USE OF IMAGING PRIOR TO REFERRAL TO A MUSCULOSKELETAL ONCOLOGIST

SYSTEMATIC LITERATURE REVIEW

Adopted by the Musculoskeletal Tumor Society
February 2018

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Disclaimer

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

Disclosure Requirement
In accordance with MSTS policy, all individuals whose names appear as authors or contributors to Systematic literature review filed a disclosure statement as part of the submission process. All panel members provided full disclosure of potential conflicts of interest prior to voting on the recommendations contained within this Systematic literature reviews.

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

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I. SUMMARY OF RECOMMENDATIONS

The following is a summary of the recommendations of the MSTS systematic literature review on the Use of Imaging Prior To Referral to a Musculoskeletal Oncologist. All readers of this summary are strongly urged to consult the full guideline and evidence report for this information. We are confident that those who read the full guideline and evidence report will see that the recommendations were developed using systematic evidence-based processes designed to combat bias, enhance transparency, and promote reproducibility.

This summary of recommendations is not intended to stand alone. Treatment decisions should be made in light of all circumstances presented by the patient. Treatments and procedures applicable to the individual patient rely on mutual communication between patient, physician, and other healthcare practitioners.

Strength of Recommendation Descriptions

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

PLAIN RADIOGRAPHS

A. Moderate evidence supports using conventional radiographs in the initial evaluation of a bone tumor of unknown etiology.

Strength of Recommendation: Moderate 

Description: Evidence from two or more "Moderate" strength studies with consistent findings, or evidence from a single "High" quality study for recommending for or against the intervention.

B. In the absence of reliable evidence, it is the opinion of the work group that conventional radiographs are a reasonable diagnostic test and may be considered during the initial evaluation of a soft tissue tumor.

Strength of Recommendation: Consensus 

Description: There is no supporting evidence. In the absence of reliable evidence, the work group is making a recommendation based on their clinical opinion.

MRI: USE OF CONTRAST

A. Strong evidence supports that contrast enhancement on MRI can assist in determining if a soft tissue tumor is benign or malignant.

Strength of Recommendation: Strong 

Description: Evidence from two or more "High" strength studies with consistent findings for recommending for or against the intervention.

B. Strong evidence supports that a heterogenous signal in a contrast-enhanced MRI can assist in determining if a soft tissue tumor is benign or malignant.

Strength of Recommendation: Strong 

Description: Evidence from two or more "High" strength studies with consistent findings for recommending for or against the intervention.

C. In the absence of reliable evidence, it is the opinion of the work group that IV contrast does not offer any advantages for detecting tumor presence over a non-contrast study.

Strength of Recommendation: Consensus 

Description: There is no supporting evidence. In the absence of reliable evidence, the work group is making a recommendation based on their clinical opinion.

MRI: MAGNET STRENGTH

In the absence of reliable evidence, it is the opinion of the work group that a magnet of at least 1.5 Tesla should be used when imaging musculoskeletal neoplasms.

Strength of Recommendation: Consensus 

Description: There is no supporting evidence. In the absence of reliable evidence, the work group is making a recommendation based on their clinical opinion.

MRI AND CT SCANS: AREA TO VISUALIZE

A. In the absence of reliable evidence, it is the opinion of the work group that MRI or CT scans performed to visualize a potentially malignant bone tumor should include a detailed assessment of the tumor and surrounding soft tissue, with additional sequences that visualize the entire bone compartment, from the proximal joint to the distal joint.

Strength of Recommendation: Consensus 

Description: There is no supporting evidence. In the absence of reliable evidence, the work group is making a recommendation based on their clinical opinion.

B. In the absence of reliable evidence, it is the opinion of the work group that MRI or CT scans performed to visualize a soft tissue tumor should include a detailed assessment of the tumor and surrounding soft tissue, including complete visualization of enhancement along fascial planes and peritumoral edema.

Strength of Recommendation: Consensus 

Description: There is no supporting evidence. In the absence of reliable evidence, the work group is making a recommendation based on their clinical opinion.

CT SCANS: STAGING

A. In the absence of reliable evidence, it is the opinion of the work group that CT chest/abdomen/pelvis scans performed in patients with a destructive bone lesion highly suspicious for metastatic disease of bone should use oral and IV contrast.

Strength of Recommendation: Consensus 

Description: There is no supporting evidence. In the absence of reliable evidence, the work group is making a recommendation based on their clinical opinion.

B. In the absence of reliable evidence, it is the opinion of the work group that staging CT scans in the setting of a destructive bone lesion should be ordered by, or in consultation with, an oncology specialist.

Strength of Recommendation: Consensus 

Description: There is no supporting evidence. In the absence of reliable evidence, the work group is making a recommendation based on their clinical opinion.

CT SCANS: PRIOR CHEST RADIOGRAPH

In the absence of reliable evidence, it is the opinion of the work group that it is not necessary to perform a chest radiograph prior to a chest CT in the staging of a bone or soft tissue malignancy.

Strength of Recommendation: Consensus 

Description: There is no supporting evidence. In the absence of reliable evidence, the work group is making a recommendation based on their clinical opinion.

ULTRASOUND

A. Moderate evidence supports that ultrasound helps to distinguish benign from malignant soft tissue tumors.

Strength of Recommendation: Moderate 

Description: Evidence from two or more "Moderate" strength studies with consistent findings, or evidence from a single "High" quality study for recommending for or against the intervention.

B. In the absence of reliable evidence, it is the opinion of the work group that ultrasounds in small (<5 cm), superficial soft tissues tumors can help distinguish between benign lipomas, vascular malformations, cystic structures, and solid tumors that require further characterization.

Strength of Recommendation: Consensus 

Description: There is no supporting evidence. In the absence of reliable evidence, the work group is making a recommendation based on their clinical opinion.

C. In the absence of reliable evidence, it is the opinion of the work group that ultrasounds in large (>5 cm), deep soft tissues tumors are unlikely to adequately assess the benign or malignant nature of the lesion and should not be the imaging modality of choice.

Strength of Recommendation: Consensus 

Description: There is no supporting evidence. In the absence of reliable evidence, the work group is making a recommendation based on their clinical opinion.

HISTORY OF PAIN

A. Moderate evidence supports that both radiographs and MRI have weak sensitivity in determining malignancy but moderate to strong specificity in determining benignity of bone tumors in patients reporting pain.

Strength of Recommendation: Moderate 

Description: Evidence from two or more "Moderate" strength studies with consistent findings, or evidence from a single "High" quality study for recommending for or against the intervention.

