

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

**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.

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FDA Clearance

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SUMMARY OF RECOMMENDATIONS

1. Imaging and Clinical Findings

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. There is no reliable evidence to suggest that MRI is a strong predictor of femur fracture.

Strength of Recommendation: Consensus ★★★★★

Description: In the absence of reliable evidence, the clinical practice guideline development group is making a recommendation based on their clinical opinion.

2. Efficacy of Bone Modifying Agents (BMAs)

In the absence of reliable evidence, it is the opinion of the workgroup that the use of BMAs may assist in reducing incidence of femur fractures in patients with metastatic carcinoma or multiple myeloma and bone lesions.

Strength of Recommendation: Consensus ★★★★★

Description: In the absence of reliable evidence, the clinical practice guideline development group is making a recommendation based on their clinical opinion.

3. Dosage Response of BMAs

Clinicians should consider decreasing the frequency of zoledronic acid dosing to 12 weeks (compared to the standard 4-week interval), as this is associated with non-inferior SRE outcomes and similar adverse event rates in patients with metastatic carcinoma or multiple myeloma. Clinicians should consider long-term use of BMAs to reduce skeletal related events in patients with multiple myeloma.

Strength of Recommendation: Strong ★★★★★

Evidence from two or more “High” quality studies with consistent findings for recommending for or against the intervention. Also requires no reasons to downgrade from the EtD framework.

4. BMAs for Various Diagnoses

In the absence of reliable evidence, it is the opinion of the workgroup that BMAs should be considered in patients with metastatic carcinoma or multiple myeloma with bone lesions at risk for fracture regardless of tumor histology.

Strength of Recommendation: Consensus ★★★★★

Description: In the absence of reliable evidence, the clinical practice guideline development group is making a recommendation based on their clinical opinion.

5. Imaging Findings and Atypical Fractures

In the absence of reliable evidence, it is the opinion of the workgroup that imaging findings of lateral cortical thickening may be associated with increased atypical femur fracture risk.

Strength of Recommendation: Consensus ★★★★★

Description: In the absence of reliable evidence, the clinical practice guideline development group is making a recommendation based on their clinical opinion.

6. Efficacy of Radiation Therapy

Clinicians should consider the use of radiation therapy to decrease the rate of femur fractures in patients with metastatic carcinoma or multiple myeloma lesions who are deemed at increased risk based on the combination of imaging findings and lesion-related pain.

Strength of Recommendation: Moderate ★★★★★

Description: Evidence from two or more “Moderate” quality studies with consistent findings recommending for or against the intervention, prognostic factor, or diagnostic test.

7. Radiation Therapy and Prophylactic Femur Stabilization

In the absence of reliable evidence, it is the opinion of the workgroup that clinicians may consider the use of radiation therapy in patients undergoing prophylactic femur stabilization to reduce pain, improve functional status, and reduce the need for further intervention.

Strength of Recommendation: Consensus ★★★★★

Description: In the absence of reliable evidence, the clinical practice guideline development group is making a recommendation based on their clinical opinion.

8. Radiation Therapy after Resection and Reconstruction

In the absence of reliable evidence, it is the opinion of the workgroup 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.

Strength of Recommendation: Consensus ★★★★★

Description: In the absence of reliable evidence, the clinical practice guideline development group is making a recommendation based on their clinical opinion.

9. 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.

Strength of Recommendation: Moderate ★★★★★

Description: Evidence from two or more “Moderate” quality studies with consistent findings recommending for or against the intervention, prognostic factor, or diagnostic test.

10. Estimating Survival and Reconstruction Method

In the absence of reliable evidence, it is the opinion of the workgroup that surgeons utilize a validated method of estimating survival of the patient in choosing the method of reconstruction. Longer survival estimates may justify more durable reconstruction methods such as arthroplasty, if clinically appropriate.

Strength of Recommendation: Consensus ★★★★★

Description: In the absence of reliable evidence, the clinical practice guideline development group is making a recommendation based on their clinical opinion.

11. Long Stem Hemiarthroplasty

In the absence of reliable evidence, 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.

Strength of Recommendation: Consensus ★★★★★

Description: In the absence of reliable evidence, the clinical practice guideline development group is making a recommendation based on their clinical opinion.

12. Cephalomedullary Nailing

In the absence of reliable evidence, it is the opinion of the workgroup that there is no advantage to routine use of cephalomedullary nails for diaphyseal metastatic lesions as there does not appear to be a high frequency of new femoral neck lesions following intramedullary nailing.

Strength of Recommendation: Consensus ★★★★★

Description: In the absence of reliable evidence, the clinical practice guideline development group is making a recommendation based on their clinical opinion.

13. Arthroplasty

Clinicians may consider arthroplasty to improve patient function and decrease the need for post-operative radiation therapy in patients with pathologic fractures from metastatic carcinoma in the femur.

Strength of Recommendation: Limited ★★☆☆

Evidence from two or more “Low” quality studies with consistent findings or evidence from a single “Moderate” quality study recommending for or against the intervention.

DEVELOPMENT GROUP ROSTER

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INTRODUCTION

Overview

The skeleton is a frequent site of metastasis in patients with cancer. Multiple myeloma is a plasma cell malignancy in which 70-80% of patients present with lytic lesions in the skeleton (Terpos, 2013). Bone lesions, whether from metastatic carcinoma or multiple myeloma, can be painful and limit physical activity. They may require radiation therapy, surgery or both. Metastatic carcinoma or myeloma bone lesions that progress to pathologic fracture diminish functional capacity and quality of life and can potentially reduce overall survival.

Despite this import, no systematically produced CPG on the management of metastatic bone carcinoma, focusing on the risk and prevention of pathological fractures, has been created that includes the clinical insight of orthopaedic surgeons. The systematic reviews and clinical practice guidelines (CPGs) that exist on these topics have largely been produced by non-surgical subspecialists and limited to the use of bone targeted agents or palliative radiation.

Previous guidelines that address the potential benefits of bone targeted agents (e.g. bisphosphonates) refer to reductions in “skeletal related events (SREs)”. This is a broad term that encompasses pathologic fractures of any bone, need for surgery or radiation, and hypercalcemia. Guidelines around the use of palliative radiotherapy have been primarily focused on short-term pain control and long-term radiation-induced side effects, without significant consideration to modifying the risk of pathologic fracture or the need for subsequent surgical intervention.

This is a major limitation of previous CPGs that we aim to address with this effort. We have decided to focus on the femur, the most common long bone affected by carcinoma and myeloma. Fractures of the femur almost always require surgery and, particularly when about the hip, dramatically alter patients’ quality of life and potentially survival (Gendi, 2016).

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, only four PICO questions yielded sufficient information meeting inclusion and quality standards to make evidence-based recommendations. The remaining recommendations were formulated based on workgroup consensus, using the available literature. We believe this is a clinically important evidentiary gap that should stimulate clinical researchers and funding agencies in the future.

As the treatment of patients with bone metastases involves multiple disciplines, this guideline was designed as a multidisciplinary effort from the outset. The project was initiated by the Musculoskeletal Tumor Society (MSTS), the primary national organization of orthopaedic oncologists. The workgroup consisted of members from MSTS, the American Society of Clinical Oncology (ASCO) and the American Society for Radiation Oncology (ASTRO). Project co-chairs from ASTRO, ASCO, and MSTS contributed to the design of the guideline, before initiating the systematic review.

Goals and Rationale

The purpose of this clinical practice guideline is to provide medical, radiation, and surgical providers with a practical and vetted set of recommendations regarding the management of patients with metastatic or myelomatous lesions of the femur. The goal is not to dictate patient care in all cases, but to provide guidance based on a systematic review of published information and consensus expert opinion.

Intended Users

Although final surgical decision-making resides with surgeons, the availability of a carefully assembled clinical guideline will assist medical oncologists, radiation oncologists, and primary care physicians in making timely and appropriate referrals.

Patient Population

These recommendations are relevant to the management of patients with metastatic or myelomatous lesions of the femur regardless of age, sex, race, ethnicity, education, or socioeconomic status.

Burden of Disease

The skeleton is a frequent site of metastatic carcinoma and myeloma. Primary sites of disease that commonly metastasize to bone include breast, lung, prostate, kidney, and thyroid. The National Cancer Institute (NCI) estimates new cases in 2017 at 252,710 for breast, 222,500 for lung, 161,360 for prostate, and 63,990 for kidney (2019). Autopsy studies have shown an incidence of bone metastases of approximately 70% in patients with breast or prostate cancer and 35% in patients with lung or kidney cancer (Coleman, 2006). The annual incidence of multiple myeloma in the United States is 3-4 cases/100,000 people (Scharschmidt, 2011).

