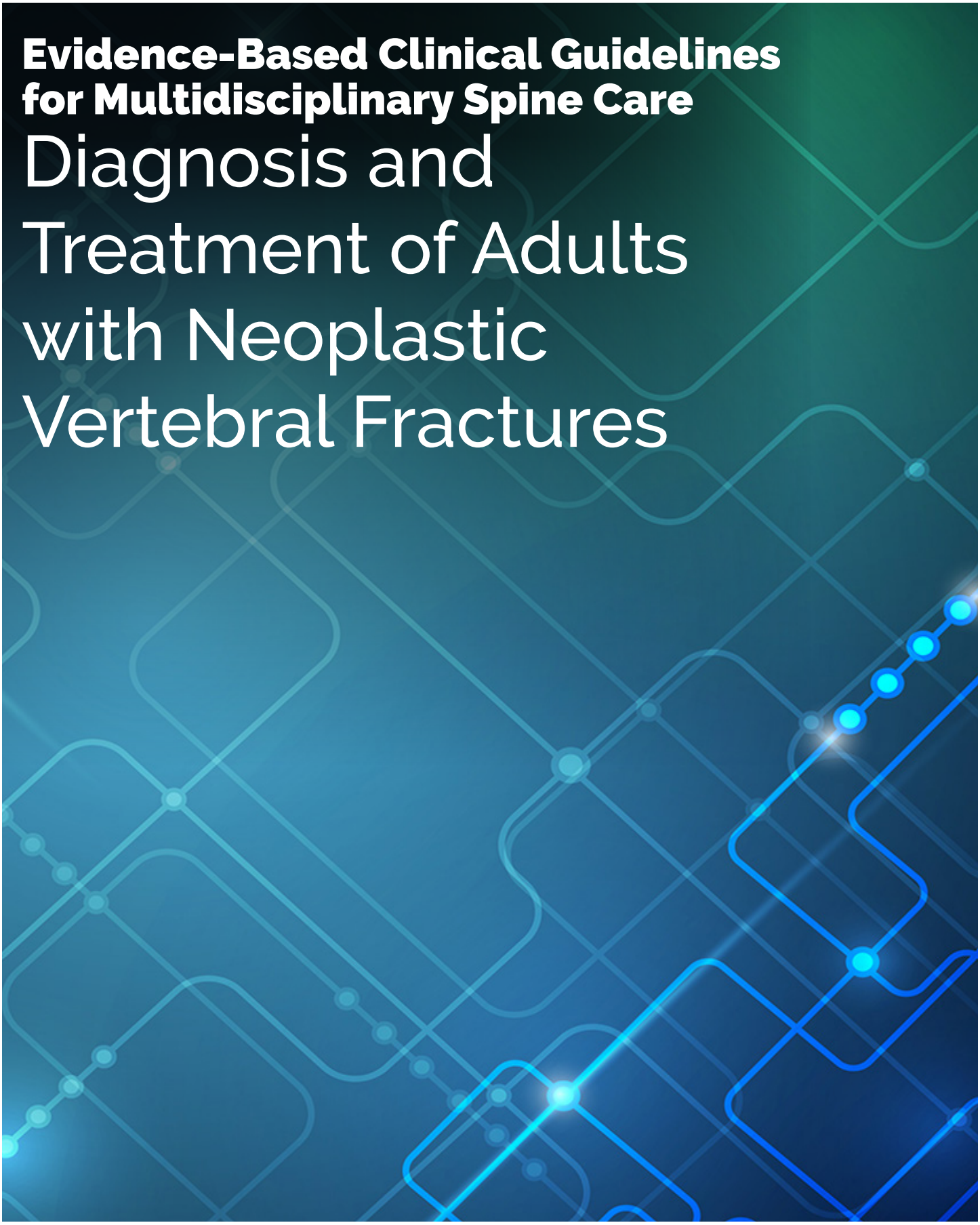
Evidence-Based Clinical Guidelines for Multidisciplinary Spine Care

Diagnosis and Treatment of Adults with Neoplastic Vertebral Fractures



NASS
NORTH AMERICAN SPINE SOCIETY

Evidence-Based Clinical Guidelines for Multidisciplinary Spine Care

Diagnosis and Treatment of Adults with Neoplastic Vertebral Fractures

North American Spine Society
7075 Veterans Blvd
Burr Ridge, IL 60527
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www.spine.org

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Preface

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Financial Statement/Disclosures

This clinical guideline was developed and funded in its entirety by the North American Spine Society (NASS). All participating authors have disclosed potential conflicts of interest consistent with NASS' disclosure policy. Disclosures of all authors and contributors are listed in the technical report associated with this document.

Comments
Comments regarding this guideline may be submitted to the NASS and will be considered in development of future revisions of the work.

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Introduction

Objective

The objective of the *North American Spine Society (NASS) Clinical Guideline for the Diagnosis and Treatment of Adults with Neoplastic Vertebral Fractures* is to provide evidence-based recommendations to address key clinical questions surrounding the diagnosis and treatment of adult patients with neoplastic vertebral fractures in order to provide guidance to promote accurate diagnosis and effective treatment. This guideline is based upon a systematic review of the evidence and reflects contemporary treatment concepts for neoplastic vertebral fractures as reflected in the highest quality clinical literature available on this subject as of **October 2020**. The goals and expected benefits of the guideline recommendations are to assist in delivering optimum management of neoplastic vertebral fractures.

Scope, Purpose and Intended User

This document was developed by the NASS Clinical Practice Guidelines Committee as an educational tool to assist practitioners who treat adult patients with neoplastic vertebral fractures. The goal is to provide a tool that assists practitioners in improving the quality and efficiency of care delivered to these patients. The NASS *Clinical Guideline for the Diagnosis and Treatment of Adults with Neoplastic Vertebral Fractures* outlines a reasonable evaluation of patients with neoplastic vertebral fractures and outlines treatment options for adult patients with this condition.

THIS GUIDELINE DOES NOT REPRESENT A "STANDARD OF CARE," nor is it intended as a fixed treatment protocol. It is anticipated that there will be patients who will require less or more treatment than the average. It is also acknowledged that in atypical cases, treatment falling outside this guideline will sometimes be necessary. This guideline should not be seen as prescribing the type, frequency or duration of intervention. Treatment should be based on the individual patient's need and provider's professional judgment and experience. This document is designed to function as a guideline and should not be used as the sole reason for authorization or denial of treatment and services. This guideline is not intended to expand or restrict a health care provider's scope of practice or to supersede applicable ethical standards or provisions of law.

Patient Population

The patient population for this guideline encompasses adults (18 years or older) with neoplastic vertebral fracture(s) defined as fracture of the vertebral body due to loss or destruction of cortical or trabecular bone structural integrity from a primary or metastatic neoplastic process. Fractures may or may not be symptomatic and may or may not result in clinically significant deformity and/or neurologic deficit.

Recommendations were developed based on a specific definition, inclusion/exclusion criteria, and the resulting literature. This clinical guideline is not intended to be a fixed treatment protocol; it is anticipated that there will be patients who require more or less investigations or treatment than what is outlined. This clinical guideline should not be construed as including all proper methods of care or excluding other acceptable methods of care reasonably directed to obtaining the same results. The ultimate judgment regarding any specific procedure or treatment is to be made by the provider and patient in light of all circumstances presented by the patient and the needs and resources particular to the locality or institution.

Definition and Inclusion/Exclusion Criteria

Definition: Fracture of the vertebral body due to loss or destruction of cortical or trabecular bone structural integrity from a primary or metastatic neoplastic process. Fractures may or may not be symptomatic and may or may not result in clinically significant deformity and/or neurologic deficit.

Inclusion Criteria:

- Age ≥ 18 years
- Spine or sacral fractures
- Single or multiple level fractures
- Simple or complex fractures
- With or without pain. Pain may be axial, radicular, generalized or combination.

Exclusion Criteria:

- Acute or chronic spine infection including epidural abscess, discitis, and/or osteomyelitis
- Major trauma
- Prior surgery at the affected level
- Isolated intradural tumor

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Glossary

Acute Fracture: This is a newly developed definition for the diagnosis of acute compression fracture that is used in this guideline. The definition uses clinical and imaging evaluation for the diagnosis that is uniform for all patients, and it does not rely on arbitrary time demarcation.

Clinical diagnosis of acute fracture: Identifiable sudden onset of pain with continued pain and radiograph/computed tomography showing compression fracture localized to the site of pain.

Imaging diagnosis of acute fracture: Unable to identify the onset of pain with continued pain. MRI shows vertebral compression with edema localized to the site of pain. Serial radiographs or computed tomography shows new or further compression of the fracture. If MRI is contraindicated, then a bone scintigraphy may show increased activity at the site of the vertebral compression.

Note:

- Selecting a set time to differentiate acute from nonacute fracture is arbitrary and should not be used.
- In patients with prolonged pain, if there is edema in the MRI, then the patient is considered to have a component of unhealed fracture.
- If the MRI has no edema, then it is not unhealed fracture.
- If the description is vague and does not provide enough detail to classify as acute, as outlined below, consider downgrading the article (still include if it meets all inclusion criteria).

Augmentation: Addition of cement to the vertebral body through a needle with or without the use of cavity producing balloon, and without addition of a permanent non cement device.

Burst Fracture: The term burst fracture often refers to high axial load injury from major trauma, which is excluded. The rare use of the term burst fracture as it refers to complex neoplastic or osteoporotic fractures is included.

Complex Fracture: Complex fracture refers to severe fractures from neoplastic or osteoporotic causes.

Hemangioma and (nondestructive tumors): Only include if the study clearly states that there is bone destruction in addition to intrinsic tumor, per this guideline's definition. For example, exclude benign hemangioma and other tumors that permeate through the marrow without trabecular destruction. (Exclude studies that do not specify bone destruction.)

MRI: MRI with edema was selected as one of the two methods of diagnosis of acute compression fracture. Although the literature search results for this guideline did not include specific validation studies for MRI, the standard of medical care is that MRI with bone marrow edema is accepted as acute fracture.

Trauma: Minor injury, such as falling while walking or standing is not considered major trauma and is included.

Surgery: If a study does not state prior spine surgery, it is interpreted as no prior spine surgery.

Nomenclature for Medical Treatment

Throughout the guideline, readers will see that what has traditionally been referred to as "nonoperative," "nonsurgical," or "conservative" care is now referred to as medical treatment. The term medical is meant to encompass pharmacological treatment, physical therapy, exercise therapy, manipulative therapy, modalities, and various types of external stimulators.

Nomenclature for Interventional Treatment

Interventional treatment is considered as a separate category from Medical Treatment and Surgical Treatment. Interventional Treatment often uses image guidance with instruments such as fluoroscopy, computed tomography, magnetic resonance imaging, ultrasound, or endoscopy, with the target visualized on a monitor screen.

Nomenclature for Surgical Treatment

Surgical treatment implies direct visualization of the treatment target with or without optical visual aids.

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Guideline Development Methodology and Process

Guideline Development Methodology

Through objective evaluation of the evidence and transparency in the process of making recommendations, it is NASS' goal to develop evidence-based clinical practice guidelines for the diagnosis and treatment of adult patients with various spinal conditions. These guidelines are developed for educational purposes to assist practitioners in their clinical decision-making processes.

Multidisciplinary Collaboration

With the goal of ensuring the best possible care for adult patients suffering from spinal disorders, NASS is committed to multidisciplinary involvement in the process of guideline development. To this end, NASS has ensured that representatives from research, medical, interventional and surgical spine specialties have participated in the development and review of NASS guidelines. To ensure broad-based representation, NASS welcomes input from other societies and specialties.

Evidence Analysis Training of All Guideline Developers

As a condition of participation, all developers completed NASS' Evidence-Based Medicine Training prior to participating in guideline development. The training includes a series of readings and exercises to prepare guideline developers for systematically evaluating literature and developing evidence-based guidelines. Participants are awarded CME credit upon completion of the course.

Disclosure of Potential Conflicts of Interest

All participants involved in guideline development have disclosed potential conflicts of interest to their colleagues in accordance with NASS' Disclosure Policy and their potential conflicts have been documented in the Technical Report associated with this guideline. NASS does not restrict involvement in guidelines based on conflicts as long as members provide full disclosure. Individuals with a conflict relevant to the subject matter were asked to recuse themselves from deliberation. Participants have been asked to update their disclosures regularly throughout the guideline development process.

Levels of Evidence and Grades of Recommendation

NASS has adopted standardized levels of evidence and grades of recommendation to assist practitioners in easily understanding the strength of the evidence and recommendations within the guidelines. The levels of evidence range from Level I (high quality randomized controlled trial) to Level V (expert consensus). Grades of recommendation indicate the strength of the recommendations made in the guideline based on the quality of the literature.