B. Limited evidence supports that a Tc99 bone scan may assist with obtaining a diagnosis or planning further diagnostic studies or treatment in patients with a bone tumor of unknown etiology and pain in the area of the tumor.

Strength of Recommendation: Limited 

*Description: Evidence from two or more "Low" strength studies with consistent findings **or** evidence from a single study for recommending for or against the intervention or diagnostic test or the evidence is insufficient or conflicting and does not allow a recommendation for or against the intervention.*

C. In the absence of reliable evidence, it is the opinion of this work group that an MRI of a bone or soft-tissue tumor of unknown etiology should be considered, and is the preferred advanced imaging study, in patients with a complaint of pain at the site of the identified tumor.

Strength of Recommendation: Consensus 

Description: There is no supporting evidence. In the absence of reliable evidence, the work group is making a recommendation based on their clinical opinion.

D. In the absence of reliable evidence, it is the opinion of this work group that contrast-enhanced CT scan of the site should be considered in patients with pain at the site of a bone or soft tissue mass when there are patient specific contraindications to MRI, such as a pacemaker or cerebral aneurysm clips.

Strength of Recommendation: Consensus 

Description: There is no supporting evidence. In the absence of reliable evidence, the work group is making a recommendation based on their clinical opinion.

E. In the absence of reliable evidence, it is the opinion of this work group that, in the setting of a bone or soft-tissue tumor of unknown etiology with a complaint of pain at the site of the identified but undiagnosed tumor, CT of the chest/abdomen/pelvis, PET-CT, and Tc99 bone scan may assist with the diagnostic workup but should be utilized at the discretion of the treating oncologic specialists.

Strength of Recommendation: Consensus 

Description: There is no supporting evidence. In the absence of reliable evidence, the work group is making a recommendation based on their clinical opinion.

HISTORY OF GROWTH

A. Moderate strength evidence supports that, in patients suspected of soft tissue tumor recurrence, an MRI of the tumor site can reliably identify neoplastic tissue and differentiate between solid and cystic areas.

Strength of Recommendation: Moderate 

Description: Evidence from two or more "Moderate" strength studies with consistent findings, or evidence from a single "High" quality study for recommending for or against the intervention.

B. In the absence of reliable evidence, it is the opinion of this work group that an MRI should be considered, and is the preferred advanced imaging study, in patients with a clear history of rapid growth of a bone or soft tissue mass.

Strength of Recommendation: Consensus 

Description: There is no supporting evidence. In the absence of reliable evidence, the work group is making a recommendation based on their clinical opinion.

C. In the absence of reliable evidence, it is the opinion of this work group that contrast-enhanced CT scan of the site should be considered in patients with a clear history of rapid growth of a bone or soft tissue mass when there are patient specific contraindications to MRI, such as a pacemaker or cerebral aneurysm clips.

Strength of Recommendation: Consensus 

Description: There is no supporting evidence. In the absence of reliable evidence, the work group is making a recommendation based on their clinical opinion.

D. In the absence of reliable evidence, it is the opinion of this work group that, in the setting of a bone or soft-tissue tumor of unknown etiology with rapid growth, CT of the chest/abdomen/pelvis, PET-CT, and Tc99 bone scan may assist with the diagnostic workup but should be utilized at the discretion of the treating oncologic specialists.

Strength of Recommendation: Consensus 

Description: There is no supporting evidence. In the absence of reliable evidence, the work group is making a recommendation based on their clinical opinion.

TUMOR SIZE

A. Strong evidence supports the use of MRI imaging for a bone or soft tissue tumor of unknown etiology with a size greater than 5 cm to assist with obtaining a diagnosis and planning further treatment.

Strength of Recommendation: Strong 

Description: Evidence from two or more "High" strength studies with consistent findings for recommending for or against the intervention.

B. In the absence of reliable evidence, the work group recommends that, in aggressive appearing bone or soft tissue tumors, advanced imaging studies be requested with the guidance of an orthopedic oncologist or musculoskeletal radiologist.

Strength of Recommendation: Consensus 

Description: There is no supporting evidence. In the absence of reliable evidence, the work group is making a recommendation based on their clinical opinion.

CORTICAL IRREGULARITY/PERIOSTEAL REACTION

Moderate evidence supports the use of an MRI scan (or CT if MRI is not available) for evaluation of cortical irregularity or periosteal reaction in patients with a potentially malignant bone tumor.

Strength of Recommendation: Moderate 

Description: Evidence from two or more "Moderate" strength studies with consistent findings, or evidence from a single "High" quality study for recommending for or against the intervention.

TUMOR INTERFACE

Moderate evidence suggests that characterizing the tumor interface (borders and zone of transition) on MRI and CT may assist with obtaining a diagnosis or planning further diagnostic studies or treatment for bone or soft tissue tumor of unknown etiology.

Strength of Recommendation: Moderate 

Description: Evidence from two or more "Moderate" strength studies with consistent findings, or evidence from a single "High" quality study for recommending for or against the intervention.

II. **INTRODUCTION**

OVERVIEW

This systematic literature review is based on a systematic review of peer-reviewed clinical manuscripts discussing various facets of musculoskeletal tumor imaging. In questions of clinical importance, but relevant publications of less than rigorous methodology available to review, we accepted lesser quality investigations or utilized expert consensus to create reasonable and pragmatic recommendations. In addition to providing guidance for practical decision-making during the initial evaluation of musculoskeletal tumors, our intention was also to highlight areas where additional research would be valuable.

This guideline is intended for all medical practitioners who are involved in the evaluation of bone and soft tissue lesions of unknown etiology. The information herein will offer evidence-based suggestions to practitioners making real clinical decisions for the use of imaging studies prior to specialty referral. Specialized cancer providers may also find this information useful and will assist in creating a unified approach to trainee and non-specialized provider education and patient management. This is not an exhaustive set of recommendations and there are undoubtedly clinical scenarios that will require specialty consultation to ensure optimal care. Ultimately, this document is to provide guidance, but the final decisions should be made in the context of patient engagement, prior experience, expert consultation, and awareness of local resources.

GOALS AND RATIONALE

The intention of this effort was to produce a vetted and thoughtful document that would provide guidance regarding imaging options and delivery in musculoskeletal tumors of unknown biological significance. The goal is not to diminish the use of advanced imaging techniques and modalities, but rather to propose a clinically meaningful approach to ensure that the correct studies are done for appropriate indications. Although diminishing the use of costly and unnecessary imaging is an intended consequence of this project, these guidelines will also provide support for the expeditious use of advanced imaging modalities when clinically indicated.