Skeletal related events (SREs) are typically defined as pathologic fracture (vertebral and/or nonvertebral), radiation therapy to bone, surgery to bone, and spinal cord compression. The definition may or may not include hypercalcemia of malignancy. SREs have been seen in 43% of breast cancer patients with bone metastases (Jensen, 2011; Body, 2006; Saunders, 2004; Schachar, 2001) and 20-50% of patients with bone metastases from lung cancer (Anghel, 2011; Terpos, 2013; Scharschmidt, 2011; Lozano-Calderon, 2014). In patients with breast cancer bone metastases, studies have shown a fracture rate of 17% (Walker, 2013; Van Poznak; Gendi, 2016) and mortality rates in the post-SRE period of 21% for patients with a single SRE and 33.5% for patients with multiple SREs (Svendsen, 2013; Coleman, 2014; Fizazi, 2011; LeVasseur, 2016;

Lipton, 2004). An analysis of U.S. economic burden of metastatic bone disease for the years 2000-2004 estimated a national cost burden of \$12.6 billion dollars, representing 17% of the \$74 billion of total direct medical cost of oncology care, estimated by the National Institutes of Health (Schulman, 2007). In 2012, Medicare paid more than \$100 million in hospital charges just for prophylactic internal fixation of the femur for metastatic disease (Gendi, 2016). In addition to the risk of fracture from metastases, there is also mounting evidence that prolonged use of bisphosphonates can itself lead to atypical pathologic fractures (Koh, 2010; Migliorati, 2005; Schilcher, 2015; Smith, 2012; Unnanuntana, 2012).

Emotional and Physical Impact

The emotional and physical impact for patients with metastatic or myelomatous lesions of the femur is quite profound. For patients with osseous metastases, the presence of these lesions denote that their cancer is Stage IV. This discovery can result in significant distress for patients and families. The physical impact can also be very consequential. Patients with metastatic or myelomatous lesions of the femur can have function-limiting pain and require radiation and/or surgery. This can lead to decreased activity and loss of interaction with their normal life and family which can have further implications for emotional health. Bone lesions that progress to pathologic fracture diminish functional capacity and quality of life and potentially reduce overall survival.

Potential Benefits, Harms, and Contraindications

This document potentially benefits providers, patients, and third parties. To providers, it can give some guidance in managing patients with multiple myeloma or metastatic carcinoma of the femur. For patients, it can assist in understanding treatment options of metastatic bone disease. For payers and policy makers, it can provide a summary of the current state of evidence and expert opinion on this topic.

One potential risk is that guidelines are incomplete or inaccurate due to the paucity of well-controlled studies on the efficacy of fracture prevention with medical and radiation interventions. In particular, if a non-surgical intervention is selected and the patient suffers a pathologic fracture of the femur, there would be significant additional harm. It is thus important for clinicians to examine all relevant clinical information and use appropriate judgement in deciding when to make referrals to surgical specialists and for surgeons when deciding to undertake prophylactic internal fixation to prevent fractures.

Future Research

Many recommendations below include a section for future research suggestions. Those recommended areas of enquiry are not an exhaustive list. The following recommendations are excerpted from the sections that follow:

- Future research should specifically assess outcomes of femur fractures in patients with metastatic carcinoma or myeloma treated with BMAs.
- Future research may further explore questions of treatment duration and decreased dosing frequency, with regard to not only SRE's, but also cost effectiveness and quality of life.

- While many of the risk factors for atypical femur fractures have been described, a validated risk calculator and/or clinical pathway to guide physicians would be helpful. As of yet, there is no evidence on which to base guidance for how long patients with AFFs or radiographic signs concerning for AFF should go on a drug “holiday”. The sharply increased risk of AFF in Asians and case reports of symptomatic and/or radiographic improvement following treatment with teriparatide may merit further investigation
- Future research should address which femur metastases are most at risk for fracture, and hence further define when radiation therapy is required. Patients who suffer local recurrence of tumor within the femur after radiation therapy appear to have an increased risk of lesion-related pain, fracture, and need for surgical intervention. Further research is needed to accurately identify specific populations of patients who are at increased risk of tumor recurrence within the femur after radiation therapy, and to determine the risks and benefits associated with any interventions that are intended to reduce these risks
- Given the increased cost of arthroplasty and the small increased risk for dislocation, the benefits of improved function and less need for radiation may not offset the cost and risks for all patients. Future studies can determine which patient characteristics are most likely to result in benefit from arthroplasty procedures in this population.
- Future direct comparisons of short and long stem options in a randomized trial would help to clarify the question. Additional studies investigating the use of short versus long stems in patients with distal disease in the femur would help to identify which patients would benefit from short versus long stem hemiarthroplasty procedures.
- Further studies would be beneficial with appropriately randomized samples, power, and follow up times, examining the intramedullary nail revision rate due to the occurrence of new femoral neck lesions in the setting of metastatic disease and pathological fractures due to diaphyseal lesions
- Future studies would be enhanced by the establishment of a multisite registry for the accumulation of prospectively collected data.

METHODS

The methods used to perform this systematic review were employed to minimize bias and enhance transparency in the selection, appraisal, and analysis of the available evidence. These processes are vital to the development of reliable, transparent, and accurate clinical recommendations.

This clinical practice guideline evaluates the impact of medical, radiology, and surgical treatments on patient outcomes. The MSTS approach incorporates practicing physicians (clinical experts) and methodologists who are free of potential conflicts of interest relevant to the topic under study, as recommended by clinical practice guideline development experts.

This clinical practice guideline was prepared by the Musculoskeletal Tumor Society (MSTS), American Society for Radiation Oncology (ASTRO), and American Society of Clinical Oncology (ASCO) Clinical Practice Guideline physician development group (clinical experts) with the assistance of the American Academy of Orthopaedic Surgeons (AAOS) Clinical Quality and Value (CQV) Department (methodologists). To develop this clinical practice guideline, the clinical practice guideline development group held an introductory meeting to establish the scope of the clinical practice guideline. As the physician experts, the clinical practice guideline development group defined the scope of the clinical practice guideline by creating PICO Questions (i.e. population, intervention, comparison, and outcome) that directed the literature search (Appendix IV). The AAOS Medical Librarian created and executed the search (see Appendix IV for search strategy).

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 V.

Defining the Strength of Recommendation

Judging the level of evidence is only a steppingstone towards arriving at the strength of a clinical practice guideline recommendation. The level of evidence (Table 1) also takes into account the quality, quantity, and the trade-off between the benefits and harms of a treatment, the magnitude of a treatment's effect, feasibility, accessibility, and whether there is data on critical outcomes. Table 2 addresses how to interpret the strength of each recommendation.

Voting on the Recommendations

The recommendations and their strength were voted on by the guideline development group members during the final meeting. If disagreement between the guideline development group occurred, there was further discussion to see whether the disagreement(s) could be resolved. Recommendations were approved and adopted in instances where a simple majority (60%) of the

guideline development group voted to approve; however, the guideline development group had consensus (100% approval) when voting on every recommendation for this guideline.

Interpreting the Strength of Evidence

Table I. Level of Evidence Descriptions





Strength	Overall Strength of Evidence	Description of Evidence Quality	Strength Visual
Strong	Strong	Evidence from two or more “High” quality studies with consistent findings for recommending for or against the intervention.	
Moderate	Moderate	Evidence from two or more “Moderate” quality studies with consistent findings, or evidence from a single “High” quality study for recommending for or against the intervention.	
Limited	Low or Conflicting Evidence	Evidence from two or more “Low” quality studies with consistent findings or evidence from a single “Moderate” quality study recommending for against the intervention or diagnostic or the evidence is insufficient or conflicting and does not allow a recommendation for or against the intervention.	
Consensus*	No Evidence	In the absence of reliable evidence, the clinical practice guideline development group is making a recommendation based on their clinical opinion. Consensus statements are published in a separate, complimentary document.	

Table II. Interpreting the Strength of a Recommendation

Strength of Recommendation	Patient Counseling (Time)	Decision Aids	Impact of Future Research
Strong	Least	Least Important, unless the evidence supports no difference between two alternative interventions	Not likely to change
Moderate	Less	Less Important	Less likely to change
Limited	More	Important	Change possible/anticipated
Consensus	Most	Most Important	Impact unknown

Peer Review

The review stage gives stakeholders an opportunity to provide evidence-based suggestions for modifications that may have been overlooked. Peer review can be requested with other medical organizations that have subject matter expertise. The chair(s) and the guideline workgroup will identify specialty societies at the introductory meeting. Organizations, not individuals, are specified. In communications with external stakeholders, confidentiality of all working drafts is important until final approval of the Guideline. Additionally, the draft document will be submitted to the MSTS membership for public comment.

