Practical Radiation Oncology (2017) 7, 4-12

practical radiation oncology
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Special Article

Palliative radiation therapy for bone metastases: Update of an ASTRO Evidence-Based Guideline

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Received 4 May 2016; revised 15 July 2016; accepted 3 August 2016

Abstract

Purpose: The purpose is to provide an update the Bone Metastases Guideline published in 2011 based on evidence complemented by expert opinion. The update will discuss new high-quality literature for the 8 key questions from the original guideline and implications for practice.

Methods and materials: A systematic PubMed search from the last date included in the original Guideline yielded 414 relevant articles. Ultimately, 20 randomized controlled trials, 32 prospective nonrandomized studies, and 4 meta-analyses/pooled analyses were selected and abstracted into evidence tables. The authors synthesized the evidence and reached consensus on the included recommendations.

Results: Available literature continues to support pain relief equivalency between single and multiple fraction regimens for bone metastases. High-quality data confirm single fraction radiation therapy may be delivered to spine lesions with acceptable late toxicity. One prospective, randomized trial confirms both peripheral and spine-based painful metastases can be successfully and safely palliated with retreatment for recurrence pain with adherence to published dosing constraints. Advanced radiation therapy techniques such as stereotactic body radiation therapy lack high-quality data, leading the panel to favor its use on a clinical trial or when results will be collected in a registry. The panel's conclusion remains that surgery, radionuclides, bisphosphonates, and kyphoplasty/vertebroplasty do not obviate the need for

Supplementary material for this article (http://dx.doi.org/10.1016/j.prro.2016.08.001) can be found at www.practicalradonc.org.

Conflicts of interest. Before initiating work on this guideline, all panelists completed disclosure statements and pertinent disclosures are published within this report. Where potential conflicts are detected, remedial measures to address them are taken and noted here. TB received research funding from Templeton Foundation and leads ongoing bone metastases study. S.Lo. participated in international oligometastases consortium partially funded by Elekta and received honoraria and travel expenses from Accuray and Varian. These disclosures were shared with the panel. The panel and guideline subcommittee chair reviewed these relationships and determined that the disclosure here is sufficient to manage potential conflicts.

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http://dx.doi.org/10.1016/j.prro.2016.08.001

external beam radiation therapy.
Conclusion: Updated data analysis confirms that radiation therapy provides excellent palliation for painful bone metastases and that retreatment is safe and effective. Although adherence to evidence-based medicine is critical, thorough expert radiation oncology physician judgment and discretion regarding number of fractions and advanced techniques are also essential to optimize outcomes when considering the patient's overall health, life expectancy, comorbidities, tumor biology, anatomy, previous treatment including prior radiation at or near current site of treatment, tumor and normal tissue response history to local and systemic therapies, and other factors related to the patient, tumor characteristics, or treatment.

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. Radiation therapy (RT) provides successful palliation of painful bone metastases that is time-efficient and associated with very few side effects.[1,2]

The American Society for Radiation Oncology (ASTRO) initially published *Palliative Radiotherapy for Bone Metastases: An ASTRO Evidence-Based Guideline* in March 2011 and evaluated it for updating in June 2014.[3] In accordance with Institute of Medicine recommendations,[4] the ASTRO guidelines subcommittee has established a formal process for reviewing guidelines more than 2 years postpublication for novel high-quality evidence. Guidelines for which new data have been published, potentially impacting practice and appropriate treatment, or that are 5 years postpublication are assessed for revision or withdrawal.

This update to the bone metastases guideline will consider new high-quality evidence for the 8 key questions (KQs) addressed by the original guideline.

Methods and materials

Process

In May 2014, the guidelines subcommittee convened a work group to review available evidence and recommend whether the bone metastases guideline should be withdrawn, updated, or left intact. The group comprised 1 colead of the original guideline, 3 topic experts (2 not involved in the original guideline), and 4 guidelines subcommittee members. After review of new literature, the work group recommended an update of all KQs from the original guideline and the proposal was approved by the ASTRO Board of Directors in November 2014. The update panel was identical to the work group.