Three prior prospective reports (Aboulafia, 2012, Miller, 2015, Nystrom, 2015) have indicated an excessive amount of inappropriate utilization of advanced imaging techniques in bone and soft tissue tumors. These investigations demonstrated that many of the choices regarding musculoskeletal imaging are made prior to referral to cancer specialists. A number of specialties, such as general surgery, primary care, pediatrics, and surgical subspecialties, show a similar trend of imaging use to orthopaedic surgeons. Therefore, the Evidence Based Medicine Committee of the Musculoskeletal Tumor Society recognized this issue as one that would benefit from a systematic literature review to help minimize unnecessary imaging and clarify indications for advanced studies that expedite referral, evaluation, diagnosis, and treatment of musculoskeletal tumors.

INTENDED USERS

This guideline may be of benefit to specialized cancer providers, practitioners in any field involved in the initial evaluation of bone and soft tissue tumors, and third parties interested in evidence based treatment decisions on this issue. For cancer providers, this document can provide an overview of the current knowledge, which can be used for information dissemination in educational opportunities for trainees and referring providers. In addition, the "Future Research" sections can provide ideas for novel investigations to help clarify or answer currently unknown questions addressed in this manuscript. Third party interests, such as insurance payers, policy makers, and governmental organizations, may find the analysis useful as a summary of current knowledge and source of clinical indications for imaging of musculoskeletal neoplasia.

Primarily, this work is intended to assist first-line providers, such as family practice physicians, orthopaedic surgeons, general surgeons, pediatricians, physician assistants, nurse practitioners, nurses, and anyone else who may encounter patients in the initial evaluation of a potential bone or soft tissue tumor. The concern for a potential malignancy is understandably stressful both for the patient and healthcare provider, and some guidance on appropriate early management, in particular ensuring that imaging is not over or underutilized, is needed.

PATIENT POPULATION

This report is relevant to the initial evaluation of any patient with a bone or soft tissue tumor of unknown etiology and biological significance regardless of age, sex, race, ethnicity, education, and socioeconomic status.

BURDEN OF DISEASE

Sarcoma, the principal primary malignancy of the musculoskeletal system, is a rare tumor accounting for 1% of all new cancer diagnoses. The American Cancer Society estimates that 12,390 soft tissue sarcomas and 3,260 bone sarcomas will be diagnosed in the United States in 2017. The American Academy of Orthopaedic Surgeons estimates that 50% of the 1.2 million new cases of cancer diagnosed each year, most notably the many subtypes of carcinoma, eventually metastasize to bone. Extrapolating data from prior reports, orthopaedic oncologists evaluate benign diagnosis in outpatient clinics at least 3 times more frequently than malignancies. The number of benign lipomas, incidental bone lesions, and other clearly indolent conditions that are evaluated by a medical practitioner but never referred to a specialty cancer service has not been estimated but is likely not an infrequent event. In summary, although sarcoma is a rare cancer, the clinical problem of determining the underlying etiology and significance of a bone or soft tissue lesion is not at all uncommon, and this is a topic that a majority of practitioners will be confronted with in daily practice.

EMOTIONAL AND PHYSICAL IMPACT

The emotional impact of a potential cancer diagnosis is clear and apparent to healthcare providers, patients, friends, and family members. There is an intangible benefit to accurately diagnosing both benign and malignant conditions quickly and accurately. For benign conditions, the clinical goal is to confirm the indolent nature of the process as soon and as minimally invasive as possible so that the patient can be reassured. For more aggressive conditions that

require an extensive work-up and multidisciplinary care, accurate recognition of a potential malignancy is dependent on obtaining appropriate confirmatory imaging tests and expediting referrals to tertiary sarcoma centers. By providing guidance as to the appropriate imaging modalities for many common clinical scenarios, this document has the potential to assist in correctly reassuring patients when the history, examination, and imaging is not concerning, and support assertive use of resources in situations where they are clinically necessary.

POTENTIAL BENEFITS, HARMS, AND CONTRAINDICATIONS

This document potentially benefits providers, patients, and third parties. To providers, it can give some guidance in managing a difficult and potentially high-risk condition. For patients, it can assist in minimizing unnecessary or costly imaging, and ensure that conditions that warrant a more assertive diagnostic strategy are recognized with mitigation of potential barriers. For payers and policy makers, it can provide a summary of the current state of evidence and expert opinion on this topic.

One potential risk is that the defined criteria may not capture the minutiae of each individual presentation of musculoskeletal neoplasia. Practitioners must take many factors into account, and these guidelines only address specific features that one may obtain from a history, physical examination, and basic radiographic studies. There may be other factors, such as personal history of cancer, environmental risk factors, or genetic predispositions that would influence the likelihood of a malignancy. If there is any concern, discussion with an orthopaedic oncologist or other cancer specialist is warranted and advised.

Many of the recommendations discuss imaging modalities that may have some small inherent risk due to contrast exposure or medical radiation. These are noted where appropriate. In addition, there may be other unique risks depending on the particular imaging modalities and specific patient comorbidities or prior procedures. These should be considered and discussed prior to performing any imaging study.

FUTURE RESEARCH

Each recommendation also includes a section for future research. This is not an exhaustive list, but rather a description of an area in need of further study to address a void in the available literature or expand on a clinically important topic.

III. METHODS

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

This systematic literature review and the systematic review upon which it is based evaluate the effectiveness of imaging prior to referral to a musculoskeletal oncologist. This section describes the methods used to prepare this guideline and systematic review, including search strategies used to identify literature, criteria for selecting eligible articles, determining the strength of the evidence, data extraction, methods of statistical analysis, and the review and approval of the guideline. The MSTS approach incorporates practicing physicians (clinical experts) and methodologists who are free of potential conflicts of interest as recommended by guideline development experts.[M10]

The MSTS understands that only high-quality guidelines are credible, and we go to great lengths to ensure the integrity of our evidence analyses. The MSTS addresses bias beginning with the selection of guideline development group members. Applicants with financial conflicts of interest (COI) related to the guideline topic cannot participate if the conflict occurred within one year of the start date of the guideline's development or if an immediate family member has, or has had, a relevant financial conflict. Additionally, all guideline development group members sign an attestation form agreeing to remain free of relevant financial conflicts for two years following the publication of the guideline.