In advance of peer review and public comment, the draft Guideline will be shared with the MSTS Executive and Evidence Based Committees for initial review and approval to release for the review stage.

In the case of this CPG, as the other speciality societies (i.e. ASCO, ASTRO) with direct subject matter expertise participated in the development of the guideline, we will seek their formal endorsement or approval, rather than peer review.

We will, however, seek peer review from AAOS, which utilizes a structured review form and requests all peer reviewers to disclose their conflicts of interest.

Public Comment

Concurrent with AAOS peer review, the draft Guideline will be disseminated to the entire MSTS membership for public comment. The membership will be notified via email sent by MSTS staff. An online form will again be used to structure and collate responses. Members will be given a three week window to submit their responses.

Once all peer review and public comments have been received, the Guideline chairs will incorporate or reject the recommendations into the draft document. A record of the submitted public and peer-review comments will be published as an electronic appendix on the [MSTS website] following final approval of the guideline, with a point-by-point reply to each non-editorial comment. Reviewers who wish to remain anonymous must notify MSTS to have their names de-identified.

MSTS Guideline Approval

The final guideline draft must be approved by the MSTS Committee on Evidence Based Medicine and the MSTS Executive Committee. The websites for these organizations are as follows

1. [MSTS Executive Committee](#)
2. [MSTS EBM Committee](#)

These decision-making bodies are described are not designated to modify the contents. Their charge is to approve or reject its publication by majority vote.

Endorsements

After approval by MSTS, the finalized Guideline will be submitted to ASCO, ASTRO and AAOS for endorsement.

Dissemination

The primary purpose of the present, full length document is to provide interested readers not only with our recommendations, but also about how we arrived at those recommendations. Shorter versions may be made available in other venues.

Completed Guidelines are announced by the Evidence Based Committee and displayed in poster form at the MSTS Annual Meeting. The short and long versions will be published on the MSTS website.

As per the memorandum of understanding signed by the three societies (MSTS, ASCO, ASTRO), the guideline is eligible to be published in their respective journals.

As this guideline was developed in conjunction with the AAOS Department of Clinical Quality and Value, it is eligible to be submitted for publication in the Journal of American Academy of Orthopedic Surgery (JAAOS), upon approval of the Guideline by the AAOS Board of Directors.

Other dissemination efforts outside of the MSTS can include

1. submitting an abridged version of the guideline for podium or poster presentation at national meeting of AAOS
2. submitting an abridged version of the guideline for podium or poster presentation at national meeting of other specialty societies with potential interest
3. submitting summary of guideline for publication in AAOS member newsletter (AAOS Now)
4. submitting summary of guideline for publication in member newsletter of other specialty societies with potential interest
5. submitting summary of guideline for publication in journals whose readership is referring doctors (e.g. primary care physicians)
6. submitting the guideline to the National Guideline Clearinghouse (Guidelines.gov)
7. announcement of publication via press release.

Implementation

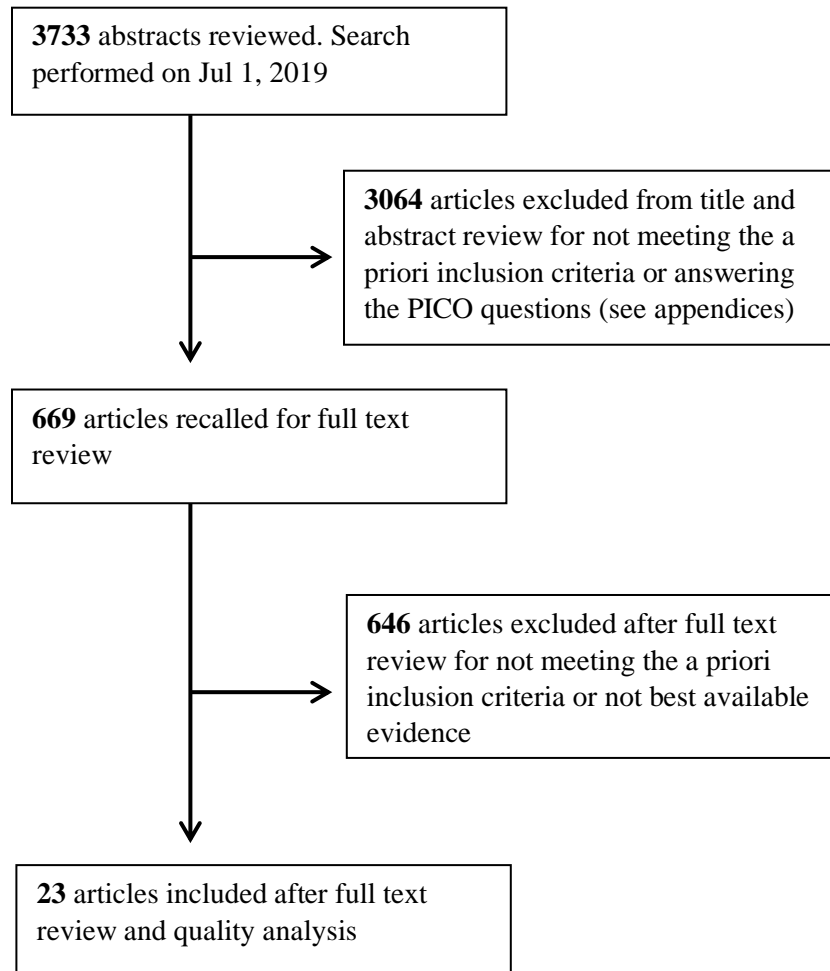
Upon approval of the Guideline by the AAOS Board of Directors, it is also eligible to be published on the AAOS OrthoGuidelines mobile app and associated website, OrthoGuidelines.org.

Depending on pre and post-publication feedback, some of the Guideline recommendations could potentially be converted into performance measures. This would further motivate clinical providers to follow evidence based clinical practice guidelines.

Revision

Any guideline represents a cross-sectional view of current treatment and may become outdated as new evidence becomes available. As such, guidelines should be revised in accordance with new evidence, changing practice, rapidly emerging treatment options, and new technology. At a minimum, a guideline should be updated or withdrawn in five years in accordance with the standards of the National Guideline Clearinghouse.

Study Attrition Flowchart



RECOMMENDATIONS

1. Imaging and Clinical Findings

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. There is no reliable evidence to suggest that MRI is a strong predictor of femur fracture.

Strength of Recommendation: Consensus ★★★★★

Description: In the absence of reliable evidence, the clinical practice guideline development group is making a recommendation based on their clinical opinion.

Rationale

Although advanced 3-dimensional imaging, multi-plane x-rays, and combinations of studies, including PET scanning (Ulaner, 2017) can demonstrate radiographic depictions of the damage caused by metastatic lesions to the proximal femur, the available literature fails to define specific parameters that can accurately predict fracture risk. Low-quality evidence (Oh, 2017; Ulaner, 2017) supports the intuitive presumption that increased bone damage in the proximal femur is associated with an increased fracture risk. Furthermore, although MRI evaluation can accurately demonstrate the intra and extraosseous extent of lesions, there is no reliable evidence that this modality can be used as a predictor for fracture. Combining clinical factors, particularly tumor pain and pain with weight bearing, may aid clinicians in deciding when to intervene surgically in order to prevent a frank pathological fracture and the associated morbidities which may then occur.

2. Efficacy of Bone Modifying Agents (BMAs)

In the absence of reliable evidence, it is the opinion of the workgroup that the use of BMAs may assist in reducing incidence of femur fractures in patients with bone lesions from metastatic carcinoma or multiple myeloma.

Strength of Recommendation: Consensus ★★★★★

Description: In the absence of reliable evidence, the clinical practice guideline development group is making a recommendation based on their clinical opinion.

Rationale

We did not identify any literature with the purpose of determining the efficacy of BMAs in reducing femur fractures or other skeletal related events specifically among patients with metastatic carcinoma or myeloma lesions involving the femur. However, there are studies among patients with metastatic carcinoma or myeloma bone lesions not explicitly localized to the femur (Fizazi, 2009; Hortobagyi, 2017; Raje 2016/18; Lipton 2000/12; Morgan 2011/13; Stopeck, 2010, Martin 2012) demonstrating reduction in skeletal related events with use of BMAs.

Due to the observed benefit in these studies of improved clinical outcomes in context of the acceptable safety profile of commonly used BMAs, it is our consensus that treatment with BMAs in patients with metastatic carcinoma or myeloma involving the femur is advised.