Through calls and e-mails, the panel formulated recommendation statements and narratives based on the literature review. The draft manuscript was reviewed by 5 expert reviewers (see Acknowledgments) and ASTRO legal counsel. The update was posted online for public comment December 2015 through January 2016. The final document was approved by the Board of Directors in April 2016.

Literature review

A systematic review was initially conducted by ASTRO staff of English-language studies in PubMed published between the last date searched in the original guideline, December 22, 2009, and June 17, 2014. Following approval of the update proposal, the review was extended through January 7, 2015. Both MeSH terms and text words were used (Appendix A). Terms common to all searches included: bone metastasis, bone metastases, radiation, and radiotherapy. Additional specific terms were incorporated for each KQ. The outcomes of interest were overall and progression-free survival, recurrence, toxicity, and quality of life.

In total, 414 references meeting the inclusion criteria were retrieved by the PubMed searches and reviewed first by ASTRO staff and then by the whole panel. The inclusion criteria were: age $\geq$18 years; bone metastases that were previously unirradiated or causing recurrent pain after radiation therapy; and treatment with external beam RT (EBRT), intensity modulated RT, or stereotactic body RT (SBRT) with or without bisphosphonates, radiopharmaceuticals, kyphoplasty, or vertebroplasty. The exclusion criteria were: nonhuman, dosimetric-only, case report, and conference abstract. The results were further refined to include only randomized controlled trials (RCTs), meta-analysis, or prospective study. Ultimately, 56 studies were included and abstracted into evidence tables. One additional article (Hoskin et al) representing significant new data for KQ8 was included in September 2015.

Grading of evidence and recommendations and consensus methodology

The recommendation statements (Table 1) were developed based on high-quality evidence in accordance with Institute of Medicine standards. Panel consensus was evaluated in 2 rounds through a modified Delphi approach. In an online survey, panelists rated agreement with each recommendation

Table 1 Grading of evidence, recommendations, and consensus methodology

Guideline recommendation	Agreement, %	Strength of recommendation	Strength of evidence
KQ 1. What fractionation schemes have been shown to be effective for the treatment of painful and/or prevention of morbidity from peripheral bone metastases?			
An updated review of high-quality data continues to show pain relief equivalency following a single 8 Gy fraction, 20 Gy in 5 fractions, 24 Gy in 6 fractions, and 30 Gy in 10 fractions for patients with previously unirradiated painful bone metastases. Patients should be made aware that SF RT is associated with a higher incidence of retreatment to the same painful site than is fractionated treatment.	100	Strong	High
KQ 2. When is SF RT appropriate for the treatment of pain and/or prevention of morbidity from uncomplicated bone metastasis involving the spine or other critical structures?			
A single 8 Gy fraction provides noninferior pain relief compared with a more prolonged RT course in painful spinal sites and may therefore be particularly convenient and sensible for patients with limited life expectancy.	100	Strong	High
KQ 3. Are there long-term side-effect risks that should limit the use of SF therapy?			
There continues to be no suggestion from available high-quality data that SF therapy produces unacceptable rates of long-term side effects that might limit its use for patients with painful bone metastases. The evidence regarding an association between higher risk for pathologic fracture after SF therapy vs fractionated therapy remains equivocal.	100%	Strong	High
KQ 4. When should patients receive retreatment with radiation to peripheral bone metastases?			
Patients with persistent or recurrent pain more than 1 month following EBRT for symptomatic, peripheral bone metastases should be considered for retreatment while adhering to normal tissue dosing constraints described in the available literature.	100%	Strong	High
KQ 5. When should patients receive retreatment with radiation to spine lesions causing recurrent pain?			
Patients with recurrent spine pain more than 1 month after initial treatment should be considered for EBRT retreatment while adhering to normal tissue dosing constraints described in the available literature.	100%	Strong	High
KQ 6. What promise does highly conformal RT hold for the primary treatment of painful bone metastasis?			
Advanced RT techniques such as SBRT as the primary treatment for painful spine bone lesions or for spinal compression should be considered in the setting of a clinical trial or with data collected in a registry given that insufficient data are available to routinely support this treatment currently.	100%	Strong	Moderate
KQ 7. When should highly conformal RT be considered for retreatment of spine lesions causing recurrent pain?			
Advanced radiation techniques such as SBRT retreatment for recurrent pain in spine bone lesions may be feasible, effective, and safe, but the panel recommends that this approach should be limited to clinical trial participation or on a registry given limited data supporting routine use.	100%	Strong	Moderate
KQ8. Does the use of surgery, radionuclides, bisphosphonates, or kyphoplasty/vertebroplasty obviate the need for palliative RT for painful bone metastasis?			
The panel reiterates that the use of surgery, radionuclides, bisphosphonates, or kyphoplasty/vertebroplasty does not obviate the need for EBRT for patients with painful bone metastases, although 2 recent trial has suggested the potential for similar, albeit less rapid, bone pain relief in prostate cancer patients following an infusion of ibandronate when compared with a single fraction of EBRT.	100%	Strong	Moderate