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Levels of Evidence for Primary Research Question[1] as adopted by the North American Spine Society, January 2005

	Types of Studies			
	Therapeutic Studies: Investigating the results of treatment	**Prognostic Studies:** Investigating the effect of a patient characteristic on the outcome of disease	**Diagnostic Studies:** Investigating a diagnostic test	**Economic and Decision Analysis:** Developing an economic or decision model
Level I	▪ High quality randomized trial with statistically significant difference or no statistically significant difference but narrow confidence intervals. ▪ Systematic Review[2] of Level I RCTs (and study results were homogenous[3])	▪ High quality prospective study[4] (all patients were enrolled at the same point in their disease with ≥80% follow-up of enrolled patients) ▪ Systematic review[2] of Level I studies	▪ Testing of previously developed diagnostic criteria on consecutive patients (with universally applied reference "gold" standard) ▪ Systematic review[2] of Level I studies	▪ Sensible costs and alternatives; values obtained from many studies with multiway sensitivity analyses ▪ Systematic review[2] of Level I studies
Level II	▪ Lesser quality RCT (eg, <80% follow-up, no blinding, or improper randomization) ▪ Prospective[4] comparative study[5] ▪ Systematic review[2] of Level II studies or Level I studies with inconsistent results	▪ Retrospective[6] study ▪ Untreated controls from an RCT ▪ Lesser quality prospective study (eg, patients enrolled at different points in their disease or <80% follow-up) ▪ Systematic review[2] of Level II studies	▪ Development of diagnostic criteria on consecutive patients (with universally applied reference "gold" standard) ▪ Systematic review[2] of Level II studies	▪ Sensible costs and alternatives; values obtained from limited studies; with multiway sensitiveity analyses ▪ Systematic review[2] of Level II studies
Level III	▪ Case control study[7] ▪ Retrospective[6] comparative study[5] ▪ Systematic review[2] of Level III studies	Case control study[7]	▪ Study of nonconsecutive patients; without consistently applied reference "gold" standard ▪ Systematic review[2] of Level III studies	▪ Analyses based on limited alternatives and costs; and poor estimates ▪ Systematic review[2] of level III studies
Level IV	Case series[8]	Case series[8]	▪ Case-control study[7] ▪ Poor reference standard	Analyses with no sensitivity analyses
Level V	Expert opinion	Expert opinion	Expert opinion	Expert opinion

1. A complete assessment of quality of individual studies requires critical appraisal of all aspects of the study design.
2. A combination of results from two or more prior studies.
3. Studies provided consistent results.
4. Study was started before the first patient enrolled.
5. Patients treated one way (eg, cemented hip arthroplasty) compared with a group of patients treated in another way (eg, uncemented hip arthroplasty) at the same institution.
6. The study was started after the first patient enrolled.
7. Patients identified for the study based on their outcome, called "cases"; eg, failed total arthroplasty, are compared to those who did not have outcome, called "controls"; eg, successful total hip arthroplasty.
8. Patients treated one way with no comparison group of patients treated in another way.

Linking Levels of Evidence to Grades of Recommendation

Grade of Recommendation	Standard Language	Levels of Evidence	
A	Recommended	Two or more consistent Level I studies	
B	Suggested	One Level I study with additional supporting Level II or III studies	Two or more consistent Level II or III studies
C	May be considered; is an option	One Level I, II, III, or IV study with supporting Level IV studies	Two or more consistent Level IV studies
I	Insufficient evidence to make recommendation for or against	A single level I, II, III, or IV study without other supporting evidence	More than one study with inconsistent findings*

*Note that in the presence of multiple consistent studies and a single outlying, inconsistent study, the Grade of Recommendation will be based on the level of consistent studies.

Grades of Recommendation for Summaries or Reviews of Studies as Adopted by the North American Spine Society

- **A:** Good evidence (Level I studies with consistent findings) for or against recommending intervention.
- **B:** Fair evidence (Level II or III studies with consistent findings) for or against recommending intervention.
- **C:** Poor quality evidence (Level IV or V studies) for or against recommending intervention.
- **I:** Insufficient or conflicting evidence not allowing a recommendation for or against intervention.

Guideline recommendations are written utilizing a standard language that indicates the strength of the recommendation. "A" recommendations indicate a test or intervention is "recommended"; "B" recommendations "suggest" a test or intervention and "C" recommendations indicate a test or intervention "may be considered" or "is an option." "I" or "Insufficient Evidence" statements clearly indicate that "there is insufficient evidence to make a recommendation for or against" a test or intervention. Work group consensus statements clearly state that "in the absence of reliable evidence, it is the work group's opinion that" a test or intervention may be appropriate.

In evaluating studies as to levels of evidence for this guideline, the study design was interpreted as establishing only a potential level of evidence. As an example, a therapeutic study designed as a randomized controlled trial would be considered a potential Level I study. The study would then be further analyzed as to how well the study design was implemented and significant shortcomings in the execution of the study would be used to downgrade the levels of evidence for the study's conclusions. In the example cited previously, reasons to downgrade the results of a potential Level I randomized controlled trial to a Level II study would include, among other possibilities: an underpowered study (patient sample too small, variance too high), inadequate randomization or masking of the group assignments and lack of validated outcome measures.

In addition, a number of studies were reviewed several times in answering different questions within this guideline. How a given question was asked might

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influence how a study was evaluated and interpreted as to its level of evidence in answering that particular question. For example, a randomized controlled trial reviewed to evaluate the difference between the outcomes of cement augmentation versus medical management of patients with neoplastic vertebral fractures might be a well-designed and implemented Level I therapeutic study. This same study, however, might be classified as providing Level II prognostic evidence if the data for the untreated controls were extracted and evaluated prognostically.

Guideline Development Process

Step 1: Recruitment of Guideline Work Group Members

NASS Clinical Practice Guideline Committee members and members of NASS Sections were solicited to participate in the guideline development process. In total, 27 work group members participated in this effort and are listed as authors. Individuals who were not able to substantively contribute to all activities required for authorship, but participated at some extent throughout the process, have been acknowledged as contributors. Names of guideline authors and contributors are listed on page 4 and disclosures are listed in the Technical Report associated with this document.

Step 2: Identification of Work Groups

The guideline panel consists of five work groups to cover the seven sections in this guideline: Natural History/Cost Effectiveness, Clinical Diagnosis/Medical Treatment, Imaging Diagnosis/ Interventional Treatment (which was further divided into two work groups), and Surgical Treatment. Senior and newer NASS Clinical Practice Guideline members were placed in work groups to ensure that groups with newer members were balanced with members who have more guideline development experience. Each work group consisted of 4 to 6 members representing multidisciplinary backgrounds. The guideline panel includes representation from the fields of neurosurgery, orthopedic surgery, physical medicine and rehabilitation, chiropractic care, physical therapy, anesthesiology, research, radiology, and nursing. NASS believes that having multidisciplinary teams involved in the guideline development process helps to minimize inadvertent biases in evaluating the literature and formulating recommendations.

Step 3: Surveying Patients

To seek patient input to help inform the development of clinical questions, NASS circulated an informal, anonymous, and voluntary Survey Monkey poll to better understand patients' experiences with vertebral fractures. The survey link was circulated through various websites and social media sites, including NASS' Facebook and Twitter pages, Know Your Back (http://www.knowyourback.org), eHealth Forums (http://www.ehealthforum.com/health/health_forums.html), Daily Strength Support Group (http://www.dailystrength.org), Drugs.com Support Group (http://www.drugs.com/answers/support-group), Consumers United for Evidence-based Healthcare (http://www.consumersunited.org), and numerous Facebook shares (of the survey link) on consumer and physician profiles. The survey was related to any vertebral fracture and results were shared with the Neoplastic Vertebral Compression Fracture Guideline panel to incorporate the patients' perspectives and priorities when developing questions. The survey included the following questions that allowed for check the box and open-ended responses:

1. Are you completing this survey as a patient who has experienced a spine compression fracture or as a caregiver on behalf of a patient who has experienced a spine compression fracture?
2. What symptoms made you or the person you care for seek medical attention for a spine compression fracture? (Check all that apply)
3. Please identify the treatment(s) received for compression fracture (check all that apply)
4. When considering options, how important are the following outcomes to you or the patient you care for?
5. Is there anything that you wish your healthcare provider had shared with you before making your decision to receive treatment for your compression fracture?

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6. What questions do you think patients with compression fractures should ask their healthcare professional when seeking diagnosis and treatment options for compression fractures?
7. Do you have any additional comments?

Step 4: Identification of Clinical Questions

Framing questions to ask in the guideline is critical to the guideline development process. Trained guideline panelists were asked to submit a list of clinical questions with the patient survey as reference. Members were asked to use the acronym "PICO" when drafting questions **if possible**. "PICO" serves to guide the development of clinical questions that include all of the necessary components to build a literature search: "P" for the patient/problem; "I" for the intervention or indicator of interest (procedures, therapies, diagnostic tests, exposure, etc.); "C" for comparison and "O" for outcome of interest. **The proposed questions were compiled into a master list and circulated to each member for review and comment.** The draft clinical question list was then submitted to the NASS Health Policy Council, Research Council, and Advocacy Council Chair for review. The councils submitted additional questions that may be useful for health policy or research purposes.

Step 5: External Review of Clinical Question Protocol

The draft list of clinical questions was made publicly available on the NASS website for a 4-week public comment period from **April 15, 2020 to May 15, 2020.** Additionally, stakeholders were invited through email solicitations to comment on the draft questions. Based on feedback, several revisions were incorporated in the clinical question list. After the comment period, an updated clinical question list with summarized changes was posted to the NASS website and circulated to all public comment period reviewers.

Step 6: Identification of Search Terms and Parameters

One of the most crucial elements of evidence analysis is the comprehensive literature search. Thorough assessment of the literature is the basis for the review of existing evidence and the formulation of evidence-based recommendations. In order to ensure a thorough literature search, NASS has instituted a Literature Search Protocol (Appendix A) which has been followed to identify literature for evaluation in guideline development. In keeping with the Literature Search Protocol, work group members have identified appropriate search terms and parameters to direct the literature search. Specific search strategies, including search terms, parameters and databases searched, are documented in the Technical Report associated with this document. The guideline definition and inclusion/exclusion criteria are outlined on page 8. Methods were determined and agreed upon a priori and not changed after the literature search.

Step 7: Completion of the Literature Search

Once each work group identified search terms/parameters, the literature search was implemented by a medical/research librarian at the American Academy of Orthopaedic Surgeons (AAOS), consistent with the Literature Search Protocol. Following these protocols ensures that NASS recommendations (1) are based on a thorough review of relevant literature; (2) are truly based on a uniform, comprehensive search strategy; and (3) represent the current best research evidence available. NASS maintains a search history in Endnote, for future use or reference.

Step 8: Review of Search Results/Identification of Literature to Review

Using Rayyan,1 at least two work group members independently reviewed all abstracts yielded from the literature search and subsequently the full-text stage to identify the literature they would review in order to address the clinical questions, in accordance with the Literature Search Protocol (Appendix A). Discrepancies were discussed until consensus was reached.

Step 9: Evidence Analysis

Members independently developed evidentiary tables summarizing study conclusions, identifying strengths and weaknesses (risk of bias) and assigning levels of evidence. In order to systematically control for potential biases, two or more work group members have reviewed each article selected and independently assigned levels of evidence to the literature using the NASS levels of evidence. Any discrepancies in scoring were resolved by discussion by two or more reviewers, and if necessary, arbitration with a larger group including work group authors, section chairs, and project lead. Final ratings are completed at a final meeting or web conference of section workgroup members including the section chair and a guideline

co-chair. Many articles have external funding sources (eg, government, research philanthropy, industry) and are described in the individual manuscript. When easily identifiable, industry funding was noted in the guideline article summaries. As a final step in the evidence analysis process, members have identified and documented gaps in the evidence to educate guideline readers about where evidence is lacking and help guide further needed research.

Step 10: Formulation of Evidence-Based Recommendations and Incorporation of Expert Consensus

Work groups held virtual meetings to discuss the evidence-based answers to the clinical questions, the grades of recommendations and the incorporation of expert consensus. Expert consensus was incorporated only where Level I-IV evidence is insufficient and the work group has deemed that a recommendation is warranted. Transparency in the incorporation of consensus is crucial and all consensus-based recommendations made in this guideline very clearly indicate that Level I-IV evidence is insufficient to support a recommendation and that the recommendation is based only on expert consensus.

Consensus Development Process

For recommendations with a consensus grading, voting was conducted using a modification of the nominal group technique in which each work group member independently and anonymously ranked a recommendation on a scale ranging from 1 ("extremely inappropriate") to 9 ("extremely appropriate"). Consensus was obtained when at least 80% of work group members ranked the recommendation as 7, 8 or 9. When the 80% threshold was not attained, up to three rounds of discussion and voting were held to resolve disagreements. If disagreements were not resolved after these rounds, no recommendation was adopted. After the recommendations were established, work group members developed the guideline content, addressing the literature supporting the recommendations.

Recommendation Development

In order to capture all relevant literature on this topic, the questions were formed to cover a broad population and did not necessarily focus on subcategorization (eg, patients with or without mechanical instability, or patients with or without severe epidural spinal cord compression). After the literature search was complete, a subcategory recommendation would be developed if there was enough evidence available to support. If the literature did not allow subcategorization, a general recommendation was made whenever possible.

Step 11: Internal Review of Draft Guideline

Guideline sections were reviewed by the section work groups that developed them. The full guideline draft was then reviewed by the entire author group. Revisions to recommendations were considered only when substantiated by a preponderance of appropriate level evidence.