This guideline and systematic review were prepared by the MSTS Use of Imaging Prior To Referral to a Musculoskeletal Oncologist physician guideline development group (clinical experts) with the assistance of the MSTS Evidence-Based Medicine (EBM) Unit in the Department of Research and Scientific Affairs (methodologists) at the MSTS. To develop this guideline, the guideline development group held an introductory webinar on April 6, 2016 to establish the scope of the guideline and the systematic reviews. As the physician experts, the guideline development group defined the scope of the guideline by creating PICO Questions (i.e. population, intervention, comparison, and outcome) that directed the literature search. When necessary, these clinical experts also provided content help, search terms and additional clarification for the MSTS Medical Librarian. The Medical Librarian created and executed the search(s). The supporting group of methodologists (MSTS EBM Unit) reviewed all abstracts, recalled pertinent full-text articles for review and evaluated the quality of studies meeting the inclusion criteria. They also abstracted, analyzed, interpreted, and/or summarized the relevant evidence for each recommendation and prepared the initial draft for the final meeting. Upon completion of the systematic reviews, the physician guideline development group participated in a four conference calls held on April 25, 2017, May 2, 2017, May 24, 2017, and June 7, 2017. During these calls, the physician experts and methodologists evaluated and integrated all material to develop the final recommendations. The final recommendations and rationales were edited, written and voted on the last call. The draft guideline recommendations and rationales received final review by the methodologists to ensure that these recommendations and rationales were consistent with the data. The draft was then completed and submitted for peer review on <DATE>.

The resulting draft guidelines were then peer-reviewed, edited in response to that review and subsequently sent for public commentary, where after additional edits were made. Thereafter, the draft guideline was sequentially approved by the MSTS Committee on Evidence-Based Medicine and the MSTS Executive Committee (see Appendix II for a description of the MSTS bodies involved in the approval process). All MSTS guidelines are reviewed and updated or retired every five years in accordance with the criteria of the National Guideline Clearinghouse.

The process of MSTS guideline development incorporates the benefits from clinical physician expertise as well as the statistical knowledge and interpretation of non-conflicted methodologists. The process also includes an extensive review process offering the opportunity for a multitude of clinical physician experts to provide input into the draft prior to publication. This process provides a sound basis for minimizing bias, enhancing transparency and ensuring the highest level of accuracy for interpretation of the evidence.

FORMULATING PICO QUESTIONS

The guideline development group began work on this guideline by constructing a set of PICO questions. These questions specify the patient population of interest (P), the intervention of interest (I), the comparisons of interest (C), and the patient-oriented outcomes of interest (O). They function as questions for the systematic review, not as final recommendations or conclusions. A full list of the original PICO questions developed for this guideline can be found in Appendix III. Once established, these *a priori* PICO questions cannot be modified until the final guideline development group meeting.

STUDY SELECTION CRITERIA

We developed *a priori* article inclusion criteria for our review. These criteria are our "rules of evidence" and articles that did not meet them are, for the purposes of this guideline, not evidence.

To be included in this systematic literature review, an article had to meet the following criteria:

- Article must be a full article report of a clinical study (studies using registry data can be included in a guideline/systematic review if it is published in a peer-reviewed journal and meets all other inclusion criteria/quality standards).
- **Retrospective non-comparative case series will be evaluated as very low-quality data**
- Medical records review, meeting abstracts, historical articles, editorials, letters, and commentaries are ***excluded***.
- Confounded studies (i.e. studies that give patients the treatment of interest AND another treatment) are ***excluded***.
- **Case series studies that have non-consecutive enrollment of patients will be evaluated as very low-quality data.**
- Controlled trials in which patients were not stochastically assigned to groups AND in which there was either a difference in patient characteristics or outcomes at baseline AND where the authors did not statistically adjust for these differences when analyzing the results are ***excluded***.
- Composite measures or outcomes are ***excluded*** even if they are patient-oriented.
- Study must appear in a peer-reviewed publication

- For any included study that uses “paper-and-pencil” outcome measures (e.g., SF-36), only those outcome measures that have been validated will be included
- For any given follow-up time point in any included study, there must be ≥ 50% patient follow-up (if the follow-up is >50% but <80%, the study quality will be downgraded by one Level)
- Study must be of humans
- Study must be published in English
- Study results must be quantitatively presented
- Study must not be an in vitro study
- Study must not be a biomechanical study
- Study must not have been performed on cadavers

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

We did not include systematic reviews or meta-analyses compiled by others or guidelines developed by other organizations. These documents are developed using different inclusion criteria than those specified by the MSTS guideline development group. Therefore, they may include studies that do not meet our inclusion criteria. We recalled these documents, if the abstract suggested they might provide an answer to one of our recommendations and searched their bibliographies for additional studies to supplement our systematic review.

BEST EVIDENCE SYNTHESIS

We included only the best available evidence for any given outcome addressing a recommendation. Accordingly, we first included the highest quality evidence for any given outcome if it was available. In the absence of two or more occurrences of an outcome at this quality, we considered outcomes of the next lowest quality until at least two or more occurrences of an outcome had been acquired. For example, if there were two ‘moderate’ quality occurrences of an outcome that addressed a recommendation, we did not include ‘low’ quality occurrences of this outcome. A summary of the evidence that met the inclusion criteria, but was not best available evidence was created and can be viewed by recommendation in Appendix XII.

MINIMALLY CLINICALLY IMPORTANT IMPROVEMENT

Wherever possible, we consider the effects of treatments in terms of the minimally clinically important difference (MCII) in addition to whether their effects are statistically significant. The MCI is the smallest clinical change that is important to patients, and recognizes the fact that there are some treatment-induced statistically significant improvements that are too small to matter to patients. However, there were no occurrences of validated MCID outcomes in the studies included in this systematic literature review.

When MCID values from the specific guideline patient population are not available, we use the following measures listed in order of priority:

1) MCID/MID
2) PASS or Impact
3) Another validated measure
4) Statistical Significance

LITERATURE SEARCHES

We begin the systematic review with a comprehensive search of the literature. Articles we consider were published prior to February 2, 2017 in four electronic databases; PubMed, EMBASE, CINAHL, and The Cochrane Central Register of Controlled Trials. The medical librarian conducts the search using key terms determined from the guideline development group's preliminary recommendations.

We supplement the electronic search with a manual search of the bibliographies of all retrieved publications, recent systematic reviews, and other review articles for potentially relevant citations. Recalled articles are evaluated for possible inclusion based on the study selection criteria and are summarized for the guideline development group who assist with reconciling possible errors and omissions.

The study attrition diagram in Appendix IV provides a detailed description of the numbers of identified abstracts and recalled and selected studies that were evaluated in the systematic review of this guideline. The search strategies used to identify the abstracts are contained in Appendix V.

METHODS FOR EVALUATING EVIDENCE

As noted earlier, we judge quality based on *a priori* PICO questions and use an automated numerical scoring process to arrive at final ratings. Extensive measures are taken to determine quality ratings so that they are free of bias.