Future Research

Future research should specifically assess outcomes of femur fractures in patients with metastatic carcinoma or myeloma treated with BMAs.

3. Dosage Response of BMAs

Clinicians should consider decreasing the frequency of zoledronic acid dosing to 12 weeks (compared to the standard 4-week interval), as this is associated with non-inferior SRE outcomes and similar adverse event rates in patients with metastatic carcinoma or multiple myeloma. Clinicians should consider long-term use of BMAs to reduce skeletal related events in patients with multiple myeloma.

Strength of Recommendation: Strong ★★★★★

Evidence from two or more “High” quality studies with consistent findings for recommending for or against the intervention. Also requires no reasons to downgrade from the EtD framework.

Rationale

The question of zoledronic acid (ZA) dosing interval, i.e. less frequent dosing, has been addressed in several non-inferiority trials, in breast cancer patients (Hortobagyi, 2017; Amadori, 2013), and in a heterogeneous cohort of patients with multiple myeloma and metastatic carcinomas (Himmelstein, 2017). These studies compared ZA 4mg dosed every 4 weeks to every 12 weeks, either upfront or after 12-15 months of 4-week ZA (Amadori, 2013). In each study, SRE rates were similar between groups, as were adverse event rates. In one study including myeloma and breast cancer patients, ZA 4mg IV was found to be superior to pamidronate 90mg IV (Rosen, 2004). ZA also has established efficacy in patients with non-small cell lung cancer and solid tumors other than breast and prostate carcinoma (Rosen, 2004). 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.

It should be noted that there are other studies that did not meet the strict scope for inclusion that examine several established BMA options for prevention of SREs in patients with multiple myeloma and metastatic carcinoma. Pamidronate 90mg IV every 3-4 weeks was found to reduce SRE's compared to placebo (Lipton, 2000; Hortobagyi, 1998). ZA 4mg IV was found to be superior to clodronic acid (Morgan, 2013). Denosumab was found to reduce risk of SREs, relative to ZA, in multiple tumor types (Lipton, 2012). Adverse event profiles differ; denosumab was associated with higher rates of hypocalcemia, while zoledronic acid was associated with acute phase reactions and renal toxicity more often. Jaw osteonecrosis rates were similar. Studies evaluating longer dosing intervals are only available for ZA, not pamidronate or denosumab.

There are few studies designed to address the question of duration of treatment with BMA's. 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. 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).

Future Research

Future research may further explore questions of treatment duration and decreased dosing frequency, with regard to not only SRE's, but also cost effectiveness and quality of life.

4. BMAs for Various Diagnoses

In the absence of reliable evidence, it is the opinion of the workgroup that BMAs should be considered in patients with metastatic carcinoma or multiple myeloma with bone lesions at risk for fracture regardless of tumor histology.

Strength of Recommendation: Consensus ★★★★★

Description: In the absence of reliable evidence, the clinical practice guideline development group is making a recommendation based on their clinical opinion.

Rationale

There is a single low-quality study by Abdel-Rahman (2018) that assessed tumor histology as a prognostic feature of skeletal related event outcomes in patients with advanced cancer and bone metastases treated with either denosumab or zoledronic acid in a clinical trial. The aforementioned study found that patients with non-small cell lung cancer had a shorter time to first skeletal related event than patients with other cancers. Despite the lack of evidence-based recommendations for this topic, clinicians should consider the use of BMAs regardless of tumor histology in patients with metastatic carcinoma or multiple myeloma with bone lesions at risk for fracture.

Although not meeting criteria for inclusion in analysis for this question in particular, there is evidence that specific BMAs may be favored by histology type. In multiple myeloma, zoledronic acid has been found to be superior to clodronate (Morgan 2011,2013) for skeletal related events, progression free survival (PFS) and overall survival (OS), whereas denosumab is non-inferior to zoledronic acid (Raje 2018) for skeletal related events and OS, but associated with a longer PFS. In patients with breast cancer, denosumab is shown to be superior to zoledronic acid in relation to reduced rates of skeletal related events, prolonged time to first skeletal related event and improved quality of life measures (Martin 2012, Stopeck 2010). In patients with prostate cancer, denosumab prolonged time to first skeletal related event compared to zoledronic acid (Fizazi, 2011). In a sub-study analysis, denosumab compared to zoledronic acid was associated with improved OS in patients with non-small cell lung cancer and bone metastases (Scagliotti, 2012)

Benefits/Harms of Implementation

The benefits of decreased fracture rates, avoiding surgical intervention and associated pain, reduction in other skeletal related events and improved survival (in some patients according to histologic type) weighed against the harms of osteonecrosis of the jaw and hypocalcemia, favor the use of BMAs in these populations. It is important for clinicians to be aware that renal insufficiency is observed more commonly for zoledronic compared to denosumab, whereas hypocalcemia is more frequently observed with denosumab.

5. Imaging Findings and Atypical Fractures

In the absence of reliable evidence, it is the opinion of the workgroup that imaging findings of lateral cortical thickening may be associated with increased atypical femur fracture risk.

Strength of Recommendation: Consensus ★★★★★

Description: In the absence of reliable evidence, the clinical practice guideline development group is making a recommendation based on their clinical opinion.

Rationale

Atypical femur fracture is a well-recognized complication of long-term administration of bone targeted agents. These fractures have consistent radiographic features, typically starting as thickening of the lateral cortex (“beaking”) in the subtrochanteric or diaphyseal femur. A transverse radiolucency that develops through the lateral thickening is concerning for impending fracture and is sometimes referred to as the “dreaded black line” (Kim, 2014). If these signs are undetected, the patient may progress onto a transverse or oblique fracture (Shane, 2014). In 70% of patients, fracture is preceded by prodromal thigh pain (Dell, 2018).

Atypical femur fractures are believed to be stress or insufficiency reactions, possibly exacerbated by reduced remodeling at the fracture site due to the action of bisphosphonates (Shane, 2014). Multiple epidemiological studies have documented increased incidence of subtrochanteric fractures as bisphosphonates became more widely prescribed, while the incidence of femoral neck and intertrochanteric fractures decreased (Shane, 2014).

The incidence of atypical femur fractures in one large population study was 55 per 100,000 person-years, compared with 1 per 100,000 person-years in bisphosphonate-naïve patients (Van De Laarschot, 2017). However, it is important to remember that an estimated 162 osteoporosis-related fractures are prevented for every 1 AFF that may be associated with treatment with an antiresorptive medication (Van De Laarschot, 2017). Asians may be up to 8 times more at risk for AFF than whites (Dell, 2018). Concurrent use of glucocorticoids is associated with increased risk of AFF (Shane, 2014), which may be relevant to patients being treated for multiple myeloma.

Dual-Energy X-ray Absorptiometry Images (DEXA) scanning, used routinely in surveillance for osteoporosis, has been shown to be effective in screening for lateral cortical thickening (Kim, 2014). DEXA scanning also requires significantly less radiation exposure than routine radiographs (Van De Laarschot, 2017). One retrospective review noted a 40% of AFFs occur in the diaphysis (Unnanuntana, 2012), therefore it is important that screening DEXA scans are extended to include the diaphysis (Unnanuntana, 2012).

If a patient suffers an atypical femur fracture, stopping bisphosphonates exposure can reduce contralateral fracture, which is otherwise ~25%. There is some evidence that treatment benefit from bisphosphonates reduces after 5 years, while risk of AFF increases from 1.78/100k/year to 113/100k/year with exposure >8 years (Dell, 2018).


Patients with symptomatic lateral cortex thickening, medial callus formation or transverse lucency should undergo prophylactic intramedullary nailing (Shane, 2014). In the case of completed fractures, external rotation of the intramedullary nail during insertion can reduce the risk of malreduction of the bowed femur and accelerate fracture union (Park, 2017).

Future Research

While many of the risk factors for atypical femur fractures have been described, a validated risk calculator and/or clinical pathway to guide physicians would be helpful. As of yet, there is no evidence on which to base guidance for how long patients with AFFs or radiographic signs concerning for AFF should go on a drug “holiday”. The sharply increased risk of AFF in Asians and case reports of symptomatic and/or radiographic improvement following treatment with teriparatide may merit further investigation.

6. Efficacy of Radiation Therapy

Clinicians should consider the use of radiation therapy to decrease the rate of femur fractures in patients with metastatic carcinoma or multiple myeloma lesions who are deemed at increased risk based on the combination of imaging findings and lesion-related pain.

Strength of Recommendation: Moderate  (Upgraded)

Description: Evidence from two or more “Moderate” quality studies with consistent findings recommending for or against the intervention, prognostic factors, or diagnostic test.

