

**THE TREATMENT OF METASTATIC CARCINOMA
AND MYELOMA OF THE FEMUR:
CLINICAL PRACTICE GUIDELINE**

Responses to Peer and Public Review

**Jointly prepared by the Musculoskeletal Tumor Society (MSTS), American Society for
Radiation Oncology (ASTRO), and American Society of Clinical Oncology (ASCO)**

Disclaimer

This clinical practice guideline (CPG) was developed by a physician volunteer clinical practice guideline development group based on a formal systematic review of the available scientific and clinical information and accepted approaches to treatment and/or diagnosis. This clinical practice guideline is not intended to be a fixed protocol, as some patients may require more or less treatment or different means of diagnosis. Clinical patients may not necessarily be the same as those found in a clinical trial. Patient care and treatment should always be based on a clinician's independent medical judgment, given the individual patient's specific clinical circumstances.

Musculoskeletal Tumor Society (MSTS)

The MSTS is made up of approximately 350 leading national and international orthopaedic surgeons who specialize in orthopaedic oncology. It is one of several orthopedic subspecialty associations in the United States. Its mission is to advance the science of orthopaedic oncology and promote high standards of patient care through excellence in education and research.

Disclosure Requirement

In accordance with Musculoskeletal Tumor Society (MSTS) policy, all individuals whose names appear as authors or contributors to this clinical practice guideline filed a disclosure statement as part of the submission process. All panel members provided full disclosure of potential conflicts of interest prior to voting on the recommendations contained within this clinical practice guideline.

Funding Source

This clinical practice guideline was funded by the Musculoskeletal Tumor Society and American Academy of Orthopaedic Surgeons and received no funding from outside commercial sources to support the development of this document.

FDA Clearance

Some drugs or medical devices referenced or described in this Clinical practice guideline may not have been cleared by the Food and Drug Administration (FDA) or may have been cleared for a specific use only. The FDA has stated that it is the responsibility of the physician to determine the FDA clearance status of each drug or device he or she wishes to use in clinical practice.

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Overview Peer and Public Review

The reviews and comments related to this clinical practice guideline are reprinted in this document and posted on the MSTS website. All peer reviewers and public commenters are required to disclose their conflict of interests. Names are removed from the forms of reviewers who requested that they remain anonymous.

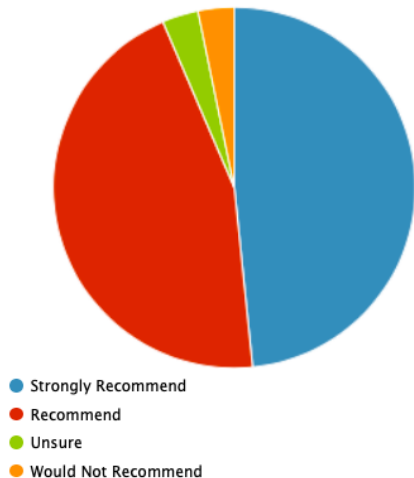
Comments were collected online during an approximately three-week period ending Feb 15, 2020. As this guideline was produced jointly by MSTS, ASTRO and ASCO, comments were solicited from all three organizations' members. As the American Academy of Orthopedic Society is a potential endorsing organization, comments were solicited via AAOS the peer review mechanism. The Clinical Practice Guideline Committee (CPGC) of ASCO provided peer review comments and posted a draft copy on their website for public comment.

Submitted Comments

A total of 31 comments were submitted on-line. Four individuals asked to remain anonymous.

Fourteen respondents identified their association as AAOS. The majority of these respondents are also MSTS members. Twelve respondents identified as ASTRO and four as MSTS. One respondent did not identify a society membership.

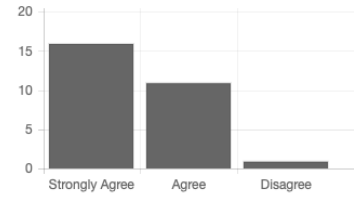
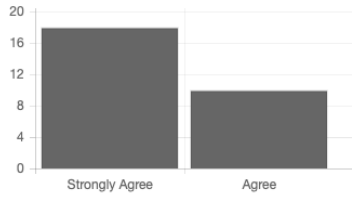
Recommendations



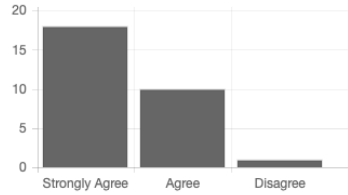
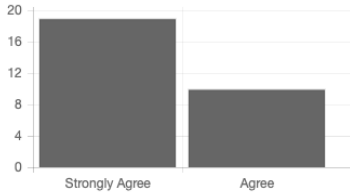
The large majority of respondents would either recommend or strongly recommend the guideline for clinical use.

Answers to the survey questions are summarized on the graphs below

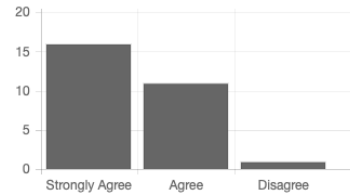
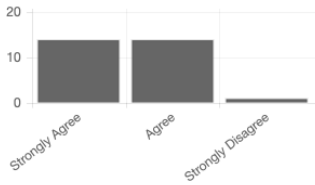
1. The overall objective(s) of the guideline is (are) specifically described. 2. The guideline development group includes individuals from all the relevant professional groups.



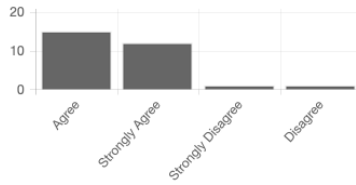
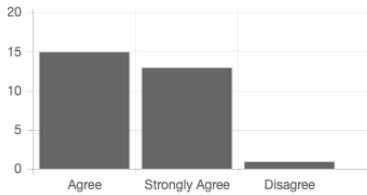
3. The guideline's target audience is clearly described. 4. The patients to whom this guideline is meant to apply are specifically described.



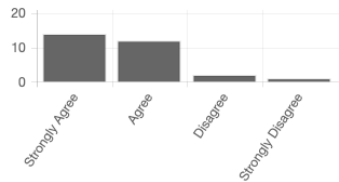
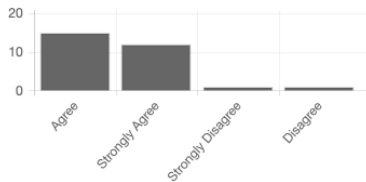
5. There is an explicit link between the recommendations and the supporting evidence. 6. The criteria used to select articles for inclusion are appropriate.



7. All important studies that met the article inclusion criteria are included. 8. The validity of the studies is appropriately appraised.



9. Health benefits, side effects, and risks are adequately addressed. 10. The grades assigned to each recommendation are appropriate.