Step 12: External Review of Draft Guideline

In order to assess clarity and perception of quality, members of NASS' Clinical Practice Guidelines Committee who were not involved in the development of this guideline were invited to review the draft guideline. These external reviewers were given the opportunity to complete the Appraisal of Guidelines for Research & Evaluation II (AGREE II) instrument and provide open-ended comments. Additionally, a public comment period was open from November 1, 2023 to November 30, 2023. Members of the public, including but not limited to subject matter experts and societies, were eligible to complete a form with rating scales and open-ended questions in order to gather feedback on draft recommendations, assess readability, content, and feasibility (eg, facilitators and barriers to implementation), and improve the overall quality of the guideline. Revisions to recommendations were considered only when substantiated by a preponderance of appropriate level evidence.

Step 13: Submission for Board Approval

After any evidence-based revisions were incorporated, the drafts were prepared for review and approval from the NASS Evidence Analysis & Research Council, followed by the NASS Board of Directors. Edits and revisions to recommendations and any other content were considered for incorporation only when substantiated by a preponderance of appropriate level evidence.

Step 14: Submission for Publication

Following NASS Board approval, the guideline was slated for publication. No revisions were made after submission for publication, but comments have been and will be saved for the next iteration.

Recommendations were developed based on a specific definition, inclusion/exclusion criteria, and the resulting literature. This clinical guideline is not intended to be a fixed treatment protocol; it is anticipated that there will be patients who require more or less investigations or treatment than what is outlined. This clinical guideline should not be construed as including all proper methods of care or excluding other acceptable methods of care reasonably directed to obtaining the same results. The ultimate judgment regarding any specific procedure or treatment is to be made by the provider and patient in light of all circumstances presented by the patient and the needs and resources particular to the locality or institution.

Step 15: Review and Revision Process

The guideline recommendations will be reviewed 3-5 years after publication, or according the NASS' topic selection and revision protocol. An EBM-trained multidisciplinary team will review and, when necessary, revise or rescind the guideline.

References:

1. Mourad Ouzzani, Hossam Hammady, Zbys Fedorowicz, and Ahmed Elmagarmid. Rayyan — a web and mobile app for systematic reviews. *Systematic Reviews.* 2016; 5:210. DOI: 10.1186/s13643-016-0384-4.
2. Brouwers M, Kho ME, Browman GP, Cluzeau F, feder G, Fervers B, Hanna S, Makarski J on behalf of the AGREE Next Steps Consortium. AGREE II: Advancing guideline development, reporting and evaluation in healthcare. *Can Med Assoc J.* Dec 2010;182:E839-842. doi: 10.1503/cmaj.090449

Recommendations were developed based on a specific definition, inclusion/exclusion criteria, and the resulting literature. This clinical guideline is not intended to be a fixed treatment protocol; it is anticipated that there will be patients who require more or less investigations or treatment than what is outlined. This clinical guideline should not be construed as including all proper methods of care or excluding other acceptable methods of care reasonably directed to obtaining the same results. The ultimate judgment regarding any specific procedure or treatment is to be made by the provider and patient in light of all circumstances presented by the patient and the needs and resources particular to the locality or institution.

Summary of Questions and Recommendations

Clinical Question	Guideline Recommendation *See recommendation sections for supporting text* A: Recommended; B: Suggested; C: May be Considered; I: Insufficient or Conflicting Evidence
Natural History	
Natural History Question 1: Does underlying histology affect the natural history of metastatic neoplastic vertebral fractures?	*A systematic review of the literature yielded no studies to adequately address this question.*
Natural History Question 2: Aside from the effects of underlying histology, what are the expected outcomes of neoplastic vertebral fractures in the absence of treatment directed at the fracture or underlying disease?	*A systematic review of the literature yielded no studies to adequately address this question.*
Cost Effectiveness	
Cost Effectiveness Question 1: In the treatment of neoplastic vertebral fractures, what is the comparative cost-effectiveness of (a) medical and/or radiation therapy alone vs (b) vertebral augmentation (with or without radiation therapy) vs (c) thermal ablation, radiofrequency ablation or cryoablation with or without augmentation vs (d) operative fusion/fixation?	*A systematic review of the literature yielded no studies to adequately address this question.*
Clinical Diagnosis	
Clinical Diagnosis Question 1: Which elements (individual or in combination) of a history, symptoms, and/or physical examination are most sensitive and specific for identifying a patient with neoplastic vertebral fracture?	*A systematic review of the literature yielded no studies to adequately address this question.*
Medical Treatment	
Medical Treatment Question 1: How do nonpharmacologic treatments (eg, bracing, physical therapy, acupuncture, massage, cannabis, exercise, etc.) compare in terms of reducing severity and duration of pain and disability in neoplastic vertebral fractures?	*A systematic review of the literature yielded no studies to adequately address this question.*
Medical Treatment Question 2: Do restrictions on patient activity alter outcomes in patients with neoplastic vertebral fractures?	*A systematic review of the literature yielded no studies to adequately address this question.*

Recommendations were developed based on a specific definition, inclusion/exclusion criteria, and the resulting literature. This clinical guideline is not intended to be a fixed treatment protocol; it is anticipated that there will be patients who require more or less investigations or treatment than what is outlined. This clinical guideline should not be construed as including all proper methods of care or excluding other acceptable methods of care reasonably directed to obtaining the same results. The ultimate judgment regarding any specific procedure or treatment is to be made by the provider and patient in light of all circumstances presented by the patient and the needs and resources particular to the locality or institution.

Medical Treatment Question 3: How do pharmacologic treatments (nonchemotherapeutic) and nonpharmacologic treatments compare with interventional treatments in terms of reducing severity and duration of pain and disability in neoplastic vertebral fractures?	There is insufficient evidence to make a recommendation for or against interventional treatment as compared to noninterventional pharmacologic treatments and nonpharmacologic treatments in terms of reducing severity and duration of pain and disability in adults with neoplastic vertebral fractures. **Grade of Recommendation: I**
Medical Treatment Question 4: Does timing or sequencing of interventions (eg, analgesics, bisphosphonates, chemotherapy, XRT, stereotactic XRT, bracing, surgery, or vertebral augmentation) improve patient outcomes?	There is insufficient evidence to make a recommendation for or against sequencing of radiation therapy and vertebral augmentation in adults with neoplastic vertebral fractures. **Grade of Recommendation: I** There is insufficient evidence to make a recommendation for or against timing of non-interventional therapy or vertebral augmentation in adults with neoplastic vertebral fractures. **Grade of Recommendation: I**
Medical Treatment Question 5: Do general and individualized physical therapy programs differ in pain and functional outcomes for patients with neoplastic vertebral fractures?	*A systematic review of the literature yielded no studies to adequately address this question.*

Recommendations were developed based on a specific definition, inclusion/exclusion criteria, and the resulting literature. This clinical guideline is not intended to be a fixed treatment protocol; it is anticipated that there will be patients who require more or less investigations or treatment than what is outlined. This clinical guideline should not be construed as including all proper methods of care or excluding other acceptable methods of care reasonably directed to obtaining the same results. The ultimate judgment regarding any specific procedure or treatment is to be made by the provider and patient in light of all circumstances presented by the patient and the needs and resources particular to the locality or institution.

Imaging	
Imaging Diagnosis Question 1: Which imaging modalities and findings are most sensitive and specific for the accurate diagnosis of and treatment planning for neoplastic vertebral fractures?	Findings on routine MRI sequences are suggested as a method to differentiate osteoporotic from neoplastic vertebral fractures. **Grade of Recommendation: B** Specific MRI sequences are suggested to differentiate osteoporotic from neoplastic vertebral fractures. **Grade of Recommendation: B** Diffusion weighted imaging (DWI) is suggested as a MR sequence to distinguish osteoporotic from neoplastic vertebral fractures. **Grade of Recommendation: B** Contrast enhanced perfusion MRI is suggested as a method to differentiate between osteoporotic and neoplastic vertebral compression fractures. **Grade of Recommendation: B** PET scan is suggested to differentiate between osteoporotic and neoplastic vertebral compression fractures. **Grade of Recommendation: B** There is insufficient evidence to make a recommendation for or against the use of bone scans to differentiate osteoporotic from neoplastic vertebral compression fractures. **Grade of Recommendation: I** There is insufficient evidence to make a recommendation for or against the use of CT to differentiate osteoporotic from neoplastic vertebral compression fractures. **Grade of Recommendation: I**

Recommendations were developed based on a specific definition, inclusion/exclusion criteria, and the resulting literature. This clinical guideline is not intended to be a fixed treatment protocol; it is anticipated that there will be patients who require more or less investigations or treatment than what is outlined. This clinical guideline should not be construed as including all proper methods of care or excluding other acceptable methods of care reasonably directed to obtaining the same results. The ultimate judgment regarding any specific procedure or treatment is to be made by the provider and patient in light of all circumstances presented by the patient and the needs and resources particular to the locality or institution.

Interventional Treatment	
Interventional Treatment Question 1: What are the criteria/indications/contraindications for vertebral augmentation in patients with neoplastic vertebral fractures?	Vertebral augmentation is suggested as a safe and effective procedure in adults with neoplastic vertebral fractures with intractable back pain despite medical management and/or those at risk of vertebral collapse, although caution is recommended because of the potential for cement extrusion. **Grade of Recommendation: B** Vertebral augmentation is suggested for the treatment of neoplastic vertebral fractures from multiple myeloma. **Grade of Recommendation: B** There is insufficient evidence to make a recommendation for or against the transoral approach in malignant C2 lesions for vertebral augmentation as a palliative procedure for adults with neoplastic vertebral fractures. **Grade of Recommendation: I**
Interventional Treatment Question 2: How do interventional treatments (augmentation, thermal ablation, radiofrequency ablation and cryoablation) compare to medical treatments in reducing severity and duration of pain and disability in patients with neoplastic vertebral fractures?	*A systematic review of the literature yielded no studies to adequately address the thermal ablation, cryoablation and radiofrequency ablation components of this question.* Vertebral augmentation is recommended for the improvement of pain and functional outcomes in the treatment of neoplastic vertebral fractures. **Grade of Recommendation: A**
Interventional Treatment Question 3: Are there specific characteristics of the fracture or the patient that influence outcomes in patients with neoplastic vertebral fractures undergoing vertebral augmentation?	Vertebral augmentation is suggested to be a safe treatment option with low rate of clinical complications in neoplastic vertebral fractures with cortical wall defects. **Grade of Recommendation: B** There is insufficient evidence to make a recommendation for or against the relationship between increasing age and a favorable response to treatment of neoplastic vertebral fractures with vertebral augmentation. **Grade of Recommendation: I**

Recommendations were developed based on a specific definition, inclusion/exclusion criteria, and the resulting literature. This clinical guideline is not intended to be a fixed treatment protocol; it is anticipated that there will be patients who require more or less investigations or treatment than what is outlined. This clinical guideline should not be construed as including all proper methods of care or excluding other acceptable methods of care reasonably directed to obtaining the same results. The ultimate judgment regarding any specific procedure or treatment is to be made by the provider and patient in light of all circumstances presented by the patient and the needs and resources particular to the locality or institution.

Interventional Treatment Question 4: What is the risk of treating multiple vertebral levels at one time, for patients with multilevel neoplastic vertebral fractures?	Vertebral augmentation may be considered as a safe treatment of multilevel neoplastic vertebral fractures at one time. **Grade of Recommendation: C**
Interventional Treatment Question 5: What is the incidence and risk factors for adjacent vertebral body fractures after vertebral augmentation for neoplastic vertebral fractures?	There is insufficient and conflicting evidence to make a recommendation for or against the incidence or risk factors for adjacent vertebral fractures after vertebral augmentation for neoplastic vertebral fractures. **Grade of Recommendation: I**
Interventional Treatment Question 6: Does the addition of vertebral augmentation to radiation therapy improve outcomes in patients with neoplastic vertebral fractures?	There is insufficient evidence to make a recommendation for or against the addition of vertebral augmentation to radiation therapy as it relates to outcomes in adults with neoplastic vertebral fractures. **Grade of Recommendation: I**
Interventional Treatment Question 7: Does the prophylactic use of vertebral augmentation reduce the risk of vertebral fracture after stereotactic radiotherapy for vertebral metastasis?	*A systematic review of the literature yielded no studies to adequately address this question.*
Interventional Treatment Question 8: Does physical therapy after augmentation affect patient outcomes, including pain and function?	*A systematic review of the literature yielded no studies to adequately address this question.*
Surgical Treatment	
Surgical Question 1: Does surgical fixation with or without fusion improve outcomes in patients with neoplastic vertebral fractures compared to nonoperative care or interventional procedures?	*A systematic review of the literature yielded no studies to adequately address this question.*
Surgical Question 2: Does the use of minimally invasive surgical approaches (eg, percutaneous pedicle screws, muscle-sparing decompression/arthrodesis techniques) improve outcomes compared to open surgical approaches in patients undergoing surgery for neoplastic vertebral fracture?	*A systematic review of the literature yielded no studies to adequately address this question.*
Surgical Question 3: In patients undergoing surgery for neoplastic vertebral fractures, are clinical and radiological outcomes affected by the types of implants used?	There is insufficient evidence to make a recommendation for or against the use of specific implants in adults undergoing surgery for neoplastic vertebral fractures. **Grade of Recommendation: I**
Surgical Question 4: In patients undergoing surgery for neoplastic vertebral fractures, are clinical and radiological outcomes affected by the use of vertebral augmentation of the implants, of the fractured vertebral body, or of adjacent levels?	*A systematic review of the literature yielded no studies to adequately address this question.*

Recommendations were developed based on a specific definition, inclusion/exclusion criteria, and the resulting literature. This clinical guideline is not intended to be a fixed treatment protocol; it is anticipated that there will be patients who require more or less investigations or treatment than what is outlined. This clinical guideline should not be construed as including all proper methods of care or excluding other acceptable methods of care reasonably directed to obtaining the same results. The ultimate judgment regarding any specific procedure or treatment is to be made by the provider and patient in light of all circumstances presented by the patient and the needs and resources particular to the locality or institution.