We evaluate the quality of evidence separately for each study using modified versions of the GRADE and QUADAS instruments. Depending on the type of study (i.e. diagnostic, prognostic, randomized control trial, or observational) the study design is evaluated using a list of standardized questions (see below for the domains evaluated for each type of study design).

DIAGNOSTIC STUDY QUALITY APPRAISAL QUESTIONS

The following questions are used to evaluate the study quality of diagnostic study designs.

1. Was the patient spectrum representative of the patients who will receive the test in practice?
2. Were the selection criteria clearly described?
3. Was the execution of the index and reference tests described in sufficient detail to permit its replication?
4. Is the reference standard likely to correctly classify the target condition?
5. Are the index test(s) results interpreted by an examiner without the knowledge of the reference tests results (or vice versa)?
6. Other Bias?

Diagnostic Study Design Quality Key

High Quality Study	<1 Flaw
Moderate Quality Study	≥1 and <2 Flaws
Low Quality Study	≥2 and <3 Flaws
Very Low Quality Study	≥3 Flaws

PROGNOSTIC STUDY QUALITY APPRAISAL QUESTIONS

The following questions are used to evaluate the study quality of prognostic study designs.

1. Was the spectrum of patients studied for this prognostic variable representative of the patient spectrum seen in actual clinical practice?
2. Was loss to follow up unrelated to key characteristics?
3. Was the prognostic factor of interest adequately measured in the study to limit potential bias?
4. Was the outcome of interest adequately measured in study participants to sufficiently limit bias?
5. Were all important confounders adequately measured in study participants to sufficiently limit potential bias?
6. Was the statistical analysis appropriate for the design of the study, limiting potential for presentation of invalid results?

Prognostic Study Design Quality Key

High Quality Study	<1 Flaw
Moderate Quality Study	≥1 and <2 Flaws
Low Quality Study	≥2 and <3 Flaws
Very Low Quality Study	≥3 Flaws

RANDOMIZED STUDY QUALITY APPRAISAL QUESTIONS

The following domains are evaluated to determine the study quality of randomized study designs.

1. Random Sequence Generation
2. Allocation Concealment
3. Blinding of Participants and Personnel
4. Incomplete Outcome Data
5. Selective Reporting
6. Other Bias

Upgrading Randomized Study Quality Questions

1. Is there a large magnitude of effect?
2. Influence of All Plausible Residual Confounding
3. Dose-Response Gradient

Randomized Study Design Quality Key

High Quality Study	<2 Flaw
Moderate Quality Study	≥2 and <4 Flaws
Low Quality Study	≥4 and <6 Flaws
Very Low Quality Study	≥6 Flaws

OBSERVATIONAL STUDY DESIGN QUALITY APPRAISAL QUESTIONS

The following questions are used to evaluate the study quality of observational study designs. Note that all observation studies begin the appraisal process at "low quality" due to design flaws inherent in observational studies.

1. Is this observational study a prospective case series?
2. Does the strategy for recruiting participants into the study differ across groups?
3. Did the study fail to balance the allocation between the groups or match groups (e.g., through stratification, matching, propensity scores)?
4. Were important confounding variables not taken into account in the design and/or analysis (e.g., through matching, stratification, interaction terms, multivariate analysis, or other statistical adjustment such as instrumental variables)?
5. Was the length of follow-up different across study groups?
6. Other Bias?

Upgrading Observational Study Quality Questions

1. Is there a large magnitude of effect?
2. Influence of All Plausible Residual Confounding
3. Dose-Response Gradient

Observational Study Design Quality Key

High Quality Study	<2 Flaw
Moderate Quality Study	≥2 and <4 Flaws
Low Quality Study	≥4 and <6 Flaws
Very Low Quality Study	≥6 Flaws

DEFINING THE STRENGTH OF THE RECOMMENDATIONS

Judging the strength of evidence is only a stepping stone towards arriving at the strength of a guideline recommendation. The strength of recommendation also takes into account the quality, quantity, and the trade-off between the benefits and harms of a treatment, the magnitude of a treatment's effect, and whether there is data on critical outcomes.

Strength of recommendation expresses the degree of confidence one can have in a recommendation. As such, the strength expresses how possible it is that a recommendation will

be overturned by future evidence. It is very difficult for future evidence to overturn a recommendation that is based on many high quality randomized controlled trials that show a large effect. It is much more likely that future evidence will overturn recommendations derived from a few small case series. Consequently, recommendations based on the former kind of evidence are given a high strength of recommendation and recommendations based on the latter kind of evidence are given a low strength.

To develop the strength of a recommendation, MSTS staff first assigned a preliminary strength for each recommendation that took only the final strength of evidence (including quality and applicability) and the quantity of evidence (see below).

Strength of Recommendation Descriptions

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

WORDING OF THE FINAL RECOMMENDATIONS

To prevent bias in the way recommendations are worded, the MSTS uses specific predetermined language stems that are governed by the evidence strengths. Each recommendation was written using language that accounts for the final strength of the recommendation. This language, and the corresponding strength, is shown in Table 9.

MSTS Guideline Language Stems

Guideline Language	Strength of Recommendation
Strong evidence supports that the practitioner should/should not do X, because…	Strong
Moderate evidence supports that the practitioner could/could not do X, because…	Moderate
Limited evidence supports that the practitioner might/might not do X, because…	Limited
In the absence of reliable evidence, it is the ***opinion*** of this guideline development group that…*	Consensus*

**Consensus based recommendations are made according to specific criteria. These criteria can be found in Appendix VII.*

APPLYING THE RECOMMENDATIONS TO CLINICAL PRACTICE

To increase the practicality and applicability of the guideline recommendations in this document, the information listed in Table 10 provides assistance in interpreting the correlation between the strength of a recommendation and patient counseling time, use of decision aids, and the impact of future research

Clinical Applicability: Interpreting the Strength of a Recommendation

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

VOTING ON THE RECOMMENDATIONS

The recommendations and their strength were voted on by the guideline development group members during the final meeting. If disagreement between the guideline development group occurred, there was further discussion to see whether the disagreement(s) could be resolved. Recommendations were approved and adopted in instance where a simple majority (>51%) of the guideline development group voted to approve.

STATISTICAL METHODS

ANALYSIS OF DIAGNOSTIC DATA

Likelihood ratios, sensitivity, specificity and 95% confidence intervals were calculated to determine the accuracy of diagnostic modalities based on two by two diagnostic contingency tables extracted from the included studies. When summary values of sensitivity, specificity, or other diagnostic performance measures were reported, estimates of the diagnostic contingency table were used to calculate likelihood ratios.