Responses

Respondent demographics

Id	Name	Last	Society Membership	Work Setting
1	Kevin	Shea	AAOS	Academic Practice
2	Madeera	Kathpal	ASTRO	Academic Practice
3	Alex	Louie	ASTRO	Academic Practice
4	Shai	Shemesh	AAOS	Academic Practice
5	Nicholas	Tedesco	AAOS	Academic Practice
6	Sushilq	Beriwal	ASTRO	Academic Practice
7	Christopher	Jahraus	ASTRO	Private Group or Practice
8	anonymous		ASTRO	Academic Practice
9	Simon	Lo	ASTRO	Academic Practice
10	Arvin	Adler	ASTRO	Private Group or Practice
11	Alan	Monroe	ASTRO	Hospital Employment
12	anonymous		ASTRO	Academic Practice
13	anonymous		Other	Private Group or Practice
14	Benjamin	Miller	AAOS	Academic Practice
15	David	Morris	ASTRO	Private Group or Practice
16	Ajay	Srivastava	AAOS	Private Group or Practice
17	Kenneth	Gundle	AAOS	Academic Practice
18	Drew	Moore	MSTS	Hospital Employment
19	Adam	Lindsay	AAOS	Academic Practice
20	Krishna	Reddy	AAOS	Hospital Employment
21	anonymous		ASTRO	Academic Practice
22	Rosanna	Wustrack	AAOS	Academic Practice
23	Richard	McGough	MSTS	Academic Practice
24	Howard	Rosenthal	AAOS	Private Group or Practice
25	Christian	Ogilvie	MSTS	Academic Practice
26	Howard	Goodman	AAOS	Academic Practice
27	Mark	Goodman	AAOS	other
28	Kristy	Weber	AAOS	Academic Practice
29	Scott	Weiner	AAOS	Academic Practice

30	anonymous		MSTS	Academic Practice
31	Joshua	Jones	ASTRO	Academic Practice

Answers to Survey Questions

ID	Name	Last	1. The overall objective(s) of the guideline is (are) specifically described.	2. The guideline development group includes individuals from all the relevant professional groups.	3. The guideline's target audience is clearly described.	4. The patients to whom this guideline is meant to apply are specifically described.	5. There is an explicit link between the recommendations and the supporting evidence.	6. The criteria used to select articles for inclusion are appropriate.	7. All important studies that met the article inclusion criteria are included.	8. The validity of the studies is appropriately appraised.	9. Health benefits, side effects, and risks are adequately addressed.	10. The grades assigned to each recommendation are appropriate.
1	Kevin	Shea	Strongly Agree	Strongly Agree	Strongly Agree	Strongly Agree	Strongly Agree	Strongly Agree	Strongly Agree	Strongly Agree	Strongly Agree	Strongly Agree
2	Madeera	Kathpal	Strongly Agree	Strongly Agree	Strongly Agree	Strongly Agree	Strongly Agree	Strongly Agree	Strongly Agree	Strongly Agree	Strongly Agree	Strongly Agree
3	Alex	Louie	Strongly Agree	Strongly Agree	Strongly Agree	Strongly Agree	Agree	Strongly Agree	Strongly Agree	Strongly Agree	Strongly Agree	Agree
4	Shai	Shemesh	Strongly Agree	Agree	Agree	Agree	Strongly Agree	Strongly Agree	Strongly Agree	Agree	Agree	Strongly Agree
5	Nicholas	Tedesco	Strongly Agree	Strongly Agree	Strongly Agree	Strongly Agree	Strongly Agree	Strongly Agree	Strongly Agree	Strongly Agree	Strongly Agree	Strongly Agree
6	Sushilq	Beriwal		Agree	Strongly Agree	Agree	Strongly Agree	Agree	Agree	Strongly Agree	Agree	Strongly Agree
7	Christopher	Jahraus	Strongly Agree	Strongly Agree	Strongly Agree	Strongly Agree	Strongly Agree		Strongly Agree	Strongly Agree	Agree	Agree
8	Anonymous											
9	Simon	Lo	Strongly Agree	Strongly Agree	Agree	Strongly Agree	Agree	Strongly Agree	Strongly Agree	Strongly Agree	Strongly Agree	Strongly Agree
10	Arvin	Adler	Strongly Agree	Agree	Strongly Agree	Strongly Agree	Strongly Agree	Strongly Agree	Agree	Strongly Agree	Strongly Agree	Strongly Agree
11	Alan	Monroe	Strongly Agree	Strongly Agree	Strongly Agree	Strongly Agree	Strongly Agree	Strongly Agree	Strongly Agree	Agree	Strongly Agree	Strongly Agree
12	Anonymous											
13	Anonymous		Strongly Agree	Agree	Strongly Agree	Strongly Agree	Agree	Agree	Agree	Agree	Strongly Agree	Strongly Agree
14	Benjamin	Miller	Strongly Agree	Strongly Agree	Strongly Agree	Strongly Agree	Agree	Agree	Agree	Agree	Agree	Disagree
15	David	Morris	Agree	Agree	Agree	Agree	Strongly Disagree	Disagree	Disagree	Strongly Disagree	Strongly Disagree	Strongly Disagree

16	Ajay	Srivastava	Strongly Agree	Strongly Agree	Strongly Agree	Strongly Agree	Strongly Agree	Strongly Agree	Strongly Agree	Strongly Agree	Strongly Agree	Strongly Agree
17	Kenneth	Gundle	Strongly Agree	Strongly Agree	Strongly Agree	Strongly Agree	Strongly Agree	Strongly Agree	Agree	Agree	Agree	Agree
18	Drew	Moore	Agree	Agree	Agree	Agree	Agree	Agree	Agree	Agree	Agree	Agree
19	Adam	Lindsay	Agree	Agree	Agree	Agree	Agree	Agree	Agree	Agree	Agree	Agree
20	Krishna	Reddy	Agree	Agree	Strongly Agree	Strongly Agree	Agree	Agree	Agree	Agree	Agree	Agree
21	Anonymous		Agree	Agree	Agree	Agree	Agree	Agree	Agree	Agree	Agree	Disagree
22	Rosanna	Wustrack	Strongly Agree	Strongly Agree	Strongly Agree	Strongly Agree	Strongly Agree	Strongly Agree	Strongly Agree	Strongly Agree	Strongly Agree	Strongly Agree
23	Richard	McGough	Agree	Agree	Agree	Agree	Strongly Agree	Agree	Agree	Agree	Agree	Strongly Agree
24	Howard	Rosenthal	Strongly Agree	Strongly Agree	Strongly Agree	Strongly Agree	Strongly Agree	Strongly Agree	Strongly Agree	Strongly Agree	Strongly Agree	Strongly Agree
25	Christina	Ogilvie	Strongly Agree	Strongly Agree	Strongly Agree	Strongly Agree	Agree	Strongly Agree	Agree	Agree	Strongly Agree	Agree
26	Howard	Goodman	Strongly Agree	Strongly Agree	Agree	Agree	Strongly Agree	Strongly Agree	Agree	Agree	Agree	Agree
27	Mark	Goodman	Agree	Disagree	Agree	Disagree	Agree	Agree	Agree	Agree	Disagree	Strongly Agree
28	Kristy	Weber	Agree	Strongly Agree	Strongly Agree	Strongly Agree	Agree	Agree	Agree	Agree	Agree	Agree
29	scott	weiner	Agree	Strongly Agree	Strongly Agree	Agree	Agree	Strongly Agree	Strongly Agree	Agree	Agree	Agree
30	Anonymous		Agree	Agree	Agree	Agree	Agree	Agree	Agree	Disagree	Agree	Agree
31	Joshua	Jones	Strongly Agree		Strongly Agree	Strongly Agree	Agree	Strongly Agree	Strongly Agree	Strongly Agree	Strongly Agree	Agree

Changes to Guideline Document

1. Page 5: Added numbers to recommendations
2. Page 14: Added additional bullet point “Future studies would be enhanced by the establishment of a multisite registry for the accumulation of prospectively collected data.
3. Page 21: Changed “Low-quality evidence supports the intuitive...” to “Low-quality evidence (Oh, 2017; Ulaner, 2017) supports the intuitive...”
4. Page 25: Added to rationale “The PICO question which guided the literature search did not yield information concerning denosumab that could be included. Therefore, no recommendation regarding denosumab was included in the final Guideline.”
5. Page 25: Added line “Further discussion on the use of BMAs in multiple myeloma can be found in the updated American Society of Clinical Oncology (ASCO) CPG on the Role of Bone-Modifying Agents in Multiple Myeloma (Anderson, 2018).”
6. Page 30: Added to end of rationale: “This recommendation addresses the question of whether radiation by itself can reduce the risk of fracture. It is not intended to alter current clinical practice wherein patients who are felt to be at high risk of pathologic fracture first undergo prophylactic stabilization.”
7. Page 32: Modified statement regarding use of survival calculator from “
8. Page 32: Added reference to Tokuhashi method and link to www.spinemet.com for estimating survival
9. Page 32: Added line to end of rationale “However, arthroplasty may still be indicated in patients with short survival time for palliation in certain clinical scenarios, for example fractured femoral neck.”