Recommendations for the Diagnosis and Treatment of Adults with Neoplastic Vertebral Fractures

Key Recommendations:

- Acute vertebral fracture is defined by the presence of edema on MRI ["Glossary and Acronyms"]
- Compared to medical treatments, vertebral augmentation is recommended for the improvement of pain and functional outcomes in the treatment of neoplastic vertebral fractures. [Interventional Treatment Question 2]

Natural History

Natural History Question 1: Does underlying histology affect the natural history of metastatic neoplastic vertebral fractures?

A systematic review of the literature yielded no studies to adequately address this question.

Future Directions for Research

The work group recognizes that it is not feasible to conduct true natural history studies for patients with neoplastic vertebral fractures.

Natural History Question 2: Aside from the effects of underlying histology, what are the expected outcomes of neoplastic vertebral fractures in the absence of treatment directed at the fracture or underlying disease?

A systematic review of the literature yielded no studies to adequately address this question.

Future Directions for Research

The work group recognizes that it is not feasible to conduct true natural history studies for patients with neoplastic vertebral fractures. Future questions should be addressed at comparing different types of treatments (medical, surgical, and rehabilitative).

Recommendations were developed based on a specific definition, inclusion/exclusion criteria, and the resulting literature. This clinical guideline is not intended to be a fixed treatment protocol; it is anticipated that there will be patients who require more or less investigations or treatment than what is outlined. This clinical guideline should not be construed as including all proper methods of care or excluding other acceptable methods of care reasonably directed to obtaining the same results. The ultimate judgment regarding any specific procedure or treatment is to be made by the provider and patient in light of all circumstances presented by the patient and the needs and resources particular to the locality or institution.

Cost-Effectiveness

Cost-Effectiveness Question 1:
In the treatment of neoplastic vertebral fractures, what is the comparative cost-effectiveness of (a) Medical and/or radiation therapy alone vs (b) Vertebral augmentation (with or without radiation therapy) vs (c) Thermal ablation, radiofrequency ablation or cryoablation with or without augmentation vs (d) Operative fusion/fixation?

A systematic review of the literature yielded no studies to adequately address this question.

Future Directions for Research

The work group recommends high-quality studies to better understand cost effectiveness and value propositions from the patient perspective for the treatment of neoplastic vertebral fractures

Clinical Diagnosis

Clinical Diagnosis Question 1:
Which elements (individual or in combination) of a history, symptoms, and/or physical examination are most sensitive and specific for identifying a patient with neoplastic vertebral fracture?

A systematic review of the literature yielded no studies to adequately address this question.

Future Directions for Research

The work group recommends high-quality studies identifying elements of a history, symptoms, and/or physical examination that are most sensitive and specific for identifying a patient with a neoplastic vertebral fracture.

Medical Treatment

Medical Treatment Question 1:
How do nonpharmacologic treatments (eg, bracing, physical therapy, acupuncture, massage, cannabis, exercise, etc.) compare in terms of reducing severity and duration of pain and disability in neoplastic vertebral fractures?

A systematic review of the literature yielded no studies to adequately address this question.

Future Directions for Research

The work group recommends high-quality studies comparing nonpharmacologic treatments in terms of reducing severity and duration of pain and disability in adults with neoplastic vertebral fractures.

Medical Treatment Question 2:
Do restrictions on patient activity alter outcomes in patients with neoplastic vertebral fractures?

A systematic review of the literature yielded no studies to adequately address this question.

Future Directions for Research

The work group recommends high-quality studies evaluating the role of activity restrictions on clinical outcomes in adults with neoplastic vertebral fractures.

Medical Treatment Question 3:
How do pharmacologic treatments (nonchemotherapeutic) and nonpharmacologic treatments compare with interventional treatments in terms of reducing severity and duration of pain and disability in neoplastic vertebral fractures?

There is insufficient evidence to make a recommendation for or against interventional treatment as compared to noninterventional pharmacologic treatments and nonpharmacologic treatments in terms of reducing severity and duration of pain and disability in adults with neoplastic vertebral fractures.

Grade of Recommendation: I

In a prospective randomized control trial study, Berenson et al[1] evaluated the effectiveness and safety of balloon kyphoplasty compared to nonsurgical fracture management for the treatment of adults with neoplastic vertebral fractures. The authors concluded that for painful vertebral fractures "in patients with cancer, kyphoplasty is an effective and safe treatment that rapidly reduces pain and improves function." The work group downgraded this potential Level I paper due to nonconsecutive and nonmasked patients, nonmasked reviewers, lack of subgroup analysis, high crossover after one month, and an unclear description of the nonsurgical management group. This paper provides Level II evidence that kyphoplasty is an effective and safe treatment in patients with neoplastic vertebral fractures for rapid reduction in pain and improvement of function in comparison to nonsurgical treatment.

References:

1. Berenson J, Pflugmacher R, Jarzem P, et al. Balloon kyphoplasty versus non-surgical fracture management for treatment of painful vertebral body compression fractures in patients with cancer: a multicentre, randomised controlled trial. *Lancet Oncol.* 2011;12(3):225-235. doi:10.1016/S1470-2045(11)70008-0

Future Directions for Research

The work group recommends further high-quality prospective comparative studies comparing interventional treatments and noninterventional treatments (eg, pharmacological, nonpharmalogical) in patients with neoplastic vertebral fractures.

Recommendations were developed based on a specific definition, inclusion/exclusion criteria, and the resulting literature. This clinical guideline is not intended to be a fixed treatment protocol; it is anticipated that there will be patients who require more or less investigations or treatment than what is outlined. This clinical guideline should not be construed as including all proper methods of care or excluding other acceptable methods of care reasonably directed to obtaining the same results. The ultimate judgment regarding any specific procedure or treatment is to be made by the provider and patient in light of all circumstances presented by the patient and the needs and resources particular to the locality or institution.

Medical Treatment Question 4:
Does timing or sequencing of interventions (eg, analgesics, bisphosphonates, chemotherapy, XRT, stereotactic XRT, bracing, surgery or vertebral augmentation) improve patient outcomes?

There is insufficient evidence to make a recommendation for or against sequencing of radiation therapy and vertebral augmentation in adults with neoplastic vertebral fractures.

Grade of Recommendation: I

In a retrospective comparative study, Hirsch et al[1] investigated the effectiveness of vertebral augmentation (VA) in relieving fracture-related pain, identify procedural and clinical variables that can influence any outcomes in the population, and assess the impact of treatment sequence on pain outcomes in patients with cancer who have received treatments of vertebral augmentation and external beam radiation therapy. The authors concluded that "a multimodality approach for the management of malignant compression fractures (MCFs) includes VA procedures. The majority of patients with MCFs have excellent palliation with this approach. In patients who receive both external beam radiation therapy (EBRT) and VA, the sequence in which they are given does not affect pain improvement outcomes."

The work group downgraded this potential Level III paper due to nonconsecutive, nonrandomized, and nonmasked patients, nonmasked reviewers, small sample size, diagnostic method not being stated, and the outcome measures used not being validated. This paper provides Level IV evidence that the sequence of vertebral augmentation and external beam radiation therapy does not affect patient outcome in the approach for the management of adults with neoplastic vertebral fracture.

References:

1. Hirsch AE, Jha RM, Yoo AJ, et al. The use of vertebral augmentation and external beam radiation therapy in the multimodal management of malignant vertebral compression fractures. *Pain Physician.* 2011;14(5):447-458.

There is insufficient evidence to make a recommendation for or against timing of noninterventional therapy or vertebral augmentation in adults with neoplastic vertebral fractures.

Grade of Recommendation: I

In a retrospective case series study, Malhotra et al[1] aimed to understand the manner in which spinal deformity affects clinical outcomes, and the impact of time on the effectiveness of spinal treatment modalities. The authors concluded that "vertebral augmentation and thoracolumbar bracing improve patient reported outcome scores in patients with spinal myeloma. However, delay in treatment negatively impacts clinical outcome, particularly if managed nonoperatively. It is important to screen and treat patients with multiple myeloma and back pain early to prevent deformity and improve quality of life." This paper provides Level IV evidence that patients with multiple myeloma and vertebral fractures respond better to kyphoplasty or thoracic-lumbar-sacral orthosis (TLSO) if treated within 195 days of presentation. Delay in noninterventional treatment of neoplastic vertebral fractures negatively impacts clinical outcomes particularly if managed with thoracolumbar bracing.

References:

1. Malhotra K, Butler JS, Yu HM, et al. Spinal disease in myeloma: cohort analysis at a specialist spinal surgery centre indicates benefit of early surgical augmentation or bracing. *BMC Cancer.* 2016;16:444. doi:10.1186/s12885-016-2495-7

Future Directions for Research
The work group recommends high-quality prospective studies evaluating the role of timing or sequencing of treatments on outcomes in patients with neoplastic vertebral fractures.

Medical Treatment Question 5:
Do general and individualized physical therapy programs differ in pain and functional outcomes for patients with neoplastic vertebral fractures?

A systematic review of the literature yielded no studies to adequately address this question.

Future Directions for Research
The work group recommends high-quality studies assessing whether general and individualized physical therapy programs differ in pain and functional outcomes for patients with neoplastic vertebral fractures.

Imaging Diagnosis

Imaging Diagnosis Question 1:
Which imaging modalities and findings are most sensitive and specific for the accurate diagnosis of and treatment planning for neoplastic vertebral fractures?

Findings on routine MRI sequences are suggested as a method to differentiate osteoporotic from neoplastic vertebral fractures.
Grade of Recommendation: B

In a retrospective observational study, Abdel-Wanis et al[1] studied the sensitivity, specificity, and validity of several MRI features in differentiating vertebral compression fractures that are caused by malignancy, osteoporosis, and infections. The authors concluded that "Combination of several MRI features can provide clues to differentiate between malignant, osteoporotic, and infective vertebral compression fractures." This paper provides Level III evidence that MRI features differentiate between malignant, osteoporotic, and infectious fractures.

In a retrospective comparative study, Baur et al[2] assessed the event, location, and form of the fluid sign in acute osteoporotic and neoplastic vertebral compression fractures at magnetic resonance (MR) imaging. The authors describe the fluid sign as signal intensity similar to cerebrospinal fluid (CSF) immediately beneath a fractured endplate. The authors concluded that "The fluid sign is featured in acute vertebral compression fractures that show bone marrow edema. It can be an additional sign of osteoporosis and rarely occurs in metastatic fractures." This paper provides Level III evidence that the fluid sign on MRI is a feature seen with osteoporotic fractures and rare in metastatic fractures.

In a retrospective observational study, Cuénod et al[3] compared the abnormality patterns found in acute osteoporotic and malignant vertebral collapses using unenhanced and gadolinium-enhanced non-fat-suppressed MR images. The authors concluded that "Gadolinium-enhanced and unenhanced MR images are useful in the differentiation of vertebral collapses." This paper provides Level III evidence that many MR Imaging findings are useful in differentiating osteoporotic from malignant compression fractures.

In a retrospective observational study, Hamimi et al[4] evaluated the different MRI signs that would help in differentiating between benign and malignant vertebral fractures. The authors concluded that "Several signs are found to favor osteoporotic or malignant vertebral fractures. Chemical shift and DWI are strong allies to morphological signs in differentiating between both entities. Depending on a group of signs rather than one sign alone would increase the diagnostic accuracy." This paper provides Level III evidence that several signs are found to favor osteoporotic or malignant vertebral fractures. Chemical shift and DWI are good adjuncts to morphological findings to differentiate between benign and malignant vertebral fractures.

In a retrospective observational study, He et al[5] investigated the differential diagnostic value of F-FDG PET/CT for benign and malignant vertebral

compression fractures, where the diagnostic accuracy was compared to MRI. The authors concluded that "Significant MRI findings such as convex posterior cortex, epidural mass formation, and pedicle enhancement are highly suggestive of malignancy. 18F-FDG PET/CT reliably differentiated the fractures of malignant from benign based on both SUVmax and 18F-FDG uptake pattern. In a situation where MRI findings are not diagnostic, 18F-FDG PET/CT provides additional information as it has high sensitivity and is semiquantitative." This paper provides Level III evidence that certain MRI findings are highly suggestive of malignancy; for equivocal MRI findings, using PET/CT imaging will increase the sensitivity for determining malignancy.

In a retrospective observational study, Fu et al[6] aimed to ascertain which conventional MRI parameters are helpful for the early differentiation between benign and malignant vertebral fractures. The authors concluded that "Certain MRI characteristics allow early differentiation of benign and malignant vertebral fractures." This paper provides Level IV evidence that several MRI findings are useful for early differentiation between osteoporotic and malignant vertebral fractures and the presence of a soft tissue mass was most predictive of malignancy.