Rationale

One observational study of moderate quality (Oh E. et al. 2017) among patients with metastatic lung cancer indicates a higher risk of fracture among patients with femoral metastases not treated with radiation therapy, as compared to those treated with radiation therapy. Other risk factors included lytic femur metastasis morphology and female gender. Though these data are limited to femur metastases from lung cancer and there is no randomized evidence to guide practice, the evidence and related recommendation was considered moderate strength given the high morbidity of femur fractures and the low morbidity of radiation therapy to the femur.

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.

Future Research

Future research should address which femur metastases are most at risk for fracture, and hence further define when radiation therapy is required. Patients who suffer local recurrence of tumor within the femur after radiation therapy appear to have an increased risk of lesion-related pain, fracture, and need for surgical intervention. Further research is needed to accurately identify specific populations of patients who are at increased risk of tumor recurrence within the femur after radiation therapy, and to determine the risks and benefits associated with any interventions that are intended to reduce these risks.

7. Radiation Therapy and Prophylactic Femur Stabilization

In the absence of reliable evidence, it is the opinion of the workgroup that clinicians may consider the use of radiation therapy in patients undergoing prophylactic femur stabilization to reduce pain, improve functional status, and reduce the need for further intervention.

Strength of Recommendation: Consensus ★★★★★

Description: In the absence of reliable evidence, the clinical practice guideline development group is making a recommendation based on their clinical opinion.

Rationale

One small, retrospective study (Townsend, 1995) demonstrated that patients receiving postoperative radiation therapy following prophylactic stabilization for femur metastases had less pain, better limb function, less need of revision surgery, and better overall survival. The small, retrospective nature of this study, hampered by selection factors, renders this low-quality evidence. However, given the low morbidity of postoperative radiation therapy, and the importance of improving quality of life outcomes and reducing the need for further surgical interventions, the use of radiation may be considered for patients with metastases to the femur requiring prophylactic stabilization.

8. Radiation Therapy after Resection and Reconstruction

In the absence of reliable evidence, it is the opinion of the workgroup 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.

Strength of Recommendation: Consensus ★★★★★

Description: In the absence of reliable evidence, the clinical practice guideline development group is making a recommendation based on their clinical opinion.

Rationale

No investigations directly compare the impact of radiation therapy after resection and reconstruction, limiting the statements that can be made about whether radiation therapy can improve outcomes in the setting of residual disease or when there is an increased risk of tumor recurrence. However, given that radiation therapy of the femur is generally well-tolerated and residual/recurrent tumor of the femur can remain/become symptomatic, the potential benefits may be felt to outweigh the harms in select patients.

9. 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.

Strength of Recommendation: Moderate  (Upgraded)

Description: Evidence from two or more “Moderate” quality studies with consistent findings recommending for or against the intervention, prognostic factors, or diagnostic test.

Rationale

One randomized study of moderate quality (Van Der Linden 2003) demonstrated that multi-fraction radiation therapy was associated with a lower risk of femoral fracture compared to single-fraction radiation therapy. 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.

10. Estimating Survival and Reconstruction Method

In the absence of reliable evidence, it is the opinion of the workgroup that surgeons utilize a validated method of estimating survival of the patient in choosing the method of reconstruction. Longer survival estimates may justify more durable reconstruction methods such as arthroplasty, if clinically appropriate.

Strength of Recommendation: Consensus ★★★★★

Description: In the absence of reliable evidence, the clinical practice guideline development group is making a recommendation based on their clinical opinion.

Rationale

Metastatic bone disease presents unique surgical challenges within a very diverse patient population. Rather than base treatment decisions on radiographs alone, surgeons may consider the use a validated means to estimate survival such as the Tokuhashi method (Tokuhashi 2005), the PATHFx tool, available at www.pathfx.org (Ogura, 2017) or the Global Spine Tumour Study Group at www.spinemet.com. Doing so helps ensure other characteristics such as oncologic diagnosis, extent of metastases, hemoglobin, and performance status are considered when deciding on a treatment course. In general, short survival estimates (1-6 months) justify less invasive and less durable approaches, such as intramedullary nails, or less commonly, other internal fixation devices. Similarly, patients with longer estimates (>6 months) require more durable solutions such as endoprostheses, whenever possible. Patients with very short survival estimates of approximately one month may not be candidates for prophylactic fixation but may benefit from minimally or non-invasive interventions such as radiotherapy, cryotherapy, or radio-frequency ablation for adequate pain relief (Meares, 2019; Kotian, 2018). However, arthroplasty may still be indicated in patients with short survival time for palliation in certain clinical scenarios, for example fractured femoral neck.

11. Long Stem Hemiarthroplasty

In the absence of reliable evidence, 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.

Strength of Recommendation: Consensus ★★★★★

Description: In the absence of reliable evidence, the clinical practice guideline development group is making a recommendation based on their clinical opinion.

Rationale

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. However, some evidence does exist demonstrating increased complication rates with the use of long stem cemented arthroplasty. Intraoperative hypotension and significant cardiopulmonary events including death have been documented in numerous studies (Herrenbruck 2002, Houdek 2017, Xing 2013), while other studies have demonstrated that long stem cemented implants are overall a relatively safe option if performed appropriately (Price 2013, Peterson 2017). The theoretical benefit of a long stem implant is to protect the majority of the femur from fracture in the setting of disease progression. However, some evidence does exist showing that reoperation rates in general are very low in this population and no difference has been appreciated based on the length of the stem chosen (Xing 2013).

Benefits/Harms of Implementation

There may also be some additional cost involved with performing a long stem technique due to implant cost, operative time, and complication rates. Although both short stem and long stem options are at times acceptable and feasible, we believe that the potential risk involved with the long stem option is not warranted without obvious, symptomatic, concerning lesions more distal in the femur.

Future Research

Future direct comparisons of short and long stem options in a randomized trial would help to clarify the question. Additional studies investigating the use of short versus long stems in patients with distal disease in the femur would help to identify which patients would benefit from short versus long stem hemiarthroplasty procedures.

12. Cephalomedullary Nailing

In the absence of reliable evidence, it is the opinion of the workgroup that there is no advantage to routine use of cephalomedullary nails for diaphyseal metastatic lesions as there does not appear to be a high frequency of new femoral neck lesions following intramedullary nailing.

Strength of Recommendation: Consensus ★★★★★

Description: In the absence of reliable evidence, the clinical practice guideline development group is making a recommendation based on their clinical opinion.

Rationale

The lack of relevant and high-quality evidence regarding this topic led to a consensus level recommendation. Though it did not meet the strict inclusion criteria for this CPG, one study examined the occurrence of femoral neck metastases posterior to intramedullary nail fixation performed for a femoral diaphyseal metastatic lesion (Moon, 2015). The study reported no new femoral neck secondary lesions occurring subsequent to the aforementioned procedure.

Benefits/Harms of Implementation

Failure to diagnose a femoral neck lesion prior to implanting an intramedullary nail, increases the risks of adverse outcomes such as implant failure and the need for additional surgery. Efforts should be made to assess the entire bone length prior to decision making. Other risks are equal to those of any intramedullary nailing procedure in a cancer patient, which should be assessed on an individual basis.

The benefits of implementing this recommendation, when correctly indicated, will be the decrease in surgical time and radiation exposure to the surgeon and operating room personnel. This has implications on cost savings to society.

Future Research

Further studies would be beneficial with appropriately randomized samples, power, and follow up times, examining the intramedullary nail revision rate due to the occurrence of new femoral neck lesions in the setting of metastatic disease and pathological fractures due to diaphyseal lesions.

13. Arthroplasty

Clinicians may consider arthroplasty to improve patient function and decrease the need for post-operative radiation therapy in patients with pathologic fractures from metastatic carcinoma in the femur.

Strength of Recommendation: Limited ★★☆☆

Evidence from two or more “Low” quality studies with consistent findings or evidence from a single “Moderate” quality study recommending for or against the intervention.

Rationale

Arthroplasty procedures carry greater potential morbidity and higher healthcare costs than internal fixation. However, these procedures may be indicated in select patients with longer expected survival and higher performance status. Four low-quality studies (Gao, H., 2016, Sarahrudi, K., 2009, Tsuda, Y., 2016, and Zacherl, M., 2011) reported comparative outcomes between arthroplasty and internal fixation for pathologic fractures of the proximal femur. Results from these studies indicate that the benefits of arthroplasty include improved function as determined by Harris Hip Scores, and a decreased need for adjuvant radiotherapy for disease control. Surgical management with both arthroplasty and internal fixation provides immediate stability to the femur and the opportunity for early post-operative mobility. The differences in outcomes are small and therefore both treatment options are reasonable.