Reviewer Detailed Responses

All society co-chairs participated in the design of the guideline, i.e. defining the PICO (key) questions. The entire workgroup was involved in writing the guidelines and rationales. Responses to reviewers below were written by the two MSTS co-chairs, Drs Felasfa Wodajo and Patrick Getty and reviewed by Drs. John Charlson and Joshua Petit, the ASCO and ASTRO co-chairs, respectively.

Reviewer #1: Kevin Shea

Id	Name	Last	Society Membership	18. Please provide a brief explanation of both your positive and negative answers in the preceding section.	Would you recommend these guidelines for use in clinical practice?	Additional Comments
1	Kevin	Shea	AAOS		Recommend	Due to the lower level of evidence, most of the recommendations issue consensus recommendations. Would this CPG be better if it was converted to an AUC?

Response

Thank you for your comments and question. An appropriate use criteria (AUC) guideline is a valid approach for consensus-based guidelines, with its own distinct methodology. However, this project was initiated as a clinical practice guideline (CPG), i.e. based on a systematic literature review and detailed statistical abstraction of the data. The methodology employed easily met well-accepted standards for a CPG. On completion of the systematic review, we of course noted the dearth of high-quality evidence for many of the PICOT questions and appropriately downgraded several of our recommendations to “consensus”.

Reviewer #2: Madeera Kathpal

Id	Name	Last	Society Membership	18. Please provide a brief explanation of both your positive and negative answers in the preceding section.	Would you recommend these guidelines for use in clinical practice?	Additional Comments
2	Madeera	Kathpal	ASTRO	Excellent guideline. Would it be appropriate to add field recommendations to the RT section questions?	Strongly Recommend	

Response

Thank you for your comments. The nuances of radiation therapy fields were outside the scope of our guideline project. However, we expect that radiation oncologists will have access to and knowledge of more detailed guidelines dedicated to palliative radiotherapy, such as [ASTRO Guideline on Palliative Radiation Therapy for Bone Metastases – Update](#) (2017).

Reviewer #3: Alex Louie

Id	Name	Last	Society Members	18. Please provide a brief explanation of both your positive and negative answers in the preceding section.	Would you recommend these guidelines for use in clinical practice?	Additional Comments
3	Alex	Louie	ASTRO	I think overall a very practical and sensible document	Recommend	<p>Specific radiation related topics, such as re-treatment and stereotactic radiation are not directly described in this document, but are touched on in the most recent ASTRO document of radiation for bone mets. This may warrant mention (recognizing that the ASTRO document refers to all bone, and the current guidelines is for femur).</p> <p>https://www.astro.org/uploadedFiles/Main_Site/Clinical_Practice/Guidelines/ASTRO_bone_mets_guideline_full_version.pdf</p>

Response

Thank you for your comments. You are correct with reference to the ASTRO CPG. The current document was intended to specifically address the issue of disease within the femur and to be applicable to general use. We expect that radiation oncologists will have access to and knowledge of the reference you mentioned.

Reviewer #5: Nicholas Tedesco

Id	Name	Last	Society Membership	18. Please provide a brief explanation of both your positive and negative answers in the preceding section.	Would you recommend these guidelines for use in clinical practice?	Additional Comments
5	Nicholas	Tedesco	AAOS	Excellent clarification on many topics that are full of conflicting information amongst trauma and arthroplasty orthopedic surgeons, medical oncologists, and radiation oncologists. I hope this will provide clarity for the general community on appropriate use of long-stem arthroplasty, recon nails, bone mineral density drugs, and radiation.	Strongly Recommend	We should have a representative try to present or disseminate these at other national conferences of the target audience to improve the extent of outreach.

Response

Thank you for your comments. It is our intention to disseminate this information as broadly as possible. That was one reason, in addition to the benefit of added expertise, that multiple specialty organizations were involved.

Reviewer #6: Sushilq Beriwal

Id	Name	Last	Society Membership	18. Please provide a brief explanation of both your positive and negative answers in the preceding section.	Would you recommend these guidelines for use in clinical practice?	Additional Comments
6	Sushilq	Beriwal	ASTRO	For RT guidelines recommend multi fraction RT in lieu of single fraction for decreasing risk of fracture based on very small difference seen in Dutch study . that study was done in patients with de novo Mets with no surgical stabilization. In patients with surgical stabilization that data is not available and in view if single fraction being more cost effective and patient friendly it should be addressed in guidelines . Also for multi fraction discussing shorter course of multi fraction should be mentioned instead of longer schedule	Strongly Recommend	

Response

Thank you for your comments. The workgroup considered whether to mention between schedules of multi-fraction therapy and decided to simplify the recommendation to differentiate only between single and multi-fraction therapy. We agree that the of data on fracture risk following single versus multi-fraction radiotherapy remains frustratingly weak. The workgroup carefully weighed the decision and in the end decided to upgrade the recommendation based on the significant morbidity of femur fractures compared to other skeletal sites.

Reviewer #7: Christopher Jahraus

Id	Name	Last	Society Membership	18. Please provide a brief explanation of both your positive and negative answers in the preceding section.	Would you recommend these guidelines for use in clinical practice?	Additional Comments
7	Christopher	Jahraus	ASTRO		Strongly Recommend	Excellent overview. XRT comments are particularly on-target and helpful.

Response

Thank you for your comments.

Reviewer #8: Trevor Royce

Id	Name	Last	Society Membership	18. Please provide a brief explanation of both your positive and negative answers in the preceding section.	Would you recommend these guidelines for use in clinical practice?	Additional Comments
8	Trevor	Royce	ASTRO		Recommend	Please consider including specific multi-fraction regimens that are deemed acceptable practice (dose per fraction and number of fractions)

Response

Thank you for your comments. The workgroup considered whether to mention between schedules of multi-fraction therapy and decided to simplify the recommendation to differentiate only between single and multi-fraction therapy.

Reviewer #9: Anonymous

Id	Name	Last	Society Membership	18. Please provide a brief explanation of both your positive and negative answers in the preceding section.	Would you recommend these guidelines for use in clinical practice?	Additional Comments
9	Anonymous		ASTRO	For the section on Recommendation for Imaging and Clinical Findings, the group may want to comment on lytic vs sclerotic vs mixed lesions. This has been found to be a predictive factor for fracture in vertebral metastases (one of the parameters of Spinal Instability Neoplastic Score).	Strongly Recommend	This is a well written guideline.

Response

Thank you for your comments. We agree with the concept but did not find specific information for the femur. We, therefore, left our statement more generic.