In a retrospective comparative study, Lee et al[7] evaluated the diagnostic role of the contrast-enhanced MRI (CE-MRI) in differentiating between malignant and benign vertebral compression fractures, focusing more so on the internal transparent trabecular bone on CE-MRI (the ''see-through sign''). The authors concluded that "The see-through sign on CE-MRI is featured in acute benign VCFs, and it can be a useful finding to differentiate between benign and malignant VCFs." This paper provides Level III evidence that the presence of the see through sign on CE-MRI is significantly more common in benign VCFs than malignant VCFs.

In a retrospective comparative study, Moulopoulos et al[8] detailed a constellation of MR criteria that can be used in the analysis of the etiology of a compression fracture. The authors showed that MR signal intensity of an involved vertebra is the strongest criterion in predicting benign versus malignant nature and multiple regression analysis showed greatest accuracy of 94% when using criteria of signal intensity, shape, location and focal convexity. The work group downgraded this potential Level II paper due to inconsistent use of a gold standard, biopsy, or follow-up MR imaging to prove the results were accurate. This paper provides Level III evidence that adding additional criteria has the potential to increase that accuracy to 94%.

In a retrospective case series study, Tan et al[9] aimed to distinguish MRI features of benign and malignant vertebral fractures and differentiate between osteoporotic, traumatic, and infectious causes. The authors concluded that "MRI can be used to accurately differentiate between benign and malignant causes of vertebral collapse." The work group downgraded this potential Level III paper due to nonconsecutive patients, small sample size, nonmasked reviewers, no consistently applied gold standard, and poor reference standard. This paper provides Level IV evidence that certain MRI findings can distinguish benign versus neoplastic vertebral fractures.

In a retrospective comparative study, Tokuda et al[10] aimed to establish whether bone single-photon emission tomography (SPECT) can be used as a substitute for magnetic resonance (MR) imaging for differentiating between malignant and benign vertebral compression fractures. The authors concluded that "Bone SPECT may be comparable with MR imaging for differentiating malignant from benign VCFs, especially, in the case of VCFs with a complete replacement of the normal fatty marrow." The work group downgraded this potential Level III paper due to no consistent application of the gold standard. This paper provides Level IV evidence that in cases of VCF with partial replacement of the normal fatty bone marrow, MRI is more accurate than SPECT imaging in distinguishing a benign vs malignant etiology; this differentiation is not possible in VCFs with complete replacement of the normal fatty marrow.

In a retrospective comparative study, Shih et al[11] aimed to characterize the MR pattern of compression fractures in benign and malignant processes. The authors concluded that "In conclusion, the differential diagnosis of a solitary vertebral collapse with either a benign or malignant cause can be easily performed by MRI." This paper provides Level III evidence that morphologic appearance of the fracture on MR imaging is useful to distinguish benign vs. malignant vertebral fracture.

In a retrospective comparative study, Pongpornsup et al[12] assessed the validity, sensitivity, and specificity of magnetic resonance imaging features in differentiating between malignant and benign compression fracture of the spine. The authors concluded that "Certain MR imaging characteristics can reliably distinguish malignant from benign compression fracture of the spine. Combination of several MRI features strongly affirmed the diagnosis of malignant compression fracture, especially in a patient where tissue biopsy is not justified." The work group downgraded this potential Level III paper due to nonconsecutive patients and no consistent or universally applied gold standard. This paper provides Level IV evidence that certain MRI features (involvement of pedicle or posterior element) were highly sensitive and specific for differentiation between malignant and osteoporotic compression fractures.

In a retrospective observational study, Ishiyama et al[13] aimed to assess the prevalence and properties of pedicle-involvement change on MRI in painful osteoporotic compression fractures and to decide whether the findings are accurately specific for malignancy. The authors concluded that "Pedicle involvement was seen frequently in patients with osteoporotic compression fractures and was not specific for malignancy in our study group." This paper provides Level IV evidence that pedicular involvement of the fracture is not necessarily specific for neoplastic vertebral fracture.

In a retrospective comparative study, Takigawa et al[14] studied the MRI features that could differentiate benign and malignant vertebral fractures. The authors concluded that "Although each MRI feature had a different meaning with a variable differentiation power, combining them led to an accurate diagnosis. This study identified the most relevant MRI features that would be helpful in discriminating benign from malignant vertebral fractures." The work group downgraded this potential Level III paper due to nonconsecutive patients and nonmasked reviewers. This paper provides Level IV evidence that with the exception of multiple myeloma, when trying to distinguish a malignant vs benign etiology in patients with VCF, using these MRI characteristics allowed a predictive value of 97.3%: posterior wall diffuse protrusion, pedicle and posterior involvement, and the benign features of a band pattern.
In a retrospective observational study, Yuh et al15 aimed to characterize and assess the MR imaging appearance of compression fractures due to benign or malignant processes to define the criteria that would be useful in differentiating these two entities. The authors concluded that "When criteria based on complete loss or preservation of bone marrow were applied for cases with incomplete loss, differentiation between benign and malignant compression fractures would be achieved with 94% accuracy." This paper provides Level IV evidence that preservation of normal-signal intensity bone marrow on MRI is helpful to identify benign and malignant vertebral compression fractures.

References

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Specific MRI sequences are suggested to differentiate osteoporotic from neoplastic vertebral fractures.

Grade of Recommendation: B

In a prospective comparative study, Schmeel et al[1] assessed the diagnostic performance of T2*-weighted magnetic resonance imaging, when used to differentiate between acute benign and neoplastic vertebral compression fractures. The authors concluded that "Quantitative assessment of vertebral bone marrow T2* relaxation times provides good diagnostic accuracy for the differentiation of acute benign and malignant VCFs." The work group downgraded this potential Level I paper due to low sample size. This paper provides Level II evidence that T2 MRI parameters provide good diagnostic accuracy to distinguish between malignant vs benign compression fractures.

In a prospective observational study, Bhugaloo et al[2] aimed to characterize and differentiate benign and malignant vertebral compression fractures compared to conventional T1 WI, T2 WI and fat suppressed contrast enhanced T1 WI in the Malaysian population by assessing the specificity and sensitivity of diffusion weighted MR imaging (DWI). The authors concluded that "When the findings on routine MR sequences are not completely conclusive for the diagnosis of acute benign or malignant vertebral body compression fracture, then the use of both contrast enhancement and diffusion weighted MR sequence may be helpful. We found that absence of contrast enhancement has a high NPV (90%) while SSFP DWI has both a high PPV (90%) and high NPV (90%) in detecting malignant vertebral compression fractures." This paper provides Level III evidence that in MRI of NVF, absence of contrast enhancement has a high negative predictive value for malignant VBCF and SSFP DWI (steady state free precession diffusion-weighted) has both a high positive predictive value and a high negative predictive value in detecting malignant VCF.

In a retrospective observational study, Eito et al[3] compared vertebrae that display neoplastic compression fractures with normal vertebrae using opposed-phase (OP) and in-phase (IP) gradient-echo (GRE) imaging. The authors concluded that "OP and IP T1-W GRE MRI of vertebral SI abnormalities can help predict the nature of compression fractures." This paper provides Level III evidence that the use of opposed phase and in phase gradient-echo imaging is useful in distinguishing osteoporotic and neoplastic fractures.

In a prospective comparative study, Ragab et al[4] sought to determine the cut-off value of the signal intensity drop for chemical shift magnetic resonance imaging with applicable sensitivity and specificity to differentiate between neoplastic and osteoporotic wedging of the spine. The authors concluded that "A chemical shift MRI is useful in order to differentiate patients with vertebral collapse due to underlying osteoporosis or neoplastic process." The work group downgraded this potential Level II paper due to small sample size and nonmasked reviewers. This paper provides Level III evidence that a chemical shift MRI

(using a cut off value of 35%) is both sensitive and specific for neoplastic VCF.

In a retrospective comparative study, Ogura et al[5] evaluated the value of in-phase/opposed phase and short TI inversion recovery (STIR) magnetic resonance imaging (MRI) of bone marrow, when it comes to differentiating between benign vertebral compression fractures and malignant vertebral compression fractures. The authors concluded "In cases of acute compression fracture, malignant bone marrow showed SIR(STIR) values less than 2.0 and SIR (in/opposed) greater than 1.0. In contrast, benign bone marrow showed SIR (STIR) values greater than 2.5. For chronic compression fracture, malignant bone marrow showed SIR (in/opposed) greater than 1.0. Bone marrow was benign in all cases with SIR (in/opposed) less than 1.0." The work group downgraded this potential Level III paper due to nonconsecutive patients, small sample size, no consistent or universal application of a gold standard, and nonmasked reviewers. This paper provides Level IV evidence that SIR and STIR imaging allows differentiation between benign and malignant compression fractures.

In a retrospective comparative study, Yamamoto et al[6] studied the value of sagittal T1-weighted MRI findings for differentiating metastatic and osteoporotic vertebral fractures. The authors concluded that "Characteristic findings with sagittal T1-weighted MRI were useful in the differential diagnosis of metastatic and osteoporotic vertebral fractures." The work group downgraded this potential Level III paper due to nonconsecutive patients. This paper provides Level IV evidence that sagittal T-1 images on MRI are useful to differentiate osteoporotic and metastatic vertebral fractures.

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Diffusion weighted imaging (DWI) is suggested as a MR sequence to distinguish osteoporotic from neoplastic vertebral fractures.

Grade of Recommendation: B

In a prospective observational study, Geneidi et al[1] assessed the usefulness of diffusion-weighted imaging (DWI) for differentiating between malignant and benign bone tumors. The authors concluded that "In conclusion we prove high specificity and sensitivity of DWI in discrimination between benign and malignant bone tumors with significant cut-off value, making it a non-invasive tool in diagnosis of bone marrow metastasis and differentiating it from other benign lesions." This paper provides Level II evidence that MRI with diffusion-weighted imaging has a diagnostic value in the discrimination between benign and malignant lesions in the vertebral body.

In a retrospective comparative study, Pozzi et al[2] investigated the value of magnetic resonance imaging (MRI) with spin-echo echo-planar diffusion-weighted imaging (SE-EPI-DWI) when it comes to differentiating between vertebral osteoporotic fractures and pathological neoplastic fractures. The authors concluded that "DWI provides reliable information to support MRI diagnosis of neoplastic

versus osteoporotic fractures. ADC value appears as a useful adjunctive parameter." The work group downgraded this potential Level I paper due to the patients not being consecutively assigned. This paper provides Level II evidence that DWI provides reliable data to distinguish between osteoporotic and malignant fractures.

In a prospective observational study, Balliu et al[3] evaluated the value of apparent diffusion coefficient (ADC), which is attained through diffusion weighted (DWI) MR, when it comes to differentiating between benign and malignant bone marrow lesions. The authors concluded that "ADC values are a useful complementary tool to characterize bone marrow lesions, in order to distinguish acute benign fractures from malignant or infectious bone lesions. However, ADC values are not valuable in order to differentiate malignancy from infection." This paper provides Level III evidence that measuring ADC values helps distinguish between benign and malignant compression fractures, but not between malignant fractures and infection.

In a prospective comparative study, Baur et al[4] studied the impact of increasing diffusion weighting of a diffusion-weighted steady-state free precession (SSFP) sequence to differentiate between acute benign and neoplastic vertebral compression fractures. The authors concluded "Increasing diffusion weighting can reduce false-positive hyperintense osteoporotic fractures or make hypointensity more obvious in cases of osteoporotic fractures." This paper provides Level III evidence that DWI using increased diffusion weighting reduces false positive signal of osteoporotic VCFs.

In a prospective comparative study, Baur et al[5] assessed the value of diffusion-weighted magnetic resonance imaging of bone marrow, when used to differentiate between benign and pathologic vertebral compression fractures. The authors concluded that "Diffusion-weighted MR imaging provided excellent distinction between pathologic and benign vertebral compression fractures." This paper provides Level III evidence that diffusion-weighted MRI is able to differentiate between pathologic and benign vertebral compression fractures.

In a prospective observational study, Biffar et al[6] studied spin-lattice (T1) and spin-spin (T2) relaxation timings as well as apparent diffusion coefficients (ADCs) of the physical properties (fat and water components) in the vertebral bone marrow (vBM) of patients who had benign and malignant vertebral lesions. The authors concluded that "All parameters exhibit significant differences between normal-appearing vBM and the lesions. However, only the ADCs determined with the DW-ssTSE differed significantly between osteoporotic fractures and malignant lesions potentially allowing for a differential diagnosis of these two entities." This paper provides Level III evidence that only the ADCs determined with DW-ssTSE differed significantly between osteoporotic and malignant lesions potentially allowing for a differential diagnosis between these two entities.