Benefits/Harms of Implementation

Despite the benefits of arthroplasty, these procedures carry a higher risk of post-operative complications such as dislocation.

Future Research

Given the increased cost of arthroplasty and the small increased risk for dislocation, the benefits of improved function and less need for radiation may not offset the cost and risks for all patients. Future studies can determine which patient characteristics are most likely to result in benefit from arthroplasty procedures in this population.

APPENDICES

Appendix I: References and Included Literature

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Appendix II - Guideline Development Group Disclosures

Prior to the development of this clinical practice guideline, clinical practice guideline development group members disclose conflicts of interest (COI). They disclose COIs in writing to the American Academy of Orthopaedic Surgeons via a private on-line reporting database and also verbally at the recommendation approval meeting.

Disclosure Items: (n) = Respondent answered 'No' to all items indicating no conflicts. 1 = Royalties from a company or supplier; 2 = Speakers bureau/paid presentations for a company or supplier; 3A = Paid employee for a company or supplier; 3B = Paid consultant for a company or supplier; 3C = Unpaid consultant for a company or supplier; 4 = Stock or stock options in a company or supplier; 5 = Research support from a company or supplier as a PI; 6 = Other financial or material support from a company or supplier; 7 = Royalties, financial or material support from publishers; 8 = Medical/Orthopaedic publications editorial/governing board; 9 = Board member/committee appointments for a society.

Voting Members' Disclosures

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American Society for Radiation Oncology: Board or committee member (\$0) Chair
ASTRO Guidelines Sub-Committee (Self)
- **John Charlson, MD - American Society of Clinical Oncology**
This individual reported nothing to disclose
- **Tracy Balboni, MD, MPH - American Society of Therapeutic Radiation Oncology**
This individual reported nothing to disclose
- **Alan Blank, MD, MS - Musculoskeletal Tumor Society**
Exparel/Pacira: Stock or stock options; Number of Shares: 0
- **Ana Cecilia Belzarena, MD - Musculoskeletal Tumor Society**
This individual reported nothing to disclose
- **Jonathan A. Forsberg, MD, PhD - Musculoskeletal Tumor Society**
The Solsidan Group, LLC: Employee (\$10,875) N/A (Both)
Zimmer: Unpaid consultant Biomet (Self)
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- **Michelle Ghert, MD, FRCSC - Musculoskeletal Tumor Society**
Wright Medical Technology, Inc.: Paid presenter or speaker (\$1,000)
Number of Presentations: 2 N/A (Self)
- **Richard W. Nicholas, MD - Musculoskeletal Tumor Society**
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- **Frank Passero, MD - American Society of Clinical Oncology**
This individual reported nothing to disclose
- **Yolanda Tseng, MD, MPhil - American Society of Therapeutic Radiation Oncology**
This individual reported nothing to disclose

Appendix III: PICO Questions Used to Define Literature Search

1. In patients with metastatic carcinoma or multiple myeloma lesions in the femur, which imaging modalities, i.e. x-ray, MRI, CT or PET/CT, offer reliable predication of the rate of pathologic fracture?
2. In patients with metastatic carcinoma or multiple myeloma lesions in the femur, is there a reduction in the rate of SREs (including femur fractures) with use of bone modifying agents?
3. In patients with metastatic carcinoma or multiple myeloma, is modifying dosage or duration of treatment with bone modifying agents associated with a change in the rate of atypical femur fracture, osteonecrosis of the jaw, hypocalcemia, or renal insufficiency?
- 4a. In patients with metastatic carcinoma or multiple myeloma treated with bone modifying agents, does the tumor histology correlate with reduction in rate of skeletal related events (SREs)?
- 4b. In patients with metastatic carcinoma or multiple myeloma lesions in the femur treated with bone modifying agents, does the tumor histology correlate with reduction in rate of femur fracture?
5. In patients with metastatic carcinoma or multiple myeloma lesions in the femur treated with bone modifying agents, are there reliable radiological (on bone scan, X-ray, CT, or MRI) or clinical findings that indicate an increased risk of atypical (“brittle bone”) fractures?
6. In patients with metastatic carcinoma or multiple myeloma lesions in the femur, does radiation therapy modify the rate of fracture?
7. In patients with metastatic carcinoma or multiple myeloma lesions in the femur undergoing prophylactic femur stabilization, what are the benefits (reduced fracture rate, pain, further intervention, etc.) associated with radiation of the femur following surgery?
8. In patients with metastatic carcinoma or multiple myeloma lesions in the femur treated with resection and reconstruction, what are the benefits (reduced fracture rate, pain, further intervention, etc.) associated with radiation of the femur following surgery?
9. In patients with metastatic carcinoma or multiple myeloma lesions in the femur, is the rate of fracture or subsequent intervention affected by single fraction vs multi-fraction radiation of the femur?
10. In patients with metastatic carcinoma or multiple myeloma lesions in the femur treated with radiation therapy, are there tumor histologies, clinical features, or therapeutic interventions associated with improved outcomes (reduced fracture rate, pain, further intervention, etc.)?
- 11a. In patients with metastatic carcinoma or multiple myeloma lesions in the femur, are there reliable imaging findings (bone scan, X-ray, CT, PET/CT, or MRI) and/or clinical characteristics (e.g. nature of pain, primary diagnosis) that indicate an increased risk of pathologic fracture without prophylactic surgery versus patients without those findings or characteristics?

11b. In patients with metastatic carcinoma or multiple myeloma lesions in the femur, are there imaging findings (bone scan, X-ray, CT, or MRI) and/or clinical characteristics (e.g. nature of pain, primary diagnosis, survival estimates at diagnosis) that predict poor outcomes with internal fixation (plate or IM rod)?

12. In patients with metastatic carcinoma or multiple myeloma lesions in the femur with pathologic fractures of the femoral neck, is it preferable to perform long or short stem hemiarthroplasty with respect to preventing future femur fractures and perioperative morbidity?

13. In patients with metastatic carcinoma or multiple myeloma lesions in the femur with pathologic fractures of the femoral diaphysis, is it preferable to perform standard or cephalomedullary nailing?

14. In patients with metastatic carcinoma or multiple myeloma lesions in the femur with pathologic fractures of the intertrochanteric or peritrochanteric femur, does arthroplasty result in improved outcomes versus treatment with internal fixation (plating or IM rod)?

15. In patients with metastatic carcinoma or multiple myeloma lesions in the femur with pathologic fractures of the intertrochanteric or subtrochanteric region, are clinical characteristics, i.e. tumor histology, or predicted survival estimate at diagnosis, related to outcomes after internal fixation (plating or IM rod)?

Appendix IV: Literature Search Strategy

Database: MEDLINE

Version: Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions, 1946 to present

Interface: Ovid

Femur-specific: PICOs 1-2, 4b-15

Date Searched: October 19, 2018

Results: 469 (468 de-duplicated)

Date of Updated Search: July 1, 2019

Results on Update: 27 (20 de-duplicated)

Additional Search Queries on Update:

- #17 limit 16 to ez=20181019-20190701
- #18 limit 16 to ed=20181019-20190701
- #19 17 or 18

LIN	SEARCH QUERY	RESULTS	NOTES/CONCEPT
#1	Bone Neoplasms/sc	17868	
#2	exp FEMUR/ or (femur or femoral or "long bone" or "long bones").ti,ab.	174383	
#3	1 and 2	748	
#4	exp Femoral Neoplasms/sc [Secondary]	435	
#5	3 or 4	1129	Secondary femoral neoplasms
#6	("metastatic bone disease" or "metastatic disease" or "metastatic lesion" or "metastatic lesions" or "osseous metastases" or "carcinoma to bone" or "bone metastases" or "bony metastases" or "skeletal metastases" or "osteolytic metastasis" or "osteolytic metastases" or "osteoblastic metastasis" or "osteoblastic metastases" or "metastatic" or "metastases" or "metastasis" or "metastasized" or "bone lesion" or "bone lesions").ti,ab.	434691	
#7	2 and 6	3891	Broad femoral mets/lesions
#8	5 or 7	4142	Femoral lesions/mets combo
#9	exp Multiple Myeloma/ or ("plasma cell myeloma" or "multiple myeloma" or "multiple myelomas" or "Kahler disease" or myelomatosis or myelomatoses or "myeloma induced bone disease" or "myeloma multiplex").ti,ab.	47580	
#10	exp Carcinoma/ or (carcinoma* or epithelioma* or epithelial).ti,ab.	1129361	
#11	10 and 8	907	Femoral mets w/carcinoma
#12	2 and 9	298	Femoral MM