Reviewer #12: Anonymous

Id	Name	Society Membership	18. Please provide a brief explanation of both your positive and negative answers in the preceding section.	Would you recommend these guidelines for use in clinical practice?	Additional Comments
12	Anonymous	ASTRO		Unsure	<p>My group and I feel that hematologic malignancies such as multiple myeloma should be separate from solid tumor recommendations.</p> <p>With that caveat, I didn't see any question/discussion on the extent of the coverage of the RT field and this may be too specific for this document. That is what we struggle with – focal over the lesion or coverage of all the hardware. Benefits to a focal field would be a potential decrease in the amount of marrow treated. Possible downsides would be that failure along the rod in the future could result in hardware failure, which is terrible. Our ortho and med onc teams pretty reliably send pts at risk of fracture for RT to possibly avoid surgery and also pts s/p stabilization for post op RT. So I would say that we agree with recommendations to treat.</p> <p>two additional publications to consider PMID: 31919088 and PMID: 31133526 as well as the references in the second paper Alvi and Epstein.</p>

Response

Thank you for your comments. The nuances of radiation therapy fields were outside the scope of our guideline project. However, we expect that radiation oncologists will have access to and knowledge of more detailed guidelines dedicated to palliative radiotherapy, such as [ASTRO Guideline on Palliative Radiation Therapy for Bone Metastases – Update \(2017\)](#).

For those interested, the references you mentioned are listed in full below:

Postoperative Radiotherapy for Multiple Myeloma of Long Bones: Should the Entire Rod Be Treated? Elhammali A, Milgrom SA, Amini B, Gunther JR, Yoder A, Ludmir EB, Moon B, Weber DM, Thomas SK, Garg N, Manasanch EE, Patel KK, Orlowski RZ, Lee HC, Bird JE, Satcher R, Lin P, Pinnix CC, Dabaja BS. Clin Lymphoma Myeloma Leuk. 2019 Aug;19(8):e465-e469.

New Paradigm for Radiation in Multiple Myeloma: lower yet effective dose to avoid radiation toxicity. Elhammali A, Amini B, Ludmir EB, Gunther JR, Milgrom SA, Pinnix CC, Andraos T, Yoder A, Weber D, Orlowski R, Manasanch E, Patel K, Strati P, Nair R, Lee HC, Thomas S, Iyer S, Kaufmann G, Garg N, Dabaja BS. Haematologica. 2020 Jan 9. pii: haematol.2019.235804.

Reviewer #14: Benjamin Miller

Id	Name	Last	Society Membership	18. Please provide a brief explanation of both your positive and negative answers in the preceding section.	Would you recommend these guidelines for use in clinical practice?	Additional Comments
14	Benjamin	Miller	AAOS	<p>There were two upgraded recommendations (use of XRT and single vs fractionated dosing).</p> <p>The literature evidence was "limited" but the work group upgraded to "moderate." For the first (use of XRT) I am not convinced that the consequences of a hypothetical femur fracture outweigh the consequences of additional potentially unnecessary radiation treatments - risks both to the patient and utilization of resources in health systems. There is no guidance regarding how to decide if a fracture is likely, and it is very subjective. I would recommend keeping with the strength of evidence given the limited literature and have this be "limited."</p> <p>A similar argument with single fraction vs multiple fraction. I am not convinced with the limited literature that upgrading is justified. I would stick with the evidence only as a "limited" strength recommendation. With more research, technology, or delivery methods, this recommendation could very well be contradicted.</p> <p>I am uncomfortable with the recommendation not to protect the femoral neck during routine IMN. Certainly there are cases, such as a retrograde IMN or plate for distal shaft lesions, where it is appropriate not to protect. However, with an antegrade femoral nail, it is a small extension of the procedure to protect the neck and has been the long accepted standard. With this recommendation, are clinicians required to extensively evaluate the femoral neck with an MRI to ensure there are no subclinical lesions? How many "missed" head or neck lesions need to occur before the risk of not protecting outweighs the benefit? It's an interesting question, but too early for a recommendation.</p>	Strongly Recommend	<p>The "Efficacy of BMA" recommendation wording is different in the summary and text. The text is more clear ("bone lesions from metastatic carcinoma and multiple myeloma" rather than "metastatic carcinoma or multiple myeloma and bone lesions")</p> <p>For "Estimating Survival" I would remove the last sentence about using an arthroplasty - it stands well on its own with the single sentence. Arthroplasty is often indicated even in patients with short survival time given location or amount of destruction, this comment serves more to confuse. This point is important and is appropriate for further clarification in the rationale section.</p>

Response

Thank you for your comments. We agree that the of data on fracture risk following single versus multi-fraction radiotherapy remains frustratingly weak. The multi-disciplinary workgroup carefully weighed the decision and, in the end, decided to upgrade the recommendation based on the significant morbidity of femur fractures compared to other skeletal sites. Similarly, with the upgraded recommendation on use of RT to prevent femur fractures. It may be useful to note that multi-

fractionated therapy for palliation of metastatic disease may now be more commonly five rather than ten fractions, which reduces the utilization burden on the health care system.

The recommendation concerning cephalomedullary nailing does have a paucity of supporting information. The purpose of this document is to assess the available information in reference to the management of patients with metastatic or myelomatous lesions of the femur and make appropriate recommendations. The use of cephalomedullary devices is widespread and promoted as the fixation of choice. The authors wanted to highlight that there is no good information to support that impression.

We appreciate your comment on the potential for confusion regarding the role of arthroplasty in the setting of a patient with short predicted survival and added a statement to the rationale to clarify this point.

Reviewer #15: David Morris

Id	Name	Last	Society Membership	18. Please provide a brief explanation of both your positive and negative answers in the preceding section.	Would you recommend these guidelines for use in clinical practice?	Additional Comments
15	David	Morris	ASTRO	<p>There are a series of concerns that I have with the issue of "Multi-Fraction Radiation" and the consensus recommendation.</p> <p>-1- The star system gives a rating of 3 stars yet there is only one reference listed which does not correlate with the grading.</p> <p>-2- The referenced article is in respect to the Dutch Bone Metastasis Study Group but the intent of the reference in relation to the study was to identify lesional risk factors for fracturing and to evaluate the influence of the treatment schedule. It specifically addresses an issue of cortical involvement and after the axial cortical involvement was corrected the fractionation schedule was not predictive.</p> <p>-3- This recommendation based on no data to support its use and is not entirely consistent with current guidelines from American Society of Radiation Oncology (ASTRO), International Lymphoma Radiation Oncology Group (ILROG), and International Myeloma Working Group. Furthermore, the American College of Radiology Appropriateness Criteria is the only group that suggests that multifraction radiation should be considered and quotes the same article and actually suggests that those patients should undergo prophylactic surgery if feasible.</p> <p>There are a series of concerns that I have in regard to the use and frequency of bone modifying agents.</p> <p>There appears to be a heavy emphasis on the use of zoledronic acid which has me concerned there is an underlying bias.</p> <p>Furthermore, there are inherent differences between carcinomas and myeloma and the role/use of bone modifying agents. There are limitations to the listed studies particularly in regard to myeloma as well as there is extremely limited data related to myeloma involvement of the femur which has me again question the 4 stars.</p> <p>I would suggest that it is best to cite in regard to myeloma the ASCO guidelines related to bone modifying agents in Multiple Myeloma "Role of Bone-Modifying Agents in Multiple Myeloma: American Society of Clinical Oncology Clinical Practice Guideline Update Journal of Clinical Oncology 36(8): 812-818, 2018 where they have a discussion of the limitations as they relate to myeloma.</p>	Would Not Recommend	<p>There are guidelines currently available from ASTRO, ACR, ASCO, ILROG, and IMWG that currently address the non-surgical issues better and more comprehensively. Nearly all the surgical guidelines are 1 star guidelines which are realistically not evidence-based and those that were not 1 star, there was a rather poor analysis of the data that had been reviewed.</p> <p>Overall, in my opinion, this review would be considered unacceptable for publication in its current form</p>