In a prospective observational study, Bhugaloo et al[7] aimed to characterize and differentiate benign and malignant vertebral compression fractures compared to conventional T1 WI, T2 WI and fat suppressed contrast enhanced T1 WI in the Malaysian population by assessing the specificity and sensitivity of diffusion weighted MR imaging (DWI). The authors concluded that "When the findings on routine MR sequences are not completely conclusive for the diagnosis of acute benign or malignant vertebral body compression fracture, then the use of both contrast enhancement and diffusion weighted MR sequence may be helpful. We found that absence of contrast enhancement has a high NPV (90%) while SSFP DWI has both a high PPV (90%) and high NPV (90%) in detecting malignant vertebral compression fractures." This paper provides Level III evidence that in MRI of NVF, absence of contrast enhancement has a high negative predictive value for malignant NVF and SSFP DWI (steady state free precession diffusion-weighted) has both a high positive predictive value and a high negative predictive value in detecting malignant VBCF.

In a prospective observational study, Geith et al[8] compared the diagnostic value of qualitative and quantitative diffusion-weighted imaging (DWI), and chemical-shift imaging in patients with acute osteoporotic and malignant vertebral compression fractures. The authors concluded that "Qualitative assessment of opposed-phase, DW-EPI, and DW single-shot TSE sequences and quantitative assessment of the DW-EPI sequence were not suitable for distinguishing between benign and malignant vertebral fractures." This paper provides Level III evidence that DWI-PSIF had the highest accuracy differentiating between benign vs malignant vertebral fractures with a sensitivity of 100%; a specificity of 88.5% and an accuracy of 93.5%.

In a retrospective observational study, Hamimi et al[9] evaluated the different MRI signs that would help in differentiating between benign and malignant vertebral fractures. The authors concluded that "Several signs are found to favor osteoporotic or malignant vertebral fractures. Chemical shift and DWI are strong allies to morphological signs in differentiating between both entities. Depending on a group of signs rather than one sign alone would increase the diagnostic accuracy." This paper provides Level III evidence that several signs are found to favor osteoporotic or malignant vertebral fractures. Chemical shift and DWI are good adjuncts to morphological findings to differentiate between benign and malignant vertebral fractures.

In a prospective comparative study, Maeda et al[10] aimed to assess the value of diffusion abnormalities quantitatively in benign and malignant vertebral compression fractures, using line scan diffusion-weighted imaging (DWI). The authors concluded that "Although the quantitative assessment of vertebral diffusion provides additional information concerning compressed vertebrae, the benign and malignant compression fracture apparent diffusion coefficient (ADC) values overlap considerably. Therefore, even a quantitative vertebral diffusion assessment may not always permit a clear distinction between benign and malignant compression fractures." This paper provides Level III evidence that quantitative assessment of ADC values using diffusion weighted imaging may not reliably distinguish between benign and malignant compression fractures due to an overlap in ADC values.

In a prospective comparative study, Mubarak et al[11] assessed the sensitivity, specificity, and validity of diffusion-weighted (DWI) magnetic resonance imaging (MRI) in the diagnosis and differentiation between malignant and benign vertebral compression fractures, in relation to histology findings and clinical follow-up. The authors concluded that "Diffusion weighted magnetic resonance imaging offers a safe, accurate and noninvasive modality to differentiate between the benign and malignant vertebral compression fracture." The work group downgraded this potential Level III paper due to small sample size, nonmasked reviewers, poor reference standard, and lack of a consistently applied gold standard. This paper provides Level IV evidence that diffusion-weighted MRI is 85% accurate in differentiating between benign and malignant vertebral compression fractures.

In a prospective comparative study, Oztekin et al[12] investigated the value of single-shot echoplanar imaging sequences (diffusion-weighted imaging (DWI)/SSH-EPI) with low b value in the differentiation between malignant metastatic tumor infiltration of vertebral bone marrow and benign vertebral fracture edema. The authors concluded that "Single-shot echo-planar imaging sequences (DWI/SSH-EPI) with low b value provided excellent distinction between metastatic tumor infiltration and benign vertebral fracture edema. Hyperintense signal intensity on DWI/SSH-EPI was highly specific for the diagnosis of metastatic tumor infiltration of the spine." This paper provides Level III evidence that diffusion-weighted imaging using single-shot echo-planar imaging is excellent in differentiating between metastatic tumor fractures from benign vertebral fractures.

In a retrospective case control study, Byun et al[13] aimed to ascertain if a steady state free precession (SSFP) DW MRI would be useful in differentiating metastases of the sacrum from sacral insufficiency fractures. The authors concluded that "SSFP diffusion-weighted MRI is capable of differentiating benign sacral insufficiency fractures from metastatic tumors of the sacrum." This paper provides Level IV evidence that SSFP DWI MRI evaluation of the sacrum can help differentiate benign from malignant fractures.

In a prospective comparative study, Park et al[14] studied the value of single shot fast spin echo diffusion-weighted MR imaging (DWSSFSE) in the differentiation between malignant metastatic tumor infiltration of vertebral bone marrow from benign vertebral fracture edema. The authors concluded that "DWSSFSE of the spine may be useful in differentiating metastatic tumor infiltration of vertebral bone marrow from benign fracture edema." This paper provides Level IV evidence that DWI is highly specific but not sensitive for metastatic tumor.
In a prospective case series study, Zhou et al[15] aimed to test the hypothesis, using a diffusion imaging technique, that malignant and benign vertebral lesions can be differentiated on the basis of tissue apparent diffusion coefficient (ADCs). The authors concluded that "quantitative ADC mapping, instead of qualitative diffusion-weighted imaging, can provide valuable information in differentiating benign

vertebral fractures from metastatic lesions." This paper provides Level IV evidence that quantitative ADC mapping is more sensitive than quantitative diffusion imaging technique.

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Contrast enhanced perfusion MRI is suggested as a method to differentiate between osteoporotic and neoplastic vertebral compression fractures.
Grade of Recommendation: B

In a retrospective observational study, Arevalo-Perez et al[1] evaluated dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) in differentiating between pathologic and benign vertebral fractures. The authors concluded that "Our data demonstrate that T1-weighted DCE-MRI has potential to differentiate between pathologic vs. benign, acute vs chronic, and most important, benign acute vs pathologic vertebral fractures." This paper provides Level II evidence that certain perfusion parameters associated with DCE-MRI are able to distinguish benign vs malignant and acute vs non-acute vertebral body fractures.

In a prospective observational study, Geith et al[2] assessed quantitative dynamic contrast-enhanced MRI (DCE-MRI) to differentiate between benign vertebral fractures from malignant vertebral fractures

based on the tracer kinetic modeling of perfusion. The authors concluded that "In spots of high plasma flow, which can be determined with a deconvolution analysis, the quantitative perfusion parameters of interstitial volume, ECV, and extraction flow are significantly different between acute osteoporotic and malignant vertebral fractures and can aid in the distinction between the two entities." This paper provides Level III evidence that high plasma flow on perfusion MRI was able to differentiate between acute osteoporotic and malignant vertebral fractures.

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PET scan is suggested to differentiate between osteoporotic and neoplastic vertebral compression fractures.

Grade of Recommendation: B

In a retrospective comparative study, Bredella et al[1] analyzed the use of fluorodeoxyglucose positron emission tomography (FDG-PET) in differentiating a benign compression fracture from a malignant compression fracture. The authors concluded that "Fluorodeoxyglucose positron emission tomography is useful in differentiating benign from malignant compression fractures. Therapy with bone marrow-stimulating agents can mimic malignant involvement." This paper provides Level III evidence that FDG-PET can be helpful in identifying malignant compression fractures.

In a retrospective comparative study, Cho et al[2] compared the ability ot MRI findings and PET/fluorodeoxyglucose positron emission tomography (FDG-PET) in differentiating between malignant and benign vertebral compression fractures. The authors concluded that "When MR imaging findings are equivocal, FDG-PET/CT can be considered as an adjunctive diagnostic method for differentiating malignant from benign VCFs. In comparison with MR imaging, FDG-PET/CT showed slightly higher sensitivity and lower specificity". This paper provides Level III evidence that FDG-PET/CT is a useful adjunctive diagnostic method for differentiating malignant vs. benign VCF when MRI results are inconclusive or unavailable.

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There is insufficient evidence to make a recommendation for or against the use of bone scans to differentiate osteoporotic from neoplastic vertebral compression fractures.

Grade of Recommendation: I

In a prospective cohort study, Thariat et al[1] investigated the value of thallium-201 (201TI) scintigraphy for differentiating between benign and malignant recent non-traumatic compression fractures. The authors concluded that "The weak sensitivity does not support the wide use of 201TI bone scintigraphy to distinguish a benign from a malignant recent non traumatic vertebral fracture. However, the high specificity suggests that such evaluation might be proposed prior to vertebral biopsy in some difficult

cases." The work group downgraded this potential Level III paper due to small sample size. This paper provides Level IV evidence that bone scintigraphy has low sensitivity and should not be used as a screening test for malignant VCF, but because of the high specificity bone scintigraphy may have some utility in difficult cases.

In a retrospective comparative study, Tokuda et al[2] aimed to establish whether bone single-photon emission tomography (SPECT) can be used as a substitute for magnetic resonance (MR) imaging for differentiating between malignant and benign vertebral compression fractures. The authors concluded that "Bone SPECT may be comparable with MR imaging for differentiating malignant from benign VCFs, especially, in the case of VCFs with a complete replacement of the normal fatty marrow." The work group downgraded this potential Level III paper due to no consistent application of the gold standard. This paper provides Level IV evidence that in cases of VCF with partial replacement of the normal fatty bone marrow, MRI is more accurate than SPECT imaging in distinguishing a benign vs malignant etiology; this differentiation is not possible in VCFs with complete replacement of the normal fatty marrow.

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There is insufficient evidence to make a recommendation for or against the use of CT to differentiate osteoporotic from neoplastic vertebral compression fractures.

Grade of Recommendation: I

In a retrospective observational study, Laredo et al[1] evaluated the usefulness of computed tomography (CT) as a means to differentiate benign from malignant causes of nontraumatic acute vertebral collapse (in relation to pain of less than 3 months in duration). The authors concluded that "CT can help distinguish benign from malignant causes of nontraumatic AVC." This paper provides Level III evidence that the presence of destruction of the vertebral anterolateral or posterior cortical bone, the cancellous bone, or pedicel as well as a paraspinal soft-tissue mass or epidural mass on CT were helpful in distinguishing benign vs malignant vertebral compression fractures.

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Future Directions for Research

The work group recommends further high-quality studies on newer CT techniques (for example: dual energy CT and photon counting CT) and the role they may play in differentiating osteoporotic from neoplastic vertebral compression fractures.

Interventional Treatment

Interventional Treatment Question 1:
What are the criteria/indications/contraindications for vertebral augmentation in patients with neoplastic vertebral fractures?

Vertebral augmentation is suggested as a safe and effective procedure in adults with neoplastic vertebral fractures with intractable back pain despite medical management and/or those at risk of vertebral collapse, although caution is recommended because of the potential for cement extrusion.

Grade of Recommendation: B

In a retrospective study, Cianfori et al[1] assessed the complications of vertebral augmentation in 48 patients with cortical erosion of the posterior wall undergoing vertebral augmentation for pain palliation and/or stabilization of neoplastic vertebral body lesions. Seventy consecutive levels with cortical erosion of the posterior wall were evaluated. The authors concluded that the "data seem to justify use of vertebral augmentation in patients with intractable pain or those at risk for vertebral collapse." As a retrospective prognostic study, this paper provides Level II evidence that vertebral augmentation can be safely performed in most adults with NVF with erosion of posterior vertebral wall using the techniques described, but caution should be exercised. For appropriate patients, pretreatment with radiation/ablation is appropriate.

In a retrospective study, Molloy et al[2] compared balloon kyphoplasty outcomes in patients with cancer-related vertebral compression fractures with posterior vertebral body wall defect (n=112) versus those without posterior vertebral body wall involvement (n=46). The authors concluded, "<balloon kyphoplasty> can alleviate pain and improve <quality of life> and function in patients with cancer-related <vertebral compression fractures> with <posterior vertebral body wall> defects with no appreciable increase in risk." As a retrospective prognostic study, this paper provides Level II evidence that vertebral augmentation is a safe and effective procedure using the techniques described for adults with metastatic vertebral fractures who also have posterior vertebral body wall (PVBW) defect with a leakage rate of 31% compared to a 20% leakage rate in those patients without a PVBW defect.

In a retrospective case control study, Hentschel et al[3] observed 53 patients with cancer vertebral body fracture who underwent vertebral augmentation, 17 of whom may have had contraindications according to previous literature. They found complications in these 17 patients, but concluded that the procedure was nevertheless safe and effective. This paper provides Level III evidence that adults with NVF may benefit from VA even with potential contraindications to the procedure and that the procedure has a reasonably low rate of cement extravasation using the techniques described in the article.

In a retrospective study, Tancioni et al[4] evaluated 11 patients with multiple myeloma with painful vertebral body fractures who underwent vertebroplasty. The authors concluded, "vertebroplasty is a safe and efficient procedure in the treatment of painful vertebral body fractures in patients with multiple myeloma, without potential contraindications, such as fractures of the posterior wall or epidural disease." The work group downgraded this potential Level II prognostic paper due to small sample size. This paper provides Level III evidence that vertebroplasty may be safe in patients with myeloma and posterior vertebral wall violation or epidural disease as the incidence of leakage is low and most are asymptomatic.

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Vertebral augmentation is suggested for the treatment of neoplastic vertebral fractures from multiple myeloma.