EBRT, external beam radiation therapy; RT, radiation therapy; SBRT, stereotactic body radiation therapy; SF, single fraction.

on a 5-point Likert scale, from strongly disagree to strongly agree. A prespecified threshold of ≥75% "agree" or "strongly agree" responses indicated consensus.[5] Following the first round, the recommendations for KQs 4 and 5, which cover reirradiation, were updated to emphasize the need for adherence to normal tissue constraints. The recommendations for KQs 6 and 7, addressing the role of highly conformal radiation therapy, initially failed to reach consensus and were revised to clarify the level of current evidence and the settings in which advanced technologies should be used. These 4 recommendations were rerated and the results replaced those from the first round. The strength of the recommendation and supporting evidence were also rated using the American College of Physicians process.[6] A strong recommendation indicated "benefit of the intervention outweighs the risk, or vice versa, and the panel has reached uniform consensus." A weak recommendation showed "benefit of the intervention equals the risk, or vice versa, and the panel has reached uniform or nonuniform consensus." The chair initially assigned the ratings, which the panel later approved.

Results

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

Guideline Statement:

A. An updated review of high-quality data continues to show pain relief equivalency following a single 8 Gy fraction, 20 Gy in 5 fractions, 24 Gy in 6 fractions, and 30 Gy in 10 fractions for patients with previously unirradiated painful bone metastases. Patients should be made aware that single-fraction (SF) RT is associated with a higher incidence of retreatment to the same painful site than is fractionated treatment. (High Quality Evidence, Strong Recommendation)

Results of series published since the initial ASTRO guideline on bone metastases[3] continue to support equivalent pain relief from the previous fractionation regimens (Table 2). Series from Gutierrez Bayard,[7] Howell,[1] and Majumder[8] all evaluated the efficacy of treatment of symptomatic bone metastases with 8 Gy/1 fraction versus 30 Gy/10 fractions and demonstrate these regimens are effective for pain relief, with response rates of 70% to 80% and decreased pain scores and narcotic use. Meeuse et al documented similar findings with comparison of 8 Gy/1 fraction and 24 Gy/6 fractions.[9] Meta-analyses by Chow et al confirm these results using combined data from 5617 patients in 25 RCTs with overall response rates of 60% versus 61% for SF and multiple fraction (MF) regimens.[10] Retreatment rates remain increased in patients with more protracted survival receiving SF in series from Gutierrez Bayard and Howell.[1,7] A meta-analysis confirmed rates of retreatment as 20% for SF and 8% for MF, although none of these findings contradict a previous study that showed that duration of pain response did not differ for patients who lived less or more than 52 weeks.[10,11]

KQ 2: When is SF RT appropriate for the treatment of pain and/or prevention of morbidity from uncomplicated bone metastasis involving the spine or other critical structures?