			<p>The last issue I have is in regard to the omission of radiation after arthroplasty. The data that receives 2 stars is based off of 4 studies. Not one of the 4 studies mentioned decreasing the need for post-operative radiation and in fact one study reported that the procedure may facilitate post-operative radiation efficacy. One of the studies was a database study only and the three other studies were retrospective and included 34 patients, 23 patients, and 31 arthroplastic procedures. In addition, the only study that mentioned radiation had 75% of the patients receiving radiation with no mention of the number who received radiation after arthroplasty. That study included 31 arthroplastic procedures and could be as much a study on the type of facility in which the patient receives their care rather than the role of radiation. Interestingly, the discussion section is suggestive that arthroplasty may actually be beneficial for post-operative radiation.</p> <p>The overall structure and content of the guideline is reasonable with important questions being addressed. The intellectual analysis of the answers and reliance on that data were not a level considered acceptable. From many of the summary responses, it is clear that the panel members did not actually read the articles that they are citing. Furthermore, the scope of the question being limited to femurs is suggestive that it really was solely meant to address surgically related questions.</p>		
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Response

Thank you for your comments. Several valid concerns are raised. You are correct that the intent of the current document is to provide guidance on the management of femur lesions. This is a very specific clinical situation involving a weight bearing bone with significant functional consequences if fracture occurs. Therefore, the recommendations do vary compared to documents created by other groups looking at bone lesions in general. Most recommendations concerning single dose versus fractionated radiation treatment for bone metastases are based on studies involving all bone lesion sites and use short term pain control as the primary end point. Our recommendations take into account the specific issues of the femur and the trend toward increased risk of fracture, re-radiation and need for surgery with single dose versus fractionated radiation. As you commented, the cited article was written with the intent of looking for risk factors, but it presented data showing increased rate of fracture in the single dose group compared to the multiple fraction group.

With regard to the concern about the grading of the recommendation, it was stated in the rationale that, "In the absence of other randomized data, the strength of this recommendation was upgraded to moderate given the significant morbidity associated with post-radiation femoral fractures which impact weight bearing and quality of life. In patients with limited life expectancies, a single fraction may be suitable to limit time on radiation treatment."

With regard to the recommendations concerning the use of Bone Modifying Agents, zoledronic acid had emphasis proportionate to the information reviewed, the differences based on diagnosis were addressed as best as could be based on the information reviewed and grading of the recommendations were consistent with the schema outlined.

We appreciate your suggestion of including a reference to the updated American Society of Clinical Oncology (ASCO) CPG on the Role of Bone-Modifying Agents in Multiple Myeloma (Anderson, 2018) and have included it in the rationale.

With regard to the use of arthroplasty, the final recommendation does indicate that in some situations, arthroplasty may be considered to improve function and reduce the need for radiation. However, that does not imply that radiation is never useful following arthroplasty. In fact, the recommendation concerning 'Radiation Therapy after Resection and Reconstruction' states that "radiation therapy may be considered after resection and reconstruction to reduce pain, improve functional status, and reduce the need for further intervention in patients with residual tumor, or those at increased risk of tumor recurrence in the setting of metastatic carcinoma or multiple myeloma of the femur." In this setting, the form of reconstruction is typically arthroplasty.

Reviewer #16: Ajay Srivastava

Id	Name	Last	Society Membership	18. Please provide a brief explanation of both your positive and negative answers in the preceding section.	Would you recommend these guidelines for use in clinical practice?	Additional Comments
16	Ajay	Srivastava	AAOS	When I look at these recommendations from average community practicing surgeon's point of view, it's difficult to decide when it's time to consider radiation therapy versus prophylactic nailing. One will look at X-ray and debate, should I get this patient to operating room or start with radiation therapy? For Example, Recommendation : "Multi-Fraction Radiation Treatment: Clinicians should consider the use of multi-fraction in lieu of single fraction radiation treatment to reduce the risk of fracture in patients with metastatic carcinoma in the femur." - Would have been helpful to know which subgroup of patient this is a better option.	Strongly Recommend	I think that routine use screws in the femoral neck while performing intramedullary nailing has minimal morbidity. Therefore protecting neck against future mets is worthwhile.

Response

Thank you for your comments. We agree that we were unable to provide strong, evidence-based recommendations for when prophylactic surgery is indicated for patients with bone lesions. Unfortunately, none of the published schemes for predicting fracture risk based on imaging findings has enough evidence to meet the criteria for a systematic review.

The recommendation concerning cephalomedullary nailing does have a paucity of supporting information. The purpose of this document is to assess the available information in reference to the management of patients with metastatic or myelomatous lesions of the femur and make appropriate recommendations. The use of cephalomedullary devices is widespread and promoted as the fixation of choice. The authors wanted to highlight that there is no good information to support that impression.

Reviewer #17: Kenneth Gundle

Id	Name	Last	Society Membership	18. Please provide a brief explanation of both your positive and negative answers in the preceding section.	Would you recommend these guidelines for use in clinical practice?	Additional Comments
17	Kenneth	Gundle	AAOS	<p>The Working Group has assembled a great range of literature on a variety of critical components of caring for patients with metastatic bone disease in the femur. While obviously a challenge in the CPG framework, I would also consider an important point for the multidisciplinary team is a statement regarding the value of prophylactic stabilization. I do not see a recommendation for (or against) prophylactic stabilization in the summary.</p> <p>The points about reconstruction options and considerations for nailing versus arthroplasty are very well stated. I would also suggest, given the changing treatment paradigm for a variety of metastatic carcinomas and myeloma, that an ongoing prospective multisite registry may be of more value for answering lingering questions. This may particular help characterize what may well be a changing and expanding group of patients for arthroplasty may be a more durable reconstruction.</p>	Strongly Recommend	

Response

Thank you for your comments. You are correct that this document did not make a recommendation specific to the value of prophylactic fixation. However, the use of prophylactic fixation is implied in the recommendation “Imaging and Clinical Findings” which states “In the absence of reliable evidence, it is the opinion of the workgroup that the combination of imaging findings and lesion-related pain is predictive of risk of pathologic femur fracture.” Prophylactic fixation is one potential response to increased risk of fracture. Unfortunately, the process did not allow for a direct statement. You are correct that an “ongoing prospective multisite registry” would be of great value. This concept has been added to the ‘Future Research’ section.

Reviewer #18: Drew Moore

Id	Name	Last	Society Membership	18. Please provide a brief explanation of both your positive and negative answers in the preceding section.	Would you recommend these guidelines for use in clinical practice?	Additional Comments
18	Drew	Moore	MSTS	<p>I don't understand why the guideline on cephalomedullary nails vs non- cephalomedullary nails was included. The risk of doing a CMN is stated as increased OR time and fluoro exposure. It's about an extra 1-2 minutes? In my opinion there is no associated risk and only potential benefit.</p> <p>I personally think this recommendation should be removed.</p>	Recommend	

Response

The recommendation concerning cephalomedullary nailing does have a paucity of supporting information. The purpose of this document is to assess the available information in reference to the management of patients with metastatic or myelomatous lesions of the femur and make appropriate recommendations. The use of cephalomedullary devices is widespread and promoted as the fixation of choice. The authors wanted to highlight that there is no good information to support that impression.