Grade of Recommendation: B

In a retrospective study, Huber et al[1] examined postkyphoplasty complications in 76 patients with multiple myeloma. The authors concluded, "By careful interdisciplinary indication setting and a standardized treatment model, kyphoplasty presents a very safe and effective procedure for the treatment of vertebral osteolyses and fractures caused by MM." As a retrospective prognostic study, the work group concluded that this paper provides Level II evidence that kyphoplasty is a safe and effective procedure for the treatment of vertebral fractures caused by multiple myeloma.

In a retrospective study, Tancioni et al[2] evaluated 11 patients with multiple myeloma with painful vertebral body fractures who underwent vertebroplasty. The authors concluded, "Vertebroplasty is a safe and efficient procedure in the treatment of painful vertebral body fractures in patients with multiple myeloma, without potential contraindications, such as fractures of the posterior wall or epidural disease." The work group downgraded this potential Level II paper due to small sample size. This paper provides Level III evidence that vertebroplasty may be safe in patients with myeloma and posterior vertebral wall violation or epidural disease as the incidence of leakage is low and most are asymptomatic.

References:

1. Huber FX, McArthur N, Tanner M, et al. Kyphoplasty for patients with multiple myeloma is a safe surgical procedure: results from a large patient cohort. *Clin Lymphoma Myeloma.* 2009;9(5):375-380. doi:10.3816/CLM.2009.n.073
2. Tancioni F, Lorenzetti M, Navarria P, et al. Vertebroplasty for pain relief and spinal stabilization in multiple myeloma. *Neurol Sci.* 2010;31(2):151-157. doi:10.1007/s10072-009-0197-5

There is insufficient evidence to make a recommendation for or against the transoral approach in malignant C2 lesions for vertebral augmentation as a palliative procedure for adults with neoplastic vertebral fractures.

Grade of Recommendation: I

In a prospective study, Anselmetti et al[1] analyzed the results of transoral vertebroplasty in 25 patients with malignant painful osteolytic lesions of C2. The authors concluded that, "transoral vertebroplasty is safe, effective, and long-lasting in the treatment of cervical pain resulting from malignant involvement of C2." This paper provides Level IV evidence that location of the neoplastic fracture in odontoid process is not necessarily a contraindication to augmentation procedure. On the contrary, transoral vertebroplasty is reported to be safe and have good outcomes.

References:

1. Anselmetti GC, Manca A, Montemurro F, et al. Vertebroplasty using transoral approach in painful malignant involvement of the second cervical vertebra (C2): a single-institution series of 25 patients. *Pain Physician.* 2012;15(1):35-42.

Future Directions for Research

The work group recommends further high-quality studies analyzing specific clinical and radiological criteria to determine eligibility for augmentation procedures.

Interventional Treatment Question 2:

How do interventional treatments (augmentation, thermal ablation, radiofrequency ablation and cryoablation) compare to medical treatments in reducing severity and duration of pain and disability in patients with neoplastic vertebral fractures?

A systematic review of the literature yielded no studies to adequately address the thermal ablation, cryoablation and radiofrequency ablation components of this question.

Vertebral augmentation is recommended for the improvement of pain and functional outcomes in the treatment of neoplastic vertebral fractures.
Grade of Recommendation: A

Berenson et al[1] conducted a multicenter randomized controlled trial to evaluate outcomes of patients with 1-3 painful neoplastic vertebral fractures, comparing patients (n=65) who underwent kyphoplasty versus patients (n=52) who received medical management. The authors concluded, "for painful VCFs in patients with cancer, kyphoplasty is an effective and safe treatment that rapidly reduces pain and improves function." This paper provides Level I evidence that balloon kyphoplasty improves functional outcomes at 1 month in comparison to medical treatment for neoplastic compression fractures. Although the work group did not downgrade the level of evidence of this paper, they noted that there was significant industry funding, no masking of reviewers, and a high rate of attrition for the 12-month follow-up.

In a prospective randomized control trial study, Yang et al[2] evaluated the effect of combined percutaneous vertebroplasty and chemotherapy treatment (n=38) compared to chemotherapy alone (n=38) in patients with multiple-myeloma-associated vertebral fracture. The authors concluded, "Percutaneous vertebroplasty had the characteristics of minimal trauma, easy operation and less complication...(and) can achieve long term analgesic effect, and enhance the spinal stability." This paper provides Level I evidence that percutaneous vertebroplasty offers better pain relief and functional outcomes than chemotherapy only for neoplastic vertebral fracture that is sustained long term (12 months).

In a retrospective comparative study, Malhotra et al[3] compared the outcomes of patients with spinal myeloma treated with balloon kyphoplasty (n=84) versus a thoracolumbar-sacral orthosis (n=99). The authors concluded, "Vertebral augmentation and thoracolumbar bracing improve patient reported outcome scores in patients with spinal myeloma. However, delay in treatment negatively impacts clinical outcome, particularly if managed non-operatively." This paper provides Level III evidence that more aggressive treatment with balloon kyphoplasty and TLSO in adults with vertebral body fractures secondary to multiple myeloma provided better outcome measure improvement compared to TLSO management alone in adults with less pain or lower SINS scores.

References

1. Berenson J, Pflugmacher R, Jarzem P, et al. Balloon kyphoplasty versus non-surgical fracture management for treatment of painful vertebral body compression fractures in patients with cancer: a multicentre, randomised controlled trial. Lancet Oncol. 2011;12(3):225-235. doi:10.1016/S1470-2045(11)70008-0
2. Yang Z, Tan J, Xu Y, et al. Treatment of MM-associated spinal fracture with percutaneous vertebroplasty (PVP) and chemotherapy. Eur Spine J. 2012;21(5):912-919. doi:10.1007/s00586-011-2105-y
3. Malhotra K, Butler JS, Yu HM, et al. Spinal disease in myeloma: cohort analysis at a specialist spinal surgery centre indicates benefit of early surgical augmentation or bracing. BMC Cancer. 2016;16:444. Published 2016 Jul 11. doi:10.1186/s12885-016-2495-7

Future Directions for Research

The work group recommends further high-quality studies to determine which patients would benefit most from ablative techniques in adults with neoplastic vertebral body fractures.

Interventional Treatment Question 3:
Are there specific characteristics of the fracture or the patient that influence outcomes in patients with neoplastic vertebral fractures undergoing vertebral augmentation?

Vertebral augmentation is suggested to be a safe treatment option with low rate of clinical complications in neoplastic vertebral fractures with cortical wall defects.

Grade of Recommendation: B

In a retrospective case series study, Molloy et al[1] compared balloon kyphoplasty outcomes in patients with cancer-related vertebral compression fractures with posterior vertebral body wall involvement (n=112) versus those without posterior vertebral body wall involvement (n=46). The authors concluded that balloon kyphoplasty "can alleviate pain and improve quality of life and function in patients with cancer-related vertebral compression fractures with posterior vertebral body wall defects with no appreciable increase in risk." This paper provides Level II evidence that balloon kyphoplasty is a safe and effective procedure using the techniques described for adults with neoplastic vertebral fractures who also have posterior vertebral body wall (PVBW) defect with a leakage rate of 31% compared to a 20% leakage rate in those pts without a PVBW defect.

In a retrospective comparative study, Yao et al[2] analyzed the risk factors by comparing bone cement leakage rates in patients with vertebral compression fractures caused by multiple myeloma (n=33) or osteoporosis (n=48) treated with percutaneous kyphoplasty. The authors concluded, "compared with osteoporosis, percutaneous kyphoplasty treatment of vertebral compression fractures caused by multiple myeloma is more prone to lead to bone cement leakage." This paper provides Level II evidence that cortical bone destruction of the vertebral wall in multiple myeloma may predispose to cement leakage after augmentation with no neurological symptoms reported.

In a retrospective case series study, Delpla et al[3] evaluated 100 patients who received preventive vertebroplasty for risk of pathological fractures. Of the 215 vertebral metastases studied, 138 were treated and 77 were untreated, resulting in 9 and 16 pathological fractures at the end of follow-up (3.1 years +/- 1.1). The authors concluded, "preventive vertebroplasty is long-term effective for consolidation of vertebral metastases and must be discussed at the early diagnosed. Quality of cement injection matters, suggesting that techniques that improve the quantity and the quality of cement diffusion into the VM must be developed." This paper provides Level II evidence that SINS score and quality of vertebral filling may affect the risk of fracture after preventive vertebroplasty for NVF.

In a retrospective study, Cianfori et al[4] assessed the complications of vertebral augmentation in 48 patients with cortical erosion of the posterior wall undergoing vertebral augmentation for pain palliation and/or stabilization of neoplastic vertebral body lesions. Seventy consecutive levels with cortical erosion of the posterior wall were evaluated. The authors concluded that the "data seem to justify use of vertebral augmentation in patients with intractable pain or those at risk for vertebral collapse." As a retrospective prognostic study, this paper provides Level II evidence that vertebral augmentation can be safely performed in most adults with NVF with erosion of posterior vertebral wall using the techniques described, but caution should be exercised. For appropriate patients, pretreatment with radiation/ablation is appropriate.

In a retrospective case control study, Hentschel et al[5] observed 53 patients with cancer vertebral body fracture who underwent vertebral augmentation, 17 of whom may have had contraindications according to previous literature. They found complications in these 17 patients, but concluded that the procedure was nevertheless safe and effective. This paper provides Level III evidence that adults with NVF may benefit from VA even with potential contraindications to the procedure and that the procedure has a reasonably low rate of cement extravasation using the techniques described in the article.

References

1. Molloy S, Sewell MD, Platinum J, et al. Is balloon kyphoplasty safe and effective for cancer-related vertebral compression fractures with posterior vertebral body wall defects?. *J Surg Oncol.* 2016;113(7):835-842. doi:10.1002/jso.24222
2. Yao XC, Du WS, Du XR, Luo H, Xu ZY. Cortical bone destruction-the major factor causing bone cement leakage after kyphoplasty in multiple myeloma. *Int J Clin Exp Med.* 2017;10(12):16506-16512

3. Delpla A, Tselikas L, De Baere T, et al. Preventive Vertebroplasty for Long-Term Consolidation of Vertebral Metastases [published correction appears in *Cardiovasc Intervent Radiol.* 2020 May;43(5):807]. *Cardiovasc Intervent Radiol.* 2019;42(12):1726-1737. doi:10.1007/s00270-019-02314-6
4. Cianfoni A, Raz E, Mauri S, et al. Vertebral augmentation for neoplastic lesions with posterior wall erosion and epidural mass. *AJNR Am J Neuroradiol.* 2015;36(1):210-218. doi:10.3174/ajnr.A4096
5. Hentschel SJ, Burton AW, Fourney DR, Rhines LD, Mendel E. Percutaneous vertebroplasty and kyphoplasty performed at a cancer center: refuting proposed contraindications. *J Neurosurg Spine.* 2005;2(4):436-440. doi:10.3171/spi.2005.2.4.0436

There is insufficient evidence to make a recommendation for or against the relationship between increasing age and a favorable response to treatment of neoplastic vertebral fractures with vertebral augmentation.

Grade of Recommendation: I

In a retrospective case control study, Jha et al[1] reviewed the efficacy of vertebral augmentation in 147 patients with cancer. The authors concluded, "vertebral augmentation provides pain relief for a majority of all compression fractures (osteoporotic and malignant) and metastatic compression fractures. Increasing age may be predictive of pain relief outcomes in metastatic compression fractures. There are special planning, imaging, and technical considerations (eg, needle placement) in using vertebral augmentation to treat cancer patients." This paper provides Level III evidence that older patients with NVFs undergoing vertebroplasty or kyphoplasty may have a better outcome compared to younger patients with NVFs.

In a retrospective study, Hirsch et al[2] evaluated 201 patients with malignant compression fractures who underwent at least one vertebral augmentation (vertebroplasty or kyphoplasty) procedure to identify variables that could influence outcomes. The authors concluded, "In patients who receive both external beam radiation therapy and vertebral augmentation, the sequence in which they are given does not affect pain improvement outcomes." The work group downgraded this potential Level III paper due to follow-up not being standardized and the diagnostic methods were not described. This paper provides Level IV evidence that in patients with neoplastic vertebral fractures, combination treatment of vertebral augmentation and external beam radiation therapy (EBRT) shows a trend towards positive response with advance age, that is not statistically significant.

References

1. Jha RM, Hirsch AE, Yoo AJ, Ozonoff A, Growney M, Hirsch JA. Palliation of compression fractures in cancer patients by vertebral augmentation: a retrospective analysis. *J Neurointerv Surg.* 2010;2(3):221-228. doi:10.1136/jnis.2010.002675
2. Hirsch AE, Jha RM, Yoo AJ, et al. The use of vertebral augmentation and external beam radiation therapy in the multimodal management of malignant vertebral compression fractures. *Pain Physician.* 2011;14(5):447-458. doi:10.36076/ppj.2011/14/447

Future Directions for Research

The work group recommends further high-quality studies to determine predictive factors that influence results of vertebral augmentation in patients with neoplastic vertebral fractures.

Interventional Treatment Question 4:

What is the risk of treating multiple vertebral levels at one time, for patients with multilevel neoplastic vertebral fractures?

Vertebral augmentation may be considered as a safe treatment of multilevel neoplastic vertebral fractures at one time.