Likelihood ratios (LR) indicate the magnitude of the change in probability of disease due to a given test result. For example, a positive likelihood ratio of 10 indicates that a positive test result is 10 times more common in patients with disease than in patients without disease. Likelihood ratios are interpreted according to previously published values, as seen in Table below.

Interpreting Likelihood Ratios

Positive Likelihood Ratio	Negative Likelihood Ratio	Interpretation
>10	<0.1	Large and conclusive change in probability
5-10	0.1-0.2	Moderate change in probability
2-5	0.2-0.5	Small (but sometimes important change in probability)
1-2	0.5-1	Small (and rarely important) change in probability

ANALYSIS OF INTERVENTION/PREVENTION DATA

When possible, we recalculate the results reported in individual studies and compile them to answer the recommendations. The results of all statistical analysis conducted by the MSTS systematic literature reviews Unit are conducted using SAS 9.4. SAS was used to determine the magnitude, direction, and/or 95% confidence intervals of the treatment effect. For data reported as means (and associated measures of dispersion) the mean difference between groups and the 95% confidence interval was calculated and a two-tailed t-test of independent groups was used to determine statistical significance. When published studies report measures of dispersion other than the standard deviation the value was estimated to facilitate calculation of the treatment effect. In studies that report standard errors or confidence intervals the standard deviation was back-calculated. In some circumstances, statistical testing was conducted by the authors and measures of dispersion were not reported. In the absence of measures of dispersion, the results of the statistical analyses conducted by the authors (i.e. the p-value) are considered as evidence. For proportions, we report the proportion of patients that experienced an outcome along with the percentage of patients that experienced an outcome. The variance of the arcsine difference was used to determine statistical significance.[M7] P-values < 0.05 were considered statistically significant.

When the data was available, we performed meta-analyses using the random effects method of DerSimonian and Laird.[M8] A minimum of three studies was required for an outcome to be considered by meta-analysis. Heterogeneity was assessed with the I-squared statistic. Meta-analyses with I-squared values less than 50% were considered as evidence. Those with I-squared larger than 50% were not considered as evidence for this guideline. All meta-analyses were performed using SAS 9.4. The arcsine difference was used in meta-analysis of proportions. In order to overcome the difficulty of interpreting the magnitude of the arcsine difference, a

summary odds ratio is calculated based on random effects meta-analysis of proportions and the number needed to treat (or harm) is calculated. The standardized mean difference was used for meta-analysis of means and magnitude was interpreted using Cohen's definitions of small, medium, and large effect.

PEER REVIEW

Following the final meeting, the guideline draft undergoes peer review for additional input from external content experts. Written comments are provided on the structured review form (see Appendix VII). All peer reviewers are required to disclose their conflicts of interest.
To guide who participates, the guideline development group identifies specialty societies at the introductory meeting. O*rganizations*, not *individuals*, are specified.

The specialty societies are solicited for nominations of individual peer reviewers after the final meeting. The peer review period is announced as it approaches and others interested are able to volunteer to review the draft. The chair of the MSTS committee on Evidence Based Medicine reviews the draft of the guideline prior to dissemination.

Some specialty societies (both orthopaedic and non-orthopaedic) ask their evidence-based practice (EBP) committee to provide review of the guideline. The organization is responsible for coordinating the distribution of our materials and consolidating their comments onto one form. The chair of the external EBP committees provides disclosure of their conflicts of interest (COI) and manages the potential conflicts of their members.

Again, MSTS asks for comments to be assembled into a single response form by the specialty society and for the individual submitting the review to provide disclosure of potentially conflicting interests. The peer review stage gives external stakeholders an opportunity to provide evidence-based direction for modifications that they believe have been overlooked. Since the draft is subject to revisions until its approval by the MSTS Executive Committee as the final step in the guideline development process, confidentiality of all working drafts is essential.

The manager of the evidence-based medicine unit drafts the initial responses to comments that address methodology. These responses are then reviewed by the guideline development group chair and vice-chair, who respond to questions concerning clinical practice and techniques. The director of the Department of Research and Scientific Affairs provides input as well. All comments received and the initial drafts of the responses are also reviewed by all members of the guideline development group. All changes to a recommendation as a result of peer review are based on the evidence and undergoes majority vote by the guideline development group members via teleconference. Final revisions are summarized in a detailed report that is made part of the guideline document throughout the remainder of the review and approval processes.

The MSTS believes in the importance of demonstrating responsiveness to input received during the peer review process and welcomes the critiques of external specialty societies. Following final approval of the guideline, all individual responses are posted on our website www.msts.org ith a point-by-point reply to each non-editorial comment. Reviewers who wish to remain anonymous notify the MSTS to have their names de-identified; their comments, our responses, and their COI disclosures are still posted.

Review of the Use of Imaging Prior To Referral to a Musculoskeletal Oncologist guideline was requested of <N> organizations and <N> external content experts were nominated to represent them. <N> individuals returned comments on the structured review form (see Appendix VI).

PUBLIC COMMENTARY

After modifying the draft in response to peer review, the guideline was subjected to a thirty-day period of "Public Commentary." Commentators consist of any person wishing to review the guideline, members of the MSTS Evidence Based Medicine Committee and the MSTS Executive Committee. The guideline is automatically forwarded to the MSTS BOD and CORQ so that they may review it and provide comment prior to being asked to approve the document. Members of the BOC and BOS are solicited for interest. If they request to see the document, it is forwarded to them for comment. Based on these bodies, a multitude of commentators have the opportunity to provide input into this guideline. Three members returned public comments.

THE MSTS GUIDELINE APPROVAL PROCESS

This final guideline draft must be approved by the MSTS Committee on Evidence Based Medicine and the MSTS Executive Committee. These decision-making bodies are described in Appendix II and are not designated to modify the contents. Their charge is to approve or reject its publication by majority vote.

REVISION PLANS

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

GUIDELINE DISSEMINATION PLANS

The primary purpose of the present document is to provide interested readers with full documentation about not only our recommendations, but also about how we arrived at those recommendations.

Shorter versions of the guideline are available in other venues. Publication of most guidelines is announced by a press release, articles authored by the guideline development group and published in journals of interest to orthopaedic oncologists and orthopaedic surgeons. Most guidelines are also distributed at the AAOS and MSTS Annual Meetings in various venues such as on Academy Row and at Committee Scientific Exhibits.

Selected guidelines are disseminated by webinar, an Online Module for the Orthopaedic Knowledge Online website, Radio Media Tours, Media Briefings, and by distributing them at relevant Continuing Medical Education (CME) courses and at the MSTS Resource Center.