Reviewer #20: Krishna Reddy

Id	Name	Last	Society Membership	18. Please provide a brief explanation of both your positive and negative answers in the preceding section.	Would you recommend these guidelines for use in clinical practice?	Additional Comments
20	Krishna	Reddy	AAOS	The MSTS is commended in its efforts to form evidence based guidelines on the subject and sets a framework to work with/within.	Recommend	Sets a framework and issues clear guidelines on treatment for MBD

Response

Thank you for your comments.

Reviewer #21: Anonymous

Id	Name	Society Membership	18. Please provide a brief explanation of both your positive and negative answers in the preceding section.	Would you recommend these guidelines for use in clinical practice?	Additional Comments
21	Anonymous	ASTRO	<p>Introduction - Organization of section order and content (e.g. including recommendations for areas of further research here instead of in a concluding/discussion section) is a bit unusual/unexpected.</p> <p>Page 21 - Are there references that can be cited for the "low-quality evidence" that is referred to in line 4?</p> <p>Page 22 - This opinion recommendation seems to be a reasonable extrapolation of other data.</p> <p>Pages 25, 26 - This section can probably be condensed to discussing relevant imaging features and studies per the recommendation at the top of the page. Consider eliminating or significantly condensing paragraphs 2 and 3.</p> <p>Page 27 - Would recommend rating the recommendation strength as "low" given quality of evidence used to make the recommendation. Though I agree that the morbidity of femur fractures is high and that of radiotherapy is low, based on your rubric for establishing recommendation strength I do not know as though that clinical context should be considered in this capacity.</p> <p>Page 29 - Agree with consensus recommendation and reasoning.</p> <p>Page 30 - Similar to reasoning for downgrading the recommendation strength on page 27, this too should be a recommendation with low strength based on one randomized study of "moderate quality". Also, would recommend inclusion of the radiation fractionations used in the referenced study (8 Gy x1 and 4 Gy x6) given these are very similar to fractionation options recommended in routine practice with longer courses of palliative radiotherapy generally discouraged (e.g. 3 Gy x10) given the US healthcare system's emphasis on cost effective care.</p> <p>Page 33 - Consider omitting this recommendation altogether given the recommendation strength of consensus/very weak and a referenced study that did not meet strict inclusion criteria. This falls outside the presentation of a systematic approach to presenting what evidence exists.</p>	Recommend	<p>Overall a nice presentation of the available evidence to address metastatic disease in bone, including considerations when selecting a management option for a given patient.</p> <p>Suggest checking to make sure that acronyms are defined in the text prior to their use.</p>

Response

Thank you for your comments. The format of the document follows the pattern established by the AAOS for CPGs. We have added mention of the specific references on Page 21. Your two comments

questioning the grading of recommendations are understandable, but in each instance the recommendations are labelled as being 'Upgraded' and the rationale for that upgrade is given.

The recommendation concerning cephalomedullary nailing does have a paucity of supporting information. The purpose of this document is to assess the available information in reference to the management of patients with metastatic or myelomatous lesions of the femur and make appropriate recommendations. The use of cephalomedullary devices is widespread and promoted as the fixation of choice. The authors wanted to highlight that there is no good information to support that impression.

Reviewer #22: Rosanna Wustrack

Id	Name	Last	Society Membership	18. Please provide a brief explanation of both your positive and negative answers in the preceding section.	Would you recommend these guidelines for use in clinical practice?	Additional Comments
22	Rosanna	Wustrack	AAOS	I found the recommendations around dosing interval for BMAs useful and new information.	Recommend	These CPG and the unanswered questions should be used by the MSTs for collaborative research.

Response

Thank you for your comments.

Reviewer #23: Richard McGough

Id	Name	Last	Society Membership	18. Please provide a brief explanation of both your positive and negative answers in the preceding section.	Would you recommend these guidelines for use in clinical practice?	Additional Comments
23	Richard	McGough	MSTS	These guidelines are well done and reflect both the current literature and, equally importantly, the accrued knowledge and experience of those of us who care for these problems. Our accrued knowledge has actually allowed and supported some of the changes that have occurred during the past two decades.	Recommend	Nicely done. Adequately reflects literature, current practice, and the need to protect and foster the treatment of metastatic disease by community orthopaedic surgeons.

Response

Thank you for your comments.

Reviewer #24: Howard Rosenthal

Id	Name	Last	Society Membership	18. Please provide a brief explanation of both your positive and negative answers in the preceding section.	Would you recommend these guidelines for use in clinical practice?	Additional Comments
24	Howard	Rosenthal	AAOS	Overall health and life expectancy need to be addressed on the individual basis. Additionally, life expectations with regard to longevity and goals need to be addressed on an individual basis	Strongly Recommend	

Response

Thank you for your comments.

Reviewer #25: Christian Ogilvie

Id	Name	Last	Society Membership	18. Please provide a brief explanation of both your positive and negative answers in the preceding section.	Would you recommend these guidelines for use in clinical practice?	Additional Comments
25	Christian	Ogilvie	MSTS	Overall excellent work. I think the arthroplasty recommendation for femur fractures should be stronger but I understand the limits of available evidence.	Strongly Recommend	

Response

Thank you for your comments.

Reviewer #27: Mark Goodman

Id	Name	Last	Society Membership	18. Please provide a brief explanation of both your positive and negative answers in the preceding section.	Would you recommend these guidelines for use in clinical practice?	Additional Comments
27	Mark	Goodman	AAOS	I found it difficult to distinguish between recommendations for minimally symptomatic lesions, impending fractures and pathologic fractures. Perhaps these should be broken down into separate statements. No discussion of the risks of surgical morbidity and mortality (other than dislocation or long stem problems) was statistically incorporated in the discussion. Perhaps an anesthesia viewpoint needs to be included?	Recommend	This was nicely done and as stated, a good starting point. The recommendations were "soft enough" to pose no medical/legal problems.

Response

Thank you for your comments. Your thoughts concerning the stratification of clinical presentation as well as the risks of surgical complications are appropriate. Unfortunately, they fell outside the parameters of the PICO questions of this project.

Reviewer #28: Kristy Weber

Id	Name	Last	Society Membership	18. Please provide a brief explanation of both your positive and negative answers in the preceding section.	Would you recommend these guidelines for use in clinical practice?	Additional Comments
28	Kristy	Weber	AAOS	<p>I appreciate the effort that went into development of this CPG. As always, it identifies problematic gaps in knowledge and will hopefully serve as a guide for better, more relevant research.</p> <p>My comments include: I would 'number' the recommendations to make it easier to correspond. I struggled a bit with rec #2 as we essentially discount the level 1 evidence about the benefit of BMAs on SREs in the overall population/anatomic location just because this is a CPG about the femur (although the femur would be the most common site in those prior randomized studies). It just seems to minimize the use of BMAs when the consensus was that they 'may' help. It is probably also not reflective of current practice where they are used routinely. Rec #3 essentially makes it more confusing when it mentions that there is strong evidence for the use of long term BMAs to reduce SREs in patients with myeloma.</p> <p>Similar concern with the radiation therapy rec for prophylactic femur stabilization...given the existing literature about use of XRT in patients with bone mets in general (to prevent progression of disease), was this only consensus because we were only reviewing the 'femur'?</p> <p>The final recommendation might be made more clear if the end of the statement said 'from metastatic carcinoma in the proximal femur'. Not specifying which portion of the femur would suggest this is also relevant for distal femur fractures where we do knee arthroplasty.</p>	Recommend	Thanks for the hard work.