#13	11 or 12	1188	FINAL PATIENT POPULATION
#14	(animals not humans).sh.	4473312	Animal filter
#15	(((comment or editorial or letter or historical article) not "clinical trial") or addresses or news or newspaper article or case reports).pt. or case report.ti.	3929676	Irrelevant pub type filter
#16	(13 not (14 or 15)) and english.lg.	469	Filtered results, English limit

Non-femur, BMAs: PICO 3, 4a

Date: November 1, 2018

Results: 1072 (1032 de-duplicated)

Date of Updated Search: July 1, 2019

Results on Update: 37 (18 de-duplicated)

Additional Search Queries on Update:

- #16 limit 15 to ez=20181019-20190701
- #17 limit 15 to ed=20181019-20190701
- #17 16 or 17

LIN	SEARCH QUERY	RESULTS	NOTES/CONCEPT
#1	exp Diphosphonates/ OR (diphosphonate* OR bisphosphonate* OR "antiresorptive agents" OR "antiresorptive agent" OR "antiresorptive drugs" OR "antiresorptive drug").ti,ab. OR exp Denosumab/ OR ("denosumab" OR "RANKL inhibitor" OR "SRC inhibitor" or "SRC inhibitors" or "deastinib" or "bosutinib" or "saracatinib" OR "GPNMB inhibitors" OR "GPNMB inhibitor" OR "chemokine receptor" or "cathepsin" or "pth inhibitor" or "pth inhibitors").ti,ab. OR exp "Bone Density Conservation Agents"/ or (pamidronate or "zoledronic acid" or ibandronate or "bone modifying agents" or "bone modifying agent" or "bone modifying inhibitor" or "bone modifying inhibitors" or "bone conserving agent" or "bone conserving agents" or "bone density conservation agent" or "bone density conservation agents" or "osteoclast inhibitor" OR "osteoclast inhibitors" or "bone targeted therapy" or "clodronate").ti,ab.	160887	BMA concept
#2	exp Carcinoma/ or (carcinoma* or epithelioma* or epithelial).ti,ab.	1130394	carcinoma
#3	exp Multiple Myeloma/ or ("plasma cell myeloma" or "multiple myeloma" or "multiple myelomas" or "Kahler disease" or myelomatosis or myelomatoses or "myeloma induced bone disease" or "myeloma multiplex").ti,ab.	47630	multiple myeloma
#4	("metastatic bone disease" or "metastatic disease" or "metastatic lesion" or "metastatic lesions" or "osseous metastases" or "carcinoma to bone" or "bone metastases" or "bony metastases" or "skeletal metastases" or "osteolytic metastasis" or "osteolytic metastases" or "osteoblastic metastasis" or "osteoblastic metastases" or "metastatic" or "metastases" or "metastasis" or "metastasized" or "bone lesion" or "bone lesions").ti,ab.	435351	metastatic concept
#5	2 and 4	191393	mets + carcinoma

#6	3 or 5	238613	Mets carcinoma or MM
#7	1 and 6	4938	disease + BMAs
#8	(animals not humans).sh.	4474784	
#9	(((comment or editorial or letter or historical article) not "clinical trial") or addresses or news or newspaper article or case reports).pt. or case report.ti.	3932666	
#10	(7 not (8 or 9)) and English.lg.	3269	
#11	exp "Pathologic fractures"/ or exp "spinal cord compression"/ or exp "hypocalcemia"/ or exp "renal insufficiency"/	183773	
#12	(skeletal or SRE or SREs or fracture* or (("spinal" or "spine") adj3 compression) or radiation or radiotherapy).ti,ab.	833885	
#13	exp "Bisphosphonate-Associated Osteonecrosis of the Jaw"/ or (exp "Jaw"/ and exp "Osteonecrosis"/) or ((osteonecrotic or osteonecrosis or necrotic) adj3 (jaw or jaws or mandible or mandibular or temporomandibular or maxilla or maxillary or maxillofacial)).ti,ab. or (hypocalcaemi* or hypocalcemi*).ti,ab. or ((kidney or renal) adj3 (insufficienc* or deterioration or failure* or disease or impairment)).ti,ab.	229327	
#14	11 OR 12 OR 13	1131116	
#15	10 AND 14	1072	

Database: Embase

Interface: Elsevier (<https://embase.com/>)

Femur-specific: PICOs 1-2, 4b-15

Date Searched: October 19, 2018

Results: 1,301 (1,080 de-duplicated)

Date of Updated Search: July 1, 2019

Results on Update: 106 (58 de-duplicated)

Additional Search Queries on Update:

- #10 #8 NOT #9 AND [english]/lim AND [19-10-2018]/sd NOT [2-7-2019]/sd

LIN	SEARCH QUERY	RESUL TS	NOTES/CONCEPT
#1	'carcinoma'/exp OR carcinoma*:ti,ab OR epithelial:ti,ab	1614294	Carcinoma concept
#2	'bone metastasis'/de AND 'femur'/exp OR ('femur tumor'/exp AND 'metastasis'/exp)	1503	Femur mets
#3	'femur'/exp OR 'femur':ti,ab OR 'femoral':ti,ab	218417	Femur
#4	'multiple myeloma'/exp OR 'multiple myeloma':ti,ab OR 'multiple myelomas':ti,ab OR 'plasma cell myeloma':ti,ab OR 'kahler	77439	MM

	disease':ti,ab OR 'myelomatosis':ti,ab OR 'myelomatoses':ti,ab OR 'myeloma induced bone disease':ti,ab OR 'myeloma multiplex':ti,ab		
#5	'metastatic bone disease':ti,ab OR 'metastatic disease':ti,ab OR 'metastatic lesion':ti,ab OR 'metastatic lesions':ti,ab OR 'osseous metastases':ti,ab OR 'bone metastases':ti,ab OR 'bony metastases':ti,ab OR 'skeletal metastases':ti,ab OR 'osteolytic metastases':ti,ab OR 'osteolytic metastasis':ti,ab OR 'osteoblastic metastasis':ti,ab OR 'osteoblastic metastases':ti,ab OR metastatic:ti,ab OR metastases:ti,ab OR metastasis:ti,ab OR metastasized:ti,ab OR 'bone lesion':ti,ab OR 'bone lesions':ti,ab	628958	Expanded MM
#6	#3 AND (#5 OR #4)	5301	Femur MM
#7	#1 AND #2	402	Carcinoma mets, femur
#8	#6 OR #7	5382	Final patient concept
#9	'cadaver'/de OR 'in vitro study'/exp OR 'abstract report'/de OR 'book'/de OR 'editorial'/de OR 'note'/de OR 'letter'/it OR 'case study'/de OR 'case report'/de OR 'conference abstract'/it OR 'chapter'/it OR 'conference paper'/it OR 'conference review'/it	1277662 9	Animal/cadaver/irrelevant pub type filter
#10	#8 NOT #9 AND [english]/lim	1301	Final results, with English limit

Non-femur, BMA-specific: PICO 3, 4a

Date: November 1, 2018

Results: 1508 (892 de-duplicated)

Date of Updated Search: July 1, 2019

Results on Update: 54 (29 de-duplicated)

Additional Search Queries on Update:

- #12 #7 AND #11 AND [1-11-2018]/sd NOT [2-7-2019]/sd

LIN	SEARCH QUERY	RESULT S	NOTES/CONCEPT
#1	'bisphosphonic acid derivative'/exp OR bisphosphonate*:ti,ab OR diphosphonate*:ti,ab OR 'denosumab'/exp OR denosumab:ti,ab OR 'rankl inhibitor':ti,ab OR 'rankl inhibitors':ti,ab OR 'src inhibitor':ti,ab OR 'src inhibitors':ti,ab OR 'deastinib':ti,ab OR 'bosutinib':ti,ab OR 'saracatinib':ti,ab OR 'gpnmb inhibitors':ti,ab OR 'gpnmb inhibitor':ti,ab OR 'chemokine receptor':ti,ab OR 'cathepsin':ti,ab OR 'pth inhibitor':ti,ab OR 'pth inhibitors':ti,ab OR 'bone density conservation agent'/exp OR pamidronate:ti,ab OR 'pamidronic acid'/exp OR 'zoledronic acid':ti,ab OR 'zolendric acid':ti,ab OR ibandronate:ti,ab OR 'ibandronic acid'/de OR 'bone modifying agents':ti,ab OR 'bone modifying agent':ti,ab OR 'bone modifying inhibitors':ti,ab OR 'bone modifying inhibitor':ti,ab OR 'bone conserving agents':ti,ab OR 'bone conserving agent':ti,ab OR 'bone density conservation agents':ti,ab OR 'bone density conservation agent':ti,ab OR 'antiresorptive agents':ti,ab OR 'antiresorptive agent':ti,ab OR 'antiresorptive drugs':ti,ab OR 'antiresorptive drug':ti,ab OR 'osteoclast inhibitors':ti,ab OR 'osteoclast inhibitor':ti,ab OR 'bone targeted therapy':ti,ab OR 'clodronate':ti,ab	107843	BMA concept