Grade of Recommendation: C

In a retrospective case series study, La Maida et al[1] assessed the rate and type of cement leakage after vertebroplasty and kyphoplasty in 14 patients with multiple myeloma vertebral fractures. The authors concluded, "kyphoplasty procedure in these patients is slightly less risky but we suggest doing it with a monopedicular approach." The work group concluded that this paper provides Level IV evidence that multilevel augmentation has higher risk of cement leakage compared to single level in patients with NVF; however, those were asymptomatic.

In a retrospective case series study, Moulin et al[2] evaluated the "safety and efficacy of multilevel thoracolumbar vertebroplasty in the simultaneous treatment of >/=6 painful pathologic compression fractures." The authors concluded, "Multilevel vertebroplasty for >/=6 pathologic compression fractures is safe and provides significant palliative benefit when performed simultaneously." The work group concluded that this paper provides Level IV evidence that multilevel vertebroplasty is safe for treatment of neoplastic vertebral fractures with low incidence of complications.

References

1. La Maida GA, Giarratana LS, Acerbi A, Ferrari V, Mineo GV, Misaggi B. Cement leakage: safety of minimally invasive surgical techniques in the treatment of multiple myeloma vertebral lesions. *Eur Spine J.* 2012;21 Suppl 1(Suppl 1):S61-S68. doi:10.1007/s00586-012-2221-3
2. Moulin B, Tselikas L, Gravel G, et al. Safety and Efficacy of Multilevel Thoracolumbar Vertebroplasty in the Simultaneous Treatment of Six or More Pathologic Compression Fractures. *J Vasc Interv Radiol.* 2020;31(10):1683-1689.e1681.

Future Directions for Research

The work group recommends any future studies discussing cement leakage should specify symptomatic vs asymptomatic and should be stratified according to single vs multiple level and tumor type.

Interventional Treatment Question 5:

What is the incidence and risk factors for adjacent vertebral body fractures after vertebral augmentation for neoplastic vertebral fractures?

There is insufficient and conflicting evidence to make a recommendation for or against the incidence and risk factors for adjacent vertebral fractures after vertebral augmentation for neoplastic vertebral fractures.

Grade of Recommendation: I

In a retrospective case series study, Kircelli et al[1] investigated the clinical results of balloon kyphoplasty for the correction of vertebral deformity from metastatic vertebral compression fractures. The authors concluded that "Balloon kyphoplasty was an effective method to reduce pain, reduce disability, and improve quality of life by eliminating kyphotic deformity in pathological vertebral compression fractures due to vertebral metastases." This paper provides Level IV evidence that 15.2% of patients with neoplastic vertebral fractures undergoing balloon KP may develop a fracture at an adjacent level.

In a retrospective case series study, Tseng et al[2] assessed whether the pain that was induced by spine metastatic tumor was different in spinal metastatic patients before and after vertebroplasty. The authors concluded that "As a treatment option for patients with malignant destruction of the vertebral column, this minimal invasive technique is emerging as one of the most promising new interventional procedures for relieving (or reducing) pain and improving stability." This paper provides Level IV evidence that adjacent level fracture is an uncommon complication following VP for neoplastic vertebral fractures.

Recommendations were developed based on a specific definition, inclusion/exclusion criteria, and the resulting literature. This clinical guideline is not intended to be a fixed treatment protocol; it is anticipated that there will be patients who require more or less investigations or treatment than what is outlined. This clinical guideline should not be construed as including all proper methods of care or excluding other acceptable methods of care reasonably directed to obtaining the same results. The ultimate judgment regarding any specific procedure or treatment is to be made by the provider and patient in light of all circumstances presented by the patient and the needs and resources particular to the locality or institution.

References:
1. Kircelli A, Çöven I. Percutaneous Balloon Kyphoplasty Vertebral Augmentation for Compression Fracture Due to Vertebral Metastasis: A 12-Month Retrospective Clinical Study in 72 Patients. *Med Sci Monit.* 2018;24:2142-2148. doi:10.12659/msm.909169
2. Tseng YY, Yang ST, Tu PH, Yang TC, Lo YL. Minimally invasive vertebroplasty in the treatment of pain induced by spinal metastatic tumor. *Minim Invasive Neurosurg.* 2008;51(5):280-284. doi:10.1055/s-0028-1082328

Future Directions for Research
The work group recommends high-quality prospective and longitudinal studies to evaluate the incidence and risk factors for adjacent vertebral body fractures after vertebral augmentation for neoplastic vertebral fractures.

Interventional Treatment Question 6:
Does the addition of vertebral augmentation to radiation therapy improve outcomes in patients with neoplastic vertebral fractures?

There is insufficient evidence to make a recommendation for or against the addition of vertebral augmentation to radiation therapy as it relates to outcomes in adults with neoplastic vertebral fractures.

Grade of Recommendation: I

In a prospective case series study, Wardak et al1 aimed to determine neoplastic vertebral fracture pain response and prevention after single-fraction stereotactic ablative radiation therapy (SABR), done conjointly with immediate vertebroplasty, for spine metastases. The authors concluded that "The combined treatment approach was found to be safe and effective after refinement of the vertebroplasty technique." This paper provides Level IV evidence that the addition of prophylactic VP with spine SABR can improve pain response when compared to historical treatment with EBRT.

References
1. Wardak Z, Bl, R, et al. A Phase 2 Clinical Trial of SABR Followed by Immediate Vertebroplasty for Spine Metastases. *Int J Radiat Oncol Biol Phys.* 2019;104(1):83-89. doi:10.1016/j.ijrobp.2019.01.072

Future Directions for Research
The work group recommends high-quality comparative studies of vertebral augmentation alone to vertebral augmentation with radiation therapy to compare functional improvement and improvements in longevity.

Interventional Treatment Question 7:
Does the prophylactic use of vertebral augmentation reduce the risk of vertebral fracture after stereotactic radiotherapy for vertebral metastasis?

A systematic review of the literature yielded no studies to adequately address this question.

Future Directions for Research
The construction of this question does not provide for a good experimental study. Therefore, the work group does not have any recommendations for future research on this topic.

Interventional Treatment Question 8:
Does physical therapy after augmentation affect patient outcomes, including pain and function?

A systematic review of the literature yielded no studies to adequately address this question.

Future Directions for Research

The work group recommends high-quality studies exploring the role of physical therapy after augmentation in patients with neoplastic vertebral fractures.

Recommendations were developed based on a specific definition, inclusion/exclusion criteria, and the resulting literature. This clinical guideline is not intended to be a fixed treatment protocol; it is anticipated that there will be patients who require more or less investigations or treatment than what is outlined. This clinical guideline should not be construed as including all proper methods of care or excluding other acceptable methods of care reasonably directed to obtaining the same results. The ultimate judgment regarding any specific procedure or treatment is to be made by the provider and patient in light of all circumstances presented by the patient and the needs and resources particular to the locality or institution.

Surgical Treatment

Surgical Question 1:
Does surgical fixation with or without fusion improve outcomes in patients with neoplastic vertebral fractures compared to nonoperative care or interventional procedures?

A systematic review of the literature yielded no studies to adequately address this question.

Future Directions for Research

The work group recommends high-quality prospective studies identifying subgroups of patients with neoplastic vertebral fractures that would benefit from surgical intervention more than interventional or nonoperative treatments.

Surgical Question 2:
Does the use of minimally invasive surgical approaches (eg, percutaneous pedicle screws, muscle-sparing decompression/arthrodesis techniques) improve outcomes compared to open surgical approaches in patients undergoing surgery for neoplastic vertebral fractures?

A systematic review of the literature yielded no studies to adequately address this question.

Future Directions for Research

The work group recommends high-quality studies comparing differences in outcomes using minimally invasive vs. open surgical techniques in patients with neoplastic vertebral fractures.

Surgical Question 3:
In patients undergoing surgery for neoplastic vertebral fractures, are clinical and radiological outcomes affected by the types of implants used?

There is insufficient evidence to make a recommendation for or against the use of specific implants in adults undergoing surgery for neoplastic vertebral fractures.
Grade of Recommendation: I

In a retrospective comparative study, Bayram et al[1] compared outcomes of palliative posterior instrumentation as compared to corpectomy with cage reconstruction in patients with thoracolumbar pathological fractures. The authors concluded that palliative posterior instrumentation "can decompress the tumor for functional improvement and can stabilize the spinal structure to provide relief." The work group downgraded this potential Level III paper due to small sample size, less than 80% follow-up, diagnostic method not stated, and the choice of procedure was at the availability of a specific surgical team. This paper provides Level IV evidence that for adults with neoplastic vertebral fractures, either palliative posterior instrumentation or corpectomy with anterior cage reconstruction combined with posterior instrumentation provide similar pain relief and survival.

References
1. Bayram S, Akgül T, Altan M, et al. Palliative Posterior Instrumentation versus Corpectomy with Cage Reconstruction Treatment for Thoracolumbar Pathological Fracture. *Asian Spine J.* 2019;13(2):318-324. doi:10.31616/asj.2018.0153

Future Directions for Research

The work group recommends high-quality prospective studies comparing differences in outcomes with different spinal implant materials or instrumentation construct designs (eg, number of levels instrumented, with or without anterior column reconstruction, etc.) as well as different surgical approaches and techniques in patients undergoing surgery for neoplastic vertebral fractures.

Surgical Question 4:
In patients undergoing surgery for neoplastic vertebral fractures, are clinical and radiological outcomes affected by the use of vertebral augmentation of the implants, of the fractured vertebral body, or of adjacent levels?

A systematic review of the literature yielded no studies to adequately address this question.

Future Directions for Research

The work group recommends high-quality prospective studies comparing differences in outcomes with and without the incorporation of augmentation techniques during surgical procedures in patients with neoplastic vertebral fractures.

Recommendations were developed based on a specific definition, inclusion/exclusion criteria, and the resulting literature. This clinical guideline is not intended to be a fixed treatment protocol; it is anticipated that there will be patients who require more or less investigations or treatment than what is outlined. This clinical guideline should not be construed as including all proper methods of care or excluding other acceptable methods of care reasonably directed to obtaining the same results. The ultimate judgment regarding any specific procedure or treatment is to be made by the provider and patient in light of all circumstances presented by the patient and the needs and resources particular to the locality or institution.

Appendices

Appendix A. Protocol for NASS Literature Searches

One of the most crucial elements of evidence analysis, to support the development of recommendations for appropriate clinical care or use of new technologies, is the comprehensive literature search. Thorough assessment of the literature is the basis for the review of existing evidence, which will be instrumental to these activities.

Background

Since the quality of a literature search directly affects the quality of recommendations made NASS adheres to a protocol to ensure that all NASS searches are conducted consistently to yield the most comprehensive results

Protocol for NASS Literature Searches

When it is determined that a literature search is needed, NASS research staff will work with the requesting parties and our contracted medical librarian to run a comprehensive search employing at a minimum the following search techniques:

1. A preliminary search of the evidence will be conducted using the following clearly defined search parameters (as determined by the content experts). In addition to the project goal and clinical question(s) of interest, the following parameters are to be provided to research staff to facilitate this systematic literature search:
   - Time frames for search;
   - Foreign and/or English language;
   - Order of results (chronological, by journal, etc.);
   - Key search terms and connectors, with or without MeSH terms to be employed;
   - Age range;

   Must answer the following questions:
   - Should duplicates be eliminated between searches?
   - Should searches be separated by term or as one large package?
   - Should human studies, animal studies or cadaver studies be included?

   This preliminary search should encompass a search of the Cochrane database when access is available.
2. Search results with abstracts will be compiled by the medical librarian in both Endnote software and a PubMed account, whenever possible. The medical librarian typically responds to requests and completes the searches within 2-5 business days. Results will be forwarded to the Research staff, who will share it with the appropriate NASS staff member or requesting party(ies). (Research staff has access to Endnote software and will maintain a database of search results for future use/documentation.)
3. NASS staff shares the search results with an appropriate content expert (NASS Committee member or other) to assess relevance of articles and identify appropriate articles to review and on which to run a "related articles" search.
4. Based on content expert's review, NASS Research staff will then coordinate with the medical librarian the second level searching to identify relevant "related articles."
5. The medical librarian will forward results to Research staff to again share with appropriate NASS staff member.
6. NASS staff shares related articles search results with an appropriate content expert (NASS Committee member or other) to assess relevance of this second set of articles, and identify appropriate articles to review and on which to run a second "related articles" search.
7. NASS Research staff will work with the medical librarian to obtain the 2nd related articles search results and any necessary full-text articles for review.
8. NASS members reviewing full-text articles should also review the references at the end of each article to identify additional articles which should be reviewed, but may have been missed in the search.

Protocol for Expedited Searches

Numbers 1, 2 and 3 should minimally be followed for any necessary expedited search. Following #3, depending on the time frame allowed, deeper searching may be conducted as described by the full protocol or request of full-text articles may occur. If full-text articles are requested, #8 should also be included. Use of the expedited protocol or any deviation from the full protocol should be documented with explanation.

Following these protocols will help ensure that NASS recommendations are (1) based on a thorough review of relevant literature; (2) are truly based on a uniform, comprehensive search strategy; and (3) represent the current best research evidence available. Research staff will maintain a search history in Endnote, for future use or reference.