Response

Thank you for your comments. We agree that numbering the recommendations would be helpful and numbers have now been added. As you noted, the strength of many of the recommendations was reduced due to the paucity of evidence when the site of disease is restricted to the femur. For example, Recommendation 3 on dosing of BMAs was not restricted to the femur, which likely contributed to the strength of that recommendation. This may also explain why that recommendation 3 for longer duration of BMA treatment with myeloma at least superficially seems to contradict the others.

Regarding the recommendation for radiation following prophylactic stabilization, there is surprisingly little literature on this topic, regardless of site. We appreciate your comment regarding the wording of the final recommendation. The applicability to the recommendation to the proximal portion of the femur is clarified in the Rationale on page 31.

Reviewer #29: Scott Weiner

Id	Name	Last	Society Membership	18. Please provide a brief explanation of both your positive and negative answers in the preceding section.	Would you recommend these guidelines for use in clinical practice?	Additional Comments
29	Scott	Weiner	AAOS	would be nice to have stronger consensus on items but that is typical for these. the guideline to 'recommend' arthroplasty for femur fractures suggests all femur fractures while may only be appropriate for femoral neck and maybe some intertrochs. nice job otherwise	Strongly Recommend	I appreciate this group taking this initiative.

Response

Thank you for your comments. The recommendation concerning arthroplasty states that “Clinicians may consider arthroplasty to improve patient function and decrease the need for post-operative radiation therapy...”. This is meant to imply consideration of arthroplasty within the context of the specific clinical scenario and is not intended as a general recommendation for arthroplasty over fixation.

Reviewer #30: Anonymous

Id	Name	Society Membership	18. Please provide a brief explanation of both your positive and negative answers in the preceding section.	Would you recommend these guidelines for use in clinical practice?	Additional Comments
30	Anonymous	MSTS	<p>page [32] arthroplasty is overemphasized: "Longer survival estimates may justify more durable reconstruction methods such as arthroplasty, if clinically appropriate. Needs to be reworked/ reworded. No literature showing that arthroplasty superior to resection and reconstruction for an intercalary metastasis (megaprosthesis with joint versus other intercalary reconstruction with retention of the adjacent native joint). Also there is a direct link to Path.fx but not to the other sources cited. As voting members of group have had close ties to Pathfx development weblinks to all should be provided to avoid the appearance of bias. Lastly, as noted by others, "Determining whether a prediction model really improves clinical care is better shown in an impact study." (CORR insights). Therefore, this whole recommendation may be a bit overstated. If retained, perhaps better to state "...it is the opinion of the workgroup that surgeons consider utilizing a validated method of estimating patient survival of the when choosing a method of reconstruction. Longer survival estimates may justify more durable reconstruction methods as clinically appropriate.</p> <p>page [33] re: long stem arthroplasty: "... it is the opinion of the workgroup that when treating a femoral neck fracture with hemiarthroplasty, use of a long stem can be associated with increased intra-operative and post-operative complications and should only be used in patients with additional lesions in the femur" recommendation is overstated based on the conflicts in the literature. Perhaps better to restate as: "...when treating a femoral neck fracture with hemiarthroplasty, use of a long stem can be associated with increased intra-operative and post-operative complications and its use should typically only be considered for those patients with additional lesions in the femur."</p>	Recommend	

Response

Thank you for your comments. We appreciate your suggestion that it offer surgeons the use of a validated survival calculator in making decisions rather than mandating it. We have modified the statement on page 32 accordingly, from "it is preferable to use validated means to estimate survival" to "surgeons may consider the use a validated means to estimate survival". Regarding other methods to predict survival in metastatic disease, we have added a references for the Tokuhashi method and to www.spinemet.com on page 32.

Regarding the recommendation for limited use of long stem arthroplasty, the document already points to the paucity of evidence in this regard ("None of the included investigations in this clinical practice guideline directly compare short versus long stem hemiarthroplasty in this population. This limits the statement that can be made recommending one option over another."), thus we have elected to leave the statement as it stands.

Reviewer #31: Joshua Jones

Id	Name	Last	Society Membership	18. Please provide a brief explanation of both your positive and negative answers in the preceding section.	Would you recommend these guidelines for use in clinical practice?	Additional Comments
31	Joshua	Jones	ASTRO	<p>In general, the guideline is very appropriate, well conducted and well written. The guidelines are clear and the level of evidence is also well described. There is one specific issue I see with the guidelines that I think is important to address:</p> <p>The guideline states: "Clinicians should consider the use of multi-fraction in lieu of single fraction radiation treatment to reduce the risk of fracture in patients with metastatic carcinoma in the femur."</p> <p>In reviewing the van der Linden study, though, the authors report a total of 14 fractures, 10 in the single fraction arm and 4 in the multi-fraction arm. When they accounted for degree of cortical destruction (the factor they found most correlated with fracture risk), the significance of multi-fraction radiotherapy versus single fraction radiotherapy disappeared. In this context, the guideline is mis-leading. While I think patients with longer life expectancy do benefit from longer courses of RT, I do not think the evidence in the literature suggests that, when fracture risk is controlled for, multi-fraction RT is protective versus single fraction RT. I would recommend changing the level of evidence for this statement, but agree that the statement itself is appropriate.</p>	Recommend	

Response

Thank you for your comments. You raise an important question for which we admit to not having definitive information.

The intent of the current document is to provide guidance on the management of femur lesions. Since the femur is a weight bearing bone, there are significant functional consequences if fracture occurs. Therefore, our recommendations are different than those created by other groups looking at bone lesions in general. As you commented, the cited article was written with the intent of looking for risk factors and argued that the increased rate of fracture in the single dose group compared to the multiple fraction group could be explained by other findings. Our recommendations take into account the specific issues of the femur and that there is a trend toward increased risk of fracture, re-radiation and need for surgery with single dose versus fractionated radiation in many studies. It was felt that despite the lack of conclusive evidence, the special circumstances of the femur deserved the potential benefit of fractionated treatment. With regard to the concern about the grading of the recommendation, it was stated in the rationale that, "In the absence of other randomized data, the strength of this recommendation was upgraded to moderate given the significant morbidity associated with post-radiation femoral fractures which impact weight bearing and quality of life. In patients with limited life expectancies, a single fraction may be suitable to limit time on radiation treatment."

ASCO Comment #1

Concerns were raised about recommendation 1's specific mention of MRI but no mention of any other modality. This confused some of the CPGC members because they weren't sure if this meant that they should or should not use other modalities. They asked this recommendation be clarified.

Response

We were unable to find strong evidence supporting the use of a specific imaging technique or scoring system to predict the risk of pathologic fracture. Thus, we did not make any specific recommendations. Nevertheless, the workgroup felt it would be beneficial to specifically mention MRI ("There is no reliable evidence to suggest that MRI is a strong predictor of femur fracture ") as it is a costly and commonly ordered test that rarely adds much value in surgical decision making.