#2	'carcinoma'/exp OR carcinoma*:ti,ab OR epithelial:ti,ab	1616268	carcinoma
#3	'multiple myeloma'/exp OR 'multiple myeloma':ti,ab OR 'multiple myelomas':ti,ab OR 'plasma cell myeloma':ti,ab OR 'kahler disease':ti,ab OR 'myelomatosis':ti,ab OR 'myelomatoses':ti,ab OR 'myeloma induced bone disease':ti,ab OR 'myeloma multiplex':ti,ab	77512	MM
#4	'bone metastasis'/de OR 'metastatic bone disease':ti,ab OR 'osseous metastases':ti,ab OR 'bone metastases':ti,ab OR 'bone metastasis':ti,ab OR 'bony metastases':ti,ab OR 'bony metastasis':ti,ab OR 'skeletal metastases':ti,ab OR 'skeletal metastasis':ti,ab OR 'osteolytic metastases':ti,ab OR 'osteolytic metastasis':ti,ab OR 'osteoblastic metastasis':ti,ab OR 'osteoblastic metastases':ti,ab OR 'bone lesion':ti,ab OR 'bone lesions':ti,ab	54857	metastatic bone
#5	'cadaver'/de OR 'in vitro study'/exp OR 'abstract report'/de OR 'book'/de OR 'editorial'/de OR 'note'/de OR 'letter'/it OR 'case study'/de OR 'case report'/de OR 'conference abstract'/it OR 'chapter'/it OR 'conference paper'/it OR 'conference review'/it	12791129	
#6	(#2 AND #4 OR #3) AND #1	6151	
#7	#6 NOT #5 AND [english]/lim	2605	
#8	'pathologic fracture'/exp OR 'spinal cord compression'/exp OR 'jaw osteonecrosis'/exp OR 'hypocalcemia'/exp OR 'kidney failure'/exp	410459	
#9	((osteonecrotic OR osteonecrosis OR necrotic) NEAR/3 (jaw OR jaws OR mandible OR mandibular OR temporomandibular OR maxilla OR maxillary OR maxillofacial)):ti,ab) OR hypocalcemi*:ti,ab OR hypocalcaemi*:ti,ab OR (((kidney OR renal) NEAR/3 (insufficienc* OR deterioration OR failure* OR disease OR impairment)):ti,ab)	330116	
#10	skeletal:ti,ab OR sre:ti,ab OR sres:ti,ab OR fracture*:ti,ab OR (((spinal OR spine) NEAR/3 compression):ti,ab) OR radiation:ti,ab OR radiotherapy:ti,ab	1089476	
#11	#8 OR #9 OR #10	1583245	
#12	#7 AND #11	1508	

Database: Cochrane Library (CENTRAL and CDSR)

Interface: Wiley (<https://www.cochranelibrary.com/central>)

Femur-specific: PICOs 1-2, 4b-15

Date Searched: October 19, 2018

Results: 24 (6 de-duplicated)

Date of Updated Search: July 1, 2019

Results on Update: 6 (2 de-duplicated)

Additional Search Queries on Update:

- #13 (#11 OR #12) NOT "conference abstract":pt with Cochrane Library publication date from Oct 2018 to Jul 2019, in Cochrane Reviews and Trials

LINE	SEARCH QUERY	RESULTS	NOTES/CONCEPT
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#1	[mh ^"Bone Neoplasms"/SC]	102	
#2	[mh Femur] OR femur:ti,ab OR femoral:ti,ab OR "long bone":ti,ab OR "long bones":ti,ab	10579	
#3	#1 AND #2	1	
#4	[mh "Femoral Neoplasms"/SC]	3	
#5	#3 OR #4	4	Secondary femoral neoplasms
#6	"metastatic":ti,ab OR "metastasized":ti,ab OR "metastasis":ti,ab OR "metastases":ti,ab OR "bone lesion":ti,ab OR "bone lesions":ti,ab	25213	
#7	#2 AND #6	96	Expanded femoral neoplasm
#8	#5 OR #7	96	Full femoral neoplasm
#9	[mh "multiple myeloma"] OR "multiple myeloma":ti,ab OR "plasma cell myeloma":ti,ab OR myelomatosis:ti,ab OR myelomatoses:ti,ab OR myeloma:ti,ab	3854	MM
#10	[mh carcinoma] OR carcinoma*:ti,ab OR epithelial:ti,ab	31663	Carcinoma
#11	#10 AND #8	18	Carcinoma + Femur
#12	#2 AND #9	18	MM + Femur
#13	(#11 OR #12) NOT "conference abstract":pt	24	Final patient concept, with abstract filter

Non-femur, BMA-specific: PICO 3, 4a

Date: October 26, 2018

Results: 216 (108 de-duplicated)

Date of Updated Search: July 1, 2019

Results on Update: 37 (16 de-duplicated)

Additional Search Queries on Update:

- #6 (#4 AND #5) NOT "conference abstract":pt with Cochrane Library publication date from Oct 2018 to Jul 2019, in Cochrane Reviews and Trials

LINE	SEARCH QUERY	RESULTS	NOTES/CONCEPT
#1	[mh carcinoma] OR carcinoma*:ti,ab OR epithelial:ti,ab	31663	carcinoma
#2	[mh "multiple myeloma"] OR "multiple myeloma":ti,ab OR "plasma cell myeloma":ti,ab OR myelomatosis:ti,ab OR myelomatoses:ti,ab OR myeloma:ti,ab	3854	MM
#3	"metastatic":ti,ab OR "metastasized":ti,ab OR "metastasis":ti,ab OR "metastases":ti,ab OR "bone lesion":ti,ab OR "bone lesions":ti,ab	25213	metastatic

#4	(#1 AND #3) OR #2	10266	mets carcinoma + MM
#5	[mh diphosphonates] or [mh denosumab] or [mh "bone density conservation agents"] or "biphosphonate":ti,ab OR "biphosphonates":ti,ab OR "diphosphonate":ti,ab OR "diphosphonates":ti,ab "antiresorptive agent":ti,ab OR "antiresorptive agents":ti,ab OR "antiresorptive drug":ti,ab OR "antiresorptive drugs":ti,ab OR denosumab:ti,ab OR pamidronate:ti,ab OR "zolendric acid":ti,ab OR ibandronate:ti,ab OR "bone modifying agents":ti,ab or "Bone modifying agent":ti,ab OR "bone modifying inhibitor":ti,ab OR "bone modifying inhibitors":ti,ab OR "bone conserving agent":ti,ab OR "bone conserving agents":ti,ab OR "bone density conservation agent":ti,ab OR "bone density conservation agents":ti,ab OR "osteoclast inhibitor":ti,ab OR "osteoclast inhibitors":ti,ab OR "bone targeted therapy":ti,ab OR "clodronate":ti,ab	3954	BMA concept
#6	(#4 AND #5) NOT "conference abstract":pt	216	

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

Standard Inclusion Criteria For All CPGs

- Article must be a full article report of a clinical study (studies using registry data can be included in a guideline if it is published in a peer-reviewed journal and meets all other inclusion criteria/quality standards).
- Retrospective non-comparative case series, medical records review, meeting abstracts, historical articles, editorials, letters, and commentaries are *excluded*.
- Confounded studies (i.e. studies that give patients the treatment of interest AND another treatment without appropriate sub-analysis or statistical adjustment) are *excluded*.
- Case series studies that have non-consecutive enrollment of patients are *excluded*.
- Controlled trials in which patients were not stochastically assigned to groups AND in which there was either a difference in patient characteristics or outcomes at baseline AND where the authors did not statistically adjust for these differences when analyzing the results are *excluded*.
- All studies of “Very Low” quality of evidence (e.g. Level V) are *excluded*.
- Study must appear in a peer-reviewed publication
- For any included study that uses “paper-and-pencil” outcome measures (e.g. Composite measures, SF-36, etc.), only those outcome measures that have been validated will be included
- For any given follow-up time point in any included study, there must be $\geq 50\%$ patient follow-up (if the follow-up is $>50\%$ but $<80\%$, the study quality will be downgraded by one Level)
- Study must be of humans
- Study must be published in English
- Study results must be quantitatively presented
- Study must not be an in vitro study
- Study must not be a biomechanical study
- Study must not have been performed on cadavers

We will only evaluate surrogate outcomes when no patient-oriented outcomes are available.