Guideline Summary NGC-8836

Guideline Title

Palliative radiotherapy for bone metastases: an ASTRO evidence-based guideline.

Bibliographic Source(s)

Lutz S, Berk L, Chang E, Chow E, Hahn C, Hoskin P, Howell D, Konski A, Kachnic L, Lo S, Sahgal A, Silverman L, von Gunten C, Mendel E, Vassil A, Bruner DW, Hartsell W, American Society for Radiation Oncology (ASTRO). Palliative radiotherapy for bone metastases: an ASTRO evidence-based guideline. Int J Radiat Oncol Biol Phys 2011 Mar 15;79 (4):965-76. [19 references] PubMed

Guideline Status

This is the current release of the guideline.

Scope

Disease/Condition(s)

Bone metastases

Guideline Category

Assessment of Therapeutic Effectiveness

Treatment

Clinical Specialty

Neurological Surgery

Neurology

Nuclear Medicine

Oncology

Radiation Oncology

Radiology

Surgery

Intended Users

Advanced Practice Nurses

Allied Health Personnel

Nurses

Patients

Physician Assistants

Physicians

Guideline Objective(s)

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

Target Population

Patients with bone metastases

Interventions and Practices Considered

1. External beam radiotherapy (EBRT)
2. Single- versus multiple-fraction radiation schedules
3. Repeat radiotherapy
4. Stereotactic body radiotherapy (considered but not recommended as primary treatment outside of clinical trials)
5. Surgical decompression and postoperative radiotherapy for spinal cord compression or spinal instability
6. Radiopharmaceuticals plus radiotherapy
7. Bisphosphonates plus radiotherapy
8. Vertebroplasty or kyphoplasty plus radiotherapy

Major Outcomes Considered

- Pain relief efficacy
- Complete and partial response rate
- Patient and caregiver convenience
- Side effects and adverse events
- Toxicity (acute and late)
- Safety
- Need for external beam radiotherapy (EBRT)

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Literature Search

Whenever possible, the Guideline relied on an evidence-based approach using a formal systematic literature review. One investigator with aid from the American Society for Radiation Oncology (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 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.

Bibliographies of the candidate studies were also reviewed to ensure that all eligible studies were evaluated, including those published before 1998.

Number of Source Documents

Of the literature sample, the investigators identified 25 randomized clinical trials, 20 prospective single-arm studies, and 4 meta-analyses/systematic reviews.

Methods Used to Assess the Quality and Strength of the Evidence

Expert Consensus

Rating Scheme for the Strength of the Evidence

Not applicable

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Whenever possible, the Guideline relied on an evidence-based approach using a formal systematic literature review.

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 reviewed all the prospective studies from every topic. The prospective studies were abstracted for the

inclusion criteria, radiotherapy methods, clinical outcomes, and toxicity.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

The Guidelines Subcommittee of the Clinical Affairs and Quality Committee, in accordance with established American Society for Radiation Oncology (ASTRO) policy, recruited a Task Force composed of recognized experts in the fields of palliative radiotherapy (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 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.

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

A formal cost analysis was not performed and published analyses were not reviewed.

Method of Guideline Validation

External Peer Review

Description of Method of Guideline Validation

After the secondary review by the Task Force as a whole, the initial draft of the Guideline was sent to external reviewers. The American Society of Radiation Oncology Board of Directors integrated this feedback and approved the final document in July 2010.

Recommendations

Major Recommendations

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 ten fractions, 24 Gy in six fractions, 20 Gy in five fractions, and a single 8-Gy fraction for patients with previously unirradiated painful bone metastases. Fractionated radiotherapy (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.

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 in the original guideline document 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. 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. 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 (see Table 2 in

the original guideline document). 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.

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 external beam RT (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 (SBRT) 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 (see Tables 3, 4, and 5 in the original guideline document). 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.

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 (see Table 6 in the original guideline document). 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 (see Table 7 in the original guideline document). The optimal dosing of postoperative EBRT could not be determined from the available data. However, longer schedules, such as 30 Gy in ten 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 (see Table 8 in the original guideline document). 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 promotes re-ossification of the damaged bone, with an acceptable risk of toxicity (see Table 9 in the original guideline document). 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. 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 (see Table 10 in the original guideline

document). 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.

Clinical Algorithm(s)

None provided

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of evidence supporting the recommendations is not specifically stated.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

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.

Potential Harms

- The frequency and severity of side effects, especially in mucosal structures, for a single 8 Gy fraction 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.
- 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 than with multi-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. 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.
- 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%. 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.
- Though the surrounding normal tissues are relatively spared by the radiopharmaceutical agents strontium-89 and samarium-153, both can cause myelosuppression, a potentially serious side effect in this population of patients. 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. 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.
- Drawbacks to the delivery of bisphosphonates can include renal impairment and osteonecrosis of the jaw.
- Side effects to percutaneous vertebroplasty may include extravasation of cement outside of the vertebral bone as well as traumatic fracture, pneumothorax, pulmonary embolism, fat emboli, dural tears, and death.

Contraindications

Contraindications

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.

Qualifying Statements

Qualifying Statements

- 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. The American Society of Radiation Oncology (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.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

End of Life Care

Living with Illness

IOM Domain

Effectiveness

Safety

Identifying Information and Availability

Bibliographic Source(s)

Lutz S, Berk L, Chang E, Chow E, Hahn C, Hoskin P, Howell D, Konski A, Kachnic L, Lo S, Sahgal A, Silverman L, von Gunten C, Mendel E, Vassil A, Bruner DW, Hartsell W, American Society for Radiation Oncology (ASTRO). Palliative radiotherapy for bone metastases: an ASTRO evidence-based guideline. Int J Radiat Oncol Biol Phys 2011 Mar 15;79 (4):965-76. [19 references] PubMed

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2011 Mar 15

Guideline Developer(s)

American Society for Radiation Oncology - Professional Association

Source(s) of Funding

American Society for Radiation Oncology

Guideline Committee

Guidelines Subcommittee of the Clinical Affairs and Quality Committee

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Financial Disclosures/Conflicts of Interest

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 American Society of Radiation Oncology 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.

A. Sahgal and E. Chang have served as consultants to Medtronic Kyphoplasty, although that relationship has ended and the authors did not participate in either the writing or reviewing of the kyphoplasty section of this report. L. Kachnic serves as a consultant to Soligenics. D. Howell serves as a consultant to Web MD and Medscape. S. Lutz has stock ownership in Tosk, Oculus, and Minerva. C. von Gunten has received funding from Wyeth, Progenics, Baxter, and Halozyme. W. Hartsell has a partnership relationship with CPTI. P. Hoskin has received funding from Varian Medical Systems and Nucleotron. E. Chow has received research funding and teaching honorarium from Novartis and Amgen. D.

Watkins Bruner has received funding from Varian Medical Systems. The Task Force reviewed these disclosures and determined that they have no impact upon the content of the report.

Guideline Status

This is the current release of the guideline.

Guideline Availability

Electronic copies: Available in Portable Document Format (PDF) from the International Journal of Radiation Oncology Biology Physics Web site.

Availability of Companion Documents

The following is available:

- Palliative radiotherapy for bone metastases: an ASTRO evidence-based guideline. Full guideline. Fairfax (VA): American Society of Radiation Oncology (ASTRO); 2011 Mar. 49 p. Electronic copies: Available from the International Journal of Radiation Oncology Biology Physics Web site.

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on April 20, 2012. The information was verified by the guideline developer on May 29, 2012.

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