ASCO Comment #2

The CPGC felt that even though denosumab is not recommended by the guideline, it will be something that a reader would expect to see at least mentioned in the recommendations somewhere (if only to say something like “no recommendation can be made for or against”). That is, its absence might raise more questions than its presence.

Response

Thank you for your comment. The broad term BMA is used in the recommendation and denosumab does get discussed in the Rationale section for Recommendation 3. For this recommendation, it seems appropriate to mention ZA by name, since alternate dosing intervals have not been studied for denosumab.

The PICO question which guided the literature search did not yield information concerning denosumab that could be included. Therefore, no recommendation regarding denosumab was included in the final guideline. We have added a statement to this effect in the rationale.

ASCO Comment #3

In Recommendation 3, there was a concern that “long-term” was not defined, especially in the context of diseases (e.g. multiple myeloma) that might have a very long course of illness. Does long-term mean 2 years? 10? Forever? Some extra detail or context may be needed.

Response

Thank you for your comments. More details about this recommendation are in the rationale (page 25): “One study in multiple myeloma patients compared ZA treatment for 4 years to 2 years, and longer treatment was associated with lower SRE rates, with similar adverse events (Aviles, 2017). Duration of treatment in a majority of the other BMA studies ranges from 1 to 3 years.”

We also added the following statement to the rationale: “Further discussion on the use of BMAs in multiple myeloma can be found in the updated American Society of Clinical Oncology (ASCO) CPG on the Role of Bone-Modifying Agents in Multiple Myeloma (Anderson, 2018).”

ASCO Comment #4

The reviewer pointed out that the text seemed to suggest that DEXA was recommended, but it is not specifically mentioned in Recommendation 5. Should it be?

Response

The rationale includes a summary of suggestions found in the reviewed literature. But the recommendation as approved by the work group only included the finding of lateral cortical thickening. The role of DEXA was not addressed in original PICOT question and subsequent literature search. However, as there is some evidence that DEXA scans can reliably identify lateral beaking, we included that information in the rationale. We also note that routinely performed DEXA scans do not always visualize enough of the femur for adequate screening

ASCO Comment #5

Several members raised the point that recommendation 6 does not really address the idea of radiation INSTEAD of surgery, it only seems to address radiation in addition to surgery. The CPGC recognized that this is a joint ASTRO guideline, and deferred to the ASTRO panel members for specifics and knows that there are likely very little data on the subject, but felt that both issues (radiation + surgery, radiation instead of surgery) should be mentioned in the recommendation for clarity.

Response

Thank you for your comments. We have added the following statement to the rationale: “This recommendation addresses the question of whether radiation by itself can reduce the risk of fracture. It is not intended to alter current clinical practice wherein patients who are felt to be at high risk of pathologic fracture first undergo prophylactic stabilization.”

ASTRO Guidelines Committee Comment #1

The number of citations, search criteria, and the corresponding recommendation strength based on a rather limited number of citations - 23 papers for more than 10 key questions. Given how central this approach was to the final guideline product several members felt that this aspect of our process should be more clearly explained.

Page 11

(Addition in bold)

One important finding from this process was the paucity of high-quality evidence available for clinicians to make decisions regarding prevention and treatment of pathologic fractures of the femur. **Search criteria required that all studies included had at least 10 patients per group and reported on study populations that were primarily comprised of metastatic carcinoma or multiple myeloma of the femur. Therefore, much of the literature addressing management of bone metastases and myeloma in general did not meet the search inclusion criteria.** The project design included 15 PICO (Patient, Intervention, Comparison, Outcome) questions. Despite a comprehensive literature search, based on these search criteria only four PICO questions yielded sufficient...

Page 15

(Addition in bold)

Literature Searches

The medical librarian conducted a comprehensive search of MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials based on key terms and concepts from the clinical practice guideline development group's PICO questions (Appendix III). Bibliographies of relevant systematic reviews were hand searched for additional references. All databases were last searched on July 1, 2019 with limits for publication dates from 1946 to present and English language. **The search strategy aimed to identify studies specifically addressing metastatic carcinoma or multiple myeloma of the femur with a minimum number of patients required for evaluation. The full search strategies are reported in Appendix IV and the inclusion criteria are reported in Appendix VI.**

Page 53

(Addition in bold)

Appendix V - Inclusion Criteria

Customized Inclusion Criteria

- Study must be of patients with metastatic carcinoma or multiple myeloma
- Study must be published in or after 1946
- Study should have 10 or more patients per group
- **Study population should consist primarily (>50%) of metastatic carcinoma or multiple myeloma of the femur**
- Consider all follow-up times

Response

Thank you for your insightful suggestions. They have been included in the document.

Online Form

MSTS MBD Guideline Peer and Public Review Form

Please submit your recommendations and comments using this form. While we cannot guarantee that your recommendations will be incorporated, all comments will receive responses which will be publicly viewable in an electronic appendix to the Guideline.

Thank you,
Evidence Based Committee
Musculoskeletal Tumor Society

Name *

First

Last

Anonymity *

- It is ok to show my name in the public report
 Please do not show my name in the public report

Email *

Society Membership *

Work Setting

- Academic Practice
 Private Group or Practice
 Hospital Employment
 other

Are you disclosures up to date on AAOS.org ? *

- yes
 no

Comments and Recommendation

Evaluate the following statements.

	Strongly Disagree	Disagree	Agree	Strongly Agree
1. The overall objective(s) of the guideline is (are) specifically described.	<input type="radio"/> 1	<input type="radio"/> 2	<input type="radio"/> 3	<input type="radio"/> 4
2. The guideline development group includes individuals from all the relevant professional groups.	<input type="radio"/> 1	<input type="radio"/> 2	<input type="radio"/> 3	<input type="radio"/> 4
3. The guideline's target audience is clearly described.	<input type="radio"/> 1	<input type="radio"/> 2	<input type="radio"/> 3	<input type="radio"/> 4
4. The patients to whom this guideline is meant to apply are specifically described.	<input type="radio"/> 1	<input type="radio"/> 2	<input type="radio"/> 3	<input type="radio"/> 4
5. There is an explicit link between the recommendations and the supporting evidence.	<input type="radio"/> 1	<input type="radio"/> 2	<input type="radio"/> 3	<input type="radio"/> 4
6. The criteria used to select articles for inclusion are appropriate.	<input type="radio"/> 1	<input type="radio"/> 2	<input type="radio"/> 3	<input type="radio"/> 4
7. All important studies that met the article inclusion criteria are included.	<input type="radio"/> 1	<input type="radio"/> 2	<input type="radio"/> 3	<input type="radio"/> 4
8. The validity of the studies is appropriately appraised.	<input type="radio"/> 1	<input type="radio"/> 2	<input type="radio"/> 3	<input type="radio"/> 4
9. Health benefits, side effects, and risks are adequately addressed.	<input type="radio"/> 1	<input type="radio"/> 2	<input type="radio"/> 3	<input type="radio"/> 4
10. The grades assigned to each recommendation are appropriate.	<input type="radio"/> 1	<input type="radio"/> 2	<input type="radio"/> 3	<input type="radio"/> 4

18. Please provide a brief explanation of both your positive and negative answers in the preceding section. If applicable, please specify the draft page and line numbers in your comments. Please feel free to also comment on the overall structure and content of the Guideline

Recommendation *

	Strongly Recommend	Recommend	Would Not Recommend	Unsure
Would you recommend these guidelines for use in clinical practice?	<input type="radio"/> 1	<input type="radio"/> 2	<input type="radio"/> 3	<input type="radio"/> 4

Additional Comments