Guideline Statement:

A. A single 8 Gy fraction provides noninferior pain relief compared with a more prolonged RT course in painful spinal sites and may therefore be particularly convenient and sensible for patients with limited life expectancy. (High Quality Evidence, Strong Recommendation)

Howell et al evaluated the subset of patients with painful vertebral metastases in the Radiation Therapy Oncology Group 97-14 trial and found they were comparable to the entire population, with partial or complete pain response in 70% versus 62% for SF versus MF arms (not significant).[1] Retreatment rates at 3 years were higher for SF versus MF: 15% versus 5% in patients with lumbar spine metastases ($P = .01$). Majumder et al documented similar response rates in terms of pain response and toxicity of treating spinal metastases with SF versus MF regimens.[8]

KQ 3: Are there long-term side-effect risks that should limit the use of SF therapy?

Guideline Statement:

A. There continues to be no suggestion from available high-quality data that SF therapy produces unacceptable rates

Table 2 New prospective studies comparing SF vs MF RT regimens (KQs 1-3)

Investigator, y	Patients (n)	Fractionation	Complete or partial response (%)	Complete response (%)	Acute and late toxicity (%)	Repeat treatment rate (%)
Chow, 2012[8]	5617 in 25 RCTs	SF	60	23	NR	20
		MF	61	24		8 [a]
Gutierrez Bayard, 2014[4]	90	8 Gy in 1 fx	79	17	NR	13.3
		30 Gy in 10 fx	88	18		8.8 [a]
			at 4 wk	at 4 wk		
Howell, 2013[5]	235	8 Gy in 1 fx	70	19	10	15
		30 Gy in 10 fx	62	17%	20 [a]	5 [a]
			at 3 mo	at 3 mo	(acute grade 2-4)	
Majumder, 2012[6]	64	8 Gy in 1 fx	85	0	No statistically	NR
		30 Gy in 10 fx	77	0	significant difference	
			at 1 month	at 1 month		
Meeuse, 2010[7]	1157	8 Gy in 1 fx	53	NR	NR	7
		24 Gy in 6 fx	56			2
			(assessable patients)			

fx, fraction; MF, multiple fractions; NR, not reported; RCT, randomized controlled trial; SF, single fraction.

[a] Statistically significant comparison.

of long-term side effects that might limit its use for patients with painful bone metastases. The evidence regarding an association between higher risk for pathologic fracture after SF therapy versus fractionated therapy remains equivocal. (High Quality Evidence, Strong Recommendation)

Majumder et al demonstrated no significant differences in toxicity in spine patients treated with SF versus MF regimens.[8] Gutierrez Bayard's small group of randomized patients showed an increased risk of pathologic fracture with SF versus MF (15.5 % vs. 4.4%), as well as increased skeletal events (28.8 % vs. 13.3%).[7] However, Bayard's study was not constructed to focus on fracture risk. Moreover, Chow's meta-analysis supports Majumder's findings and found similar incidences of pathologic fracture between SF and MF treatment (3.3% vs. 3%).[10]

KQ 4: When should patients receive retreatment with radiation to peripheral bone metastases?

Guideline Statement:

A. Patients with persistent or recurrent pain more than 1 month following EBRT for symptomatic, peripheral bone metastases should be considered for retreatment while adhering to normal tissue dosing constraints described in the available literature. (High Quality Evidence, Strong Recommendation)

Findings support use of reirradiation, given its association with moderate pain relief regardless of prior response to palliative RT (Table 3).[11,12]

A systematic review and meta-analysis of trials including patients receiving reirradiation for painful bone metastases demonstrated moderate palliative efficacy, with overall pain response rate of 58%.[11] Also, an international, multicenter, RCT of patients receiving retreatment for painful bone metastases not complicated by spinal cord compression or pathologic fracture showed that[1]: response rates were 45% in the SF arm and 51% in the MF arm,[2] there was no clinically significant difference in response between 8 Gy in a SF and 20 Gy in 5 fractions,[3] acute toxicities were more common in the MF arm, and[4] overall pain response did not correlate with previous response to RT nor did it correlate with dose fractionation.[12] Patients were excluded from the trial if they initially received treatment to the ribs or extremities that exceeded 30 Gy in 10 fractions.

KQ 5: When should patients receive retreatment with radiation to spine lesions causing recurrent pain?

