	2006	130
Prospective studies using kyphoplasty										
Kyphoplasty in treatment of osteolytic vertebral compression fractures resulting from MM	18/55	MM	Short form-36 (0–100)	23	55	0	0	Dudeney	2002	131
Combination kyphoplasty and spinal radiosurgery	26/26	Various histologic types	Visual analog scale (0–10)	8	3	0	0	Gerszten	2005	132
Functional outcomes of kyphoplasty for treatment of osteoporotic and osteolytic vertebral compression fractures	56	MM	Short form-36 (0–100)	28	48	NR	NR	Khanna	2006	133
Kyphoplasty enhances function and structural alignment in MM	19/46	MM	NR	NR	NR	0	0	Lane	2004	134
Balloon kyphoplasty in treatment of metastatic disease of spine	65/99	Various histologic types	Visual analog scale (0–10)	8	3	0	0	Pflugmacher	2008	135

Abbreviations: Levels = treated vertebral levels; MM = multiple myeloma; H = hemangioma.

* Of 37 patients, 36 had partial or complete pain relief.

The references listed in Table 10 correspond to those cited in the full manuscript published online and contained in the Supplemental Materials section.

Surgical decompression and stabilization plus postoperative RT should be considered for selected patients with single-level spinal cord compression or spinal instability, unless the patients have an anticipated life expectancy that is too short. Kyphoplasty and vertebroplasty might be useful for the treatment of lytic osteoclastic spinal metastases or in cases of spinal instability for which surgery is not feasible or indicated. They do not obviate the need for EBRT, and no data are available to suggest that the addition of vertebroplasty or kyphoplasty further improve symptoms or has a greater effect on clinically significant endpoints than EBRT alone. Additional prospective trials are needed to better define whether a patient population exists 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 bone metastases quality-of-life questionnaire (18, 19). The proper management of painful osseous metastases demands prompt discovery, appropriate pharmacologic management, and the data-driven use of palliative EBRT.

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