Other dissemination efforts outside of the MSTS will include submitting the guideline to the National Guideline Clearinghouse and distributing the guideline at other medical specialty societies' meetings.

IV.**RECOMMENDATIONS**

PLAIN RADIOGRAPHS

A. Moderate evidence supports using conventional radiographs in the initial evaluation of a bone tumor of unknown etiology.

Strength of Recommendation: Moderate 

Description: Evidence from two or more "Moderate" quality studies with consistent findings, or evidence from a single "High" quality study for recommending for or against the intervention.

B. In the absence of reliable evidence, it is the opinion of the work group that conventional radiographs are a reasonable diagnostic test and may be considered during the initial evaluation of a soft tissue tumor.

Strength of Recommendation: Consensus 

Description: There is no supporting evidence. In the absence of reliable evidence, the work group is making a recommendation based on their clinical opinion.

RATIONALE

One high quality study (Oudenhoven et al) found was a prospective series of 200 hand lesions with histology as the gold standard. Four moderate studies utilized radiographs in a similar way to evaluate bone tumors, and when combined with the high-quality study in meta-analysis, were shown to detect benignity and malignancy with high accuracy as compared to histology (76.5% sensitivity and 86.4% specificity).

With respect to the diagnosis of soft tissue tumors of unknown etiology, there is scant published literature regarding the value of conventional radiographs of the tumor site to assist with obtaining a diagnosis or planning further diagnostic studies or treatment. In the absence of reliable evidence, it is the opinion of this work group that certain radiographic findings can be very helpful when present; such as phleboliths in hemangiomas, characteristic ossification patterns of myositis ossificans, mineralization within the substance of the tumor, density of the tumor, and cortical involvement of the underlying bone. However, many times conventional radiographs will not add any additional information regarding the identity of the tumor. Thus, our work group agreed that this test should be regarded as a justifiable, although not universally critical, diagnostic study at initial evaluation of soft tissue tumors.

RISKS AND HARMS OF IMPLEMENTING THIS RECOMMENDATION

There is a radiation dose associated with conventional radiographs but it is small enough to pose no real risk to the patient.

FUTURE RESEARCH

Although this recommendation would be further strengthened by additional efforts to perform high quality prospective studies comparing the correlation with radiographic appearance to histologic diagnosis, the work group agreed that there is enough anecdotal experience, minimal risk, and low cost to recommend plain radiographs as the initial evaluation in all evaluations for a possible bone tumor. Prospective studies could be done to establish how often initial radiographs contribute to obtaining a diagnosis and planning further diagnostic studies and treatment when a soft tissue tumor of unknown etiology is discovered or suspected.

RESULTS

STUDY QUALITY TABLE 1: PLAIN RADIOGRAPHS

Study	Representative Population	Clear Selection Criteria	Detailed Enough to Replicate	Reference Standard Identifies Target Condition	Blinding	Other Bias?	Inclusion	Strength
Caracciolo,J.T., 2016	●	◑	●	◑	●	◑	Include	Moderate Quality
Hillmann,A., 2001	●	◑	●	●	●	◑	Include	Moderate Quality
Inai,R., 2015	●	●	●	○	●	○	Include	Low Quality
Oudenhoven,L.F., 2006	●	●	●	●	●	◑	Include	High Quality
Soderlund,V., 2004	●	●	●	●	○	◑	Include	Moderate Quality
Strobel,K., 2008	●	●	●	○	●	○	Include	Low Quality
Thommesen,P., 1976	●	◑	●	●	○	◑	Include	Low Quality
Voegeli,E., 1976	●	◑	●	●	◑	◑	Include	Moderate Quality
Wanken,J.J., 1973	●	◑	●	●	●	◑	Include	Moderate Quality
Weger,C., 2013	●	●	●	●	○	◑	Include	Moderate Quality

SUMMARY OF DATA FINDINGS

SUMMARY TABLE 1: PICO 1 - RADIOGRAPH VS HISTOPATHOLOGY

Outcome	Tumor Type	Imaging Method	Diagnostic Threshold	High	Moderate				
				Oudenhoven,L.F., 2006	Caracciolo,J.T., 2016	Hillmann,A., 2001	Soderlund,V., 2004	Voegeli,E., 1976	Weger,C., 2013**
Tumor Diagnosis	Bone tumors	Radiograph	Radiologist interpretation				**88.46** **81.6**		
Malignancy	Bone tumors	Radiograph	Neovascularity, presense of irregular tumor vessels/lakes, arteriovenous shunting					77.55 **82.3**	
			Radiologist interpretation	40.74 **97.1**			77.27 **96.7**		30 **100**
			Radiologist interpretation(margins, matrix pattern, periosteal reaction)			**85.71** 46			
			Ill defined margins (Lodwick-Madewell grade II or III)		**87.2** 69.1				
		Radiograph(direct magnification)	Radiologist interpretation(margins, matrix pattern, periosteal reaction)			**92.86** 74.6			

DATA TABLE 1: PICO 1 - BONE TUMOR DIAGNOSIS

Quality	Author	N	Study Notes	Tumor Type	Imaging VS. Reference	Index Cutoff	Sens|Spec	LR+|LR-	Rule In Test	Rule Out Test
Moderate Quality	Soderlund,V., 2004	177		bone tumors or tumor-like/normal	radiograph VS. Cytology(fine needle aspiration biopsy)	radiologist interpretation	0.8846|0.816	4.81|0.14	WEAK	**MODERATE**