Guideline Statement:

A. Patients with recurrent spine pain more than 1 month after initial treatment should be considered for EBRT retreatment while adhering to normal tissue dosing constraints described in the available literature. (High Quality Evidence, Strong Recommendation)

Both a meta-analysis and a prospective retreatment trial for painful bone metastases with EBRT have included spine metastases patients, with findings supporting moderate treatment efficacy.[11,12] The meta-analysis included 36% of patients with spine sites and showed a 58% overall response rate at all sites, revealing minimal toxicity and no radiation myelopathy.[11] The international, multicenter randomized controlled trial of retreatment to 8 Gy × 1 or 4 Gy × 5 included 28% patients who received prior spine RT to doses of 6, 7, or 8 Gy × 1; 4.5 Gy × 4, or 4 Gy × 5 (biologically equivalent doses $\leq$60 Gy_2) to the thoracic, lumbar, and/or sacral spine (28% SF, 29% MF). The study excluded patients with spinal cord compression or initial courses of RT of higher dose intensity, such as patients who received a prior RT dose $\geq$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.[12] For these spine patients, there were no differences in pain response whether retreatment was provided using SF or MF. The overall pain response for all sites was 45% for SF and 51% for MF. Spinal and cauda equina compression rates were 2% in SF arm versus 1% in MF arm, and there were no cases of radiation myelopathy.

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

Guideline Statement:

A. Advanced RT techniques such as SBRT as the primary treatment for painful spine bone lesions or for spinal cord compression should be considered in the setting of a clinical

Table 3 New prospective studies describing repeat treatment (KQs 4-5)

Investigator, y	Patients (n)	Initial fractionation	Retreatment fractionation	Overall pain relief with retreatment (%)
Chow, 2014[10]	850	Single in 66%, multiple in 34%	8 Gy in 1 fx	45
			20 Gy in 5 fx	51
				at 2 months (per protocol analysis)
Huisman, 2012[9]	527 in 7 studies	Mostly 8 Gy in 1 fx	Any	58

fx, fraction.

trial or with data collected in a registry given that insufficient data are available to routinely support this treatment currently. (Moderate Quality Evidence, Strong Recommendation)

Advanced RT techniques such as SBRT provide a high biologically equivalent dose to the target. Although there are scant data regarding the use of SBRT for nonspine metastases, highly conformal therapy can allow for treatment of vertebral bones and surrounding paraspinal areas with relative sparing of adjacent neural structures. However, SBRT efficacy and safety data are derived from lower quality studies with variable exclusion criteria that often report local control as the primary outcome, making it difficult to compare with existing external beam studies that report pain relief (Appendix B). This method of treatment may be more frequently associated with a pain flare.[13] The technological advantages of SBRT do merit its use in patients on clinical trials that adhere to strict methodologies for patient setup as well as control of intrafraction motion and that measure variables including pain relief, local control, vertebral body fracture, radiation myelopathy, and spinal cord compression. Practitioners should closely adhere to quality and safety considerations for SBRT delivery as described in an ASTRO white paper.[14] SBRT use for patients who present with spinal cord compression should be considered only with great caution given the absence of a physical separation between the target and adjacent normal critical structures. The use of curative intent SBRT for oligometastases is not addressed in this guideline. Eligible patients with spine bone metastases should continue to be considered for available SBRT trials to clarify the optimal treatment approach.

KQ 7: When should highly conformal RT be considered for retreatment of spine lesions causing recurrent pain?

Guideline Statement:

A. Advanced radiation techniques such as SBRT retreatment for recurrent pain in spine bone lesions may be feasible, effective, and safe, but the panel recommends that this approach should be limited to clinical trial participation or on a registry given limited data supporting routine use. (Moderate Quality Evidence, Strong Recommendation)

It is feasible to deliver retreatment to sites of recurrent metastatic spine pain with SBRT, but research in this area is limited. With meticulous patient positioning, SBRT may provide greater spinal cord sparing than conventional EBRT and may be the preferred choice when the spinal cord has received previous RT dosing, particularly when the initial spinal RT course was of a dose intensity higher than those allowed in the Chow et al bone metastases retreatment study. Once again, practitioners should use existing ASTRO white paper safety recommendations.[14] In general, specifics of SBRT retreatment dosing and target delineation are insufficiently defined to allow SBRT retreatment outside a clinical trial or when results will be captured in a data registry, and there is no high-level evidence of superiority of SBRT over conventional EBRT for pain control. The use of retreatment, curative intent SBRT for oligometastatic spine disease is not addressed in this guideline.

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

Guideline Statement:

A. The panel reiterates that the use of surgery, radionuclides, bisphosphonates, or kyphoplasty/vertebroplasty does not obviate the need for EBRT for patients with painful bone metastases, although 1 recent trial has suggested the potential for similar, albeit less rapid, bone pain relief in prostate cancer patients following an infusion of ibandronate when compared with a single fraction of EBRT. (Moderate Quality Evidence, Strong Recommendation).

Surgery and EBRT for spinal cord compression

After comprehensive review of available data, the original guideline concluded surgery does not obviate the need for postoperative EBRT for patients with spinal cord compression. Updated literature review by the current panel did not identify any new high-quality data to add to previously published recommendations.[15] The panel continues to encourage an interdisciplinary approach to patient selection for surgical decompression and recommends consideration of clinical trials investigating the potential role of advanced radiation techniques (see KQ6) in this setting. Longer schedules, such as 30 Gy in 10 fractions in the phase 3 trial by Patchell, continue to be most commonly prescribed after surgery.[16] Eligible patients with spinal cord compression should continue to be considered for available dose fractionation trials to clarify the optimal treatment schedule.

Radiopharmaceuticals and EBRT

There has been an abundance of recently published studies, including clinical trials, affirming the safety and efficacy of familiar agents, samarium-153 and strontium-89, as well as rhenium-186 and radium-223 (Table 4).[17-28] Most intriguing is the growing evidence that, in patients with bone-only or bone-dominant disease, these agents may provide benefits beyond pain relief, including prevention of skeletal-related events and improved survival, although appropriate use of radiopharmaceuticals with the intention of improving survival is not addressed in this guideline.[18,29,30] Regarding the benefit of EBRT, a phase 3 RCT of samarium-153 with or without EBRT (8 Gy × 1 in 90% receiving EBRT) in metastatic prostate cancer with painful

Table 4 New prospective studies investigating use of radionuclides (KQ 8)

Investigator, y	Patients (n), site of origin	Radionuclide	Complete or partial response (%)	Complete response (%)	Acute toxicity (%)	Subsequent EBRT required (%)	Survival
Studies using radium-223							
Nilsson, 2012[17]	100, prostate	223Ra •5 kBq/kg •25 kBq/kg •50 kBq/kg •100 kBq/kg	 40 63 56 71 at 8 wk	NR	97% had ≥1 treatment-related adverse event(s)	21	38% at 24 mo
Nilsson, 2013[18]	64, prostate	EBRT plus 223Ra EBRT plus placebo	NR	NR	NR	NR	30% 13% at 24 months
Parker, 2013[19]	122, prostate	223Ra •25 kBq/kg •50 kBq/kg •80 kBq/kg	NR	NR	92% had ≥1 adverse event(s)	11	43% at 24 mo
Parker, 2013[20]	921, prostate	223Ra Placebo	NR	NR	93 96	NR	NR
Sartor, 2014[21]	921, prostate	223Ra Placebo	NR	NR	NR	30 34[a]	NR
Studies using rhenium-188							
Cheng, 2011[30]	64, all histologies	188Re-HEDP •20 kBq/kg •30 kBq/kg •40 kBq/kg •50 kBq/kg	 61 64 86 86 at 8 wk	 0 7 14 21 at 8 wk	30	NR	NR
Pirayesh, 2013[22]	19, all histologies	186Re-HEDP	78% had at least 1-wk response	47	NR	NR	NR
Studies using samarium-153							
Baczyk, 2013[13]	177, prostate	153Sm 153Sm + EBRT	85 89	43 63	No statistically significant difference	NR	NR
Petersen, 2010[23]	22, prostate	153Sm	75% at ≥1 follow-up visits	NR	NR	NR	50% at 28 wk
Storto, 2013[24]	24, prostate	153Sm-EDTMP No therapy	100% 0% at 8 wk	NR	NR	NR	NR
Studies using strontium-89							
Liu, 2014[25]	26, all histologies	89Sr with dendritic cell vaccine	40	0	NR	NR	58% at 36 mo
Yamada, 2012[14]	16, breast cancer	89Sr and zoledronic acid	88	31	NR	NR	NR
Zorga, 2011[26]	49, all histologies	89Sr	77	NR	Hemotoxicity in 80%	NR	NR

*Statistically significant comparison.

EBRT, external beam radiation therapy; EDTMP, ethylenediamine tetra(methylene phosphonic acid); HEDP, hydroxyethylidenediphosphonate; kBq, kilobecquerel; NR, not reported; Ra, radium; Re, rhenium; Sm, samarium; Sr, strontium.

bony metastases demonstrated a significant improvement in pain relief with addition of EBRT and no extra toxicity.[17]

Bisphosphonates and EBRT

The updated literature review highlights continued accumulation of data demonstrating benefits from bisphosphonates and similar medications (ie, denosumab) in reducing skeletal-related events.[31-36] In addition to practical advantages associated with denosumab, several prospective trials have suggested improved efficacy compared with bisphosphonates.[31-33] New prospective trials also confirm these medications can be given safely with palliative radiation, both EBRT and radiopharmaceuticals.[18,19] Although bisphosphonates do not routinely obviate the need for EBRT, 2 recently published prospective, randomized

trial did demonstrate similar pain relief and quality of life at 4 and 12 weeks after receiving either intravenous infusion of a single 6-mg dose of ibandronate or a single 8-Gy fraction of EBRT for painful prostate cancer bone metastases. Pain relief was more rapid in the group treated with EBRT, whereas toxicities were different but minimal in each arm of the study.[37] Further studies may further elucidate circumstances where EBRT may be omitted.

Kyphoplasty or vertebroplasty and EBRT

The updated literature review demonstrates no new high-quality data, reinforcing the previous panel's statement that no prospective data suggest either kyphoplasty or vertebroplasty obviate the need for EBRT for painful bone metastases. The short list of available, small series on kyphoplasty or vertebroplasty plus radiation (EBRT, SBRT, or interstitial samarium-153), now includes a new prospective study of 11 patients treated with vertebroplasty and samarium-153.[20] However, these limited data do not allow definitive statements regarding combined regimens and highlight the importance of future prospective trials addressing proper patient selection, efficacy, toxicity, and timing in relation to radiation therapy.

Future directions

Clarification of several remaining uncertainties will better define appropriate care of patients with symptomatic bone metastases. A more robust definition of "uncomplicated" bone metastases will aid decision-making for surgery and fractionation, although 1 recent paper does review the topic and state, "Uncomplicated" bone metastases can be defined as: presence of painful bone metastases unassociated with impending or existing pathologic fracture or existing spinal cord or cauda equina compression."[38] The value of intensity modulated RT and image guided RT for patients receiving standard fractionation for new and recurrent painful lesions needs to be determined. Similarly, completion of prospective, randomized trials will better define proper use of SBRT for newly discovered and recurrent spine bone lesions. Development of higher quality data will further address the best combinations of EBRT with bisphosphonates and radiopharmaceuticals.[39] Studies will require excellent follow-up to further evaluate patient reported outcome measures such as ongoing levels of pain as well as pain medicine usage. In general, expert radiation oncology physician judgment and discretion regarding number of fractions and advanced techniques is essential to optimize patient outcomes when considering the patient's overall health, life expectancy, comorbidities, tumor biology, anatomy, previous treatment including prior radiation at or near current site of treatment, tumor and normal tissue response history to local and systemic therapies, and other factors related to the patient, tumor characteristics, or treatment.

Acknowledgments

The authors thank the expert reviewers: Edward Chow MBBS, MSc, PhD; William Hartsell MD; Peter Johnstone MD; Peter Hoskin MD; and Yvette van der Linden MD, PhD; and acknowledge Caroline Patton and Margaret Amankwa-Sakyi for literature review and administrative support.

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