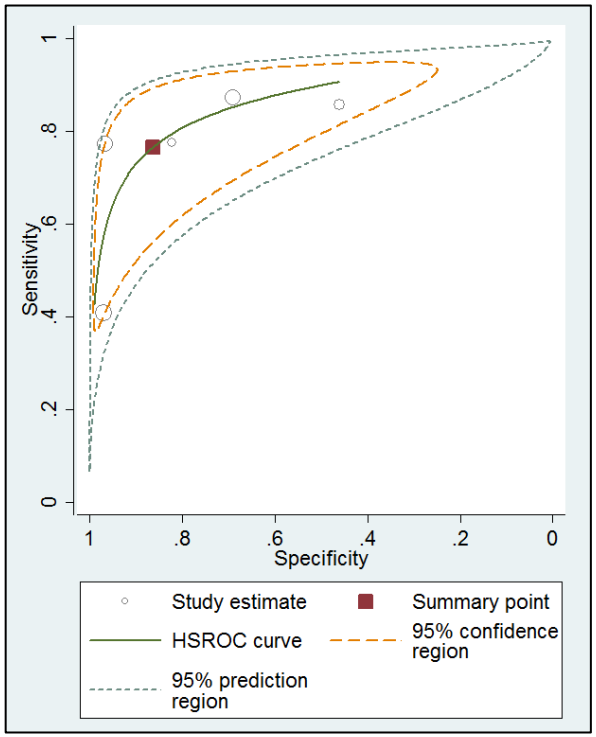
DATA TABLE 2: PICO 1 - MALIGNANCY

Quality	Author	N	Study Notes	Tumor Type	Imaging VS. Reference	Index Cutoff	Sens|Spec	LR+|LR-	Rule In Test	Rule Out Test
High Quality	Oudenhoven,L.F., 2006	200	benign includes indeterminate	bone tumors (hand) (malignant vs benign/indeterminate)	radiograph VS. histology	radiologist interpretation	0.4074|0.971	14.10|0.61	**STRONG**	POOR
Moderate Quality	Caracciolo, J.T., 2016	183	13 metastases; no histo confirmation in 4 benign lesions	Bone lesions	Radiograph VS. Histopathology	Ill defined margins (L/M grade 2-3)	0.872|0.691	2.8|0.185	WEAK	**MODERATE**
Moderate Quality	Hillmann,A., 2001	91	avg of 3 readers	bone tumors	Radiograph(plain) VS. Histopathology(surgery or biopsy)	radiologist interpretation(margins, matrix pattern, periosteal reaction)	0.8571|0.460	1.59|0.31	POOR	WEAK
Moderate Quality	Hillmann,A., 2001	91	avg of 3 readers	bone tumors	Radiograph(direct magnification) VS. Histopathology(surgery or biopsy)	radiologist interpretation(margins, matrix pattern, periosteal reaction)	0.9286|0.746	3.66|0.10	WEAK	**STRONG**
Moderate Quality	Voegeli,E., 1976	66		bone tumors	arteriography(urogafin) VS. histology(open biopsy or surgical removal)	neovascularity, presense of irregular tumor vessels/lakes, arteriovenous shunting	0.9184|1	91.84|0.08	**STRONG**	**STRONG**
Moderate Quality	Voegeli,E., 1976	66		bone tumors	radiograph VS. histology(open biopsy or surgical removal)	neovascularity, presense of irregular tumor vessels/lakes, arteriovenous shunting	0.7755|0.823	4.40|0.27	WEAK	WEAK

Quality	Author	N	Study Notes	Tumor Type	Imaging VS. Reference	Index Cutoff	Sens|Spec	LR+|LR-	Rule In Test	Rule Out Test
Moderate Quality	Wanken,J.J., 1973	30	pediatric pts	bone tumors or tumor-like	roentgenogram VS. Pathology	active uptake	0.6364|0.894	6.05|0.41	**MODERATE**	WEAK
Moderate Quality	Wanken,J.J., 1973	30	pediatric pts	bone tumors or tumor-like	clinical diagnosis VS. Pathology	clinician interpretation	0.2727|0.736	1.04|0.99	POOR	POOR
Moderate Quality	Soderlund,V., 2004	177		bone tumors or tumor-like/normal	radiograph VS. Cytology(fine needle aspiration biopsy)	radiologist interpretation	0.7727|0.967	23.96|0.24	**STRONG**	WEAK
Moderate Quality	Weger,C., 2013	85	66% pain pts	osteolytic lesions of os calcis	Radiograph(plain) VS. Histopathology(biopsy)	radiologist interpretation	0.3|1	30.00|0.70	**STRONG**	POOR
Low Quality	Strobel,K., 2008	50		bone tumors	xray VS. histology(US or CT-guided biopsy or resection) or CFU(4pts; 12mo)	radiologist interpretation(ill-defined lesion, cortical destruction, periosteal reactions)	0.8485|0.647	2.40|0.23	WEAK	WEAK
Low Quality	Thommesen,P., 1976	34	all pts under 20 years old; 80% with pain	bone tumors	radiograph VS. Histology(biopsy)	radiologist interpretation	0.9412|0.083	1.03|0.71	POOR	POOR
Low Quality	Inai,R., 2015	279		bone tumors(extremities and trunk)	radiograph VS. histology or CFU(102 pts; 12mo including CT or MRI)	ill-defined margin, permeative bone or cortical bone destruction, or periosteal response	0.4706|0.921	5.96|0.58	**MODERATE**	POOR

DETAILED DATA FINDINGS

FIGURE 1: PICO 1 HSROC META-ANALYSIS - RADIOGRAPH VS HISTOPATHOLOGY FOR DETERMINING MALIGNANCY OF BONE TUMORS



Meta-analysis of diagnostic accuracy

Log likelihood = -31.697196 Number of studies = 5

	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
Bivariate						
E(logitSe)	1.178423	.3946214			.4049793	1.951867
E(logitSp)	1.85085	.6764715			.5249907	3.17671
Var(logitSe)	.6168908	.5002868			.1258636	3.023546
Var(logitSp)	2.116673	1.431428			.5623644	7.966909
Corr(logits)	-.9843632	.1507088			-1	.9999986
HSROC						
Lambda	2.963755	.2974594			2.380745	3.546765
Theta	.1219682	.5318696			-.9204771	1.164413
beta	.6164544	.2915316	2.11	0.034	.045063	1.187846
s2alpha	.0357363	.3434433			2.36e-10	5414581
s2theta	1.133763	.7905471			.2890671	4.446781
Summary pt.						
Se	.7646641	.0710133			.5998834	.87565
Sp	.8642269	.0793763			.628314	.9599484
DOR	20.6822	8.396386			9.333253	45.83111
LR+	5.631928	2.867242			2.076377	15.27594
LR-	.272308	.0626451			.173476	.4274461
1/LR-	3.672313	.8448247			2.339476	5.764487

Covariance between estimates of E(logitSe) & E(logitSp) -.2242634

Reference	Quality	Sens | Spec	LR+ | LR-
Oudenhoven,L.F., 2006	High Quality	0.4074|0.9711	14.10|0.61
Caracciolo,J.T., 2016	Moderate Quality	0.872|0.691	2.8|0.185
Hillmann,A., 2001	Moderate Quality	0.8571|0.4603	1.59|0.31
Soderlund,V., 2004	Moderate Quality	0.7727|0.9677	23.96|0.24
Voegeli,E., 1976	Moderate Quality	0.7755|0.8235	4.40|0.27

MRI: USE OF CONTRAST

A. Strong evidence supports that contrast enhancement on MRI can assist in determining if a soft tissue tumor is benign or malignant.

Strength of Recommendation: Strong ★★★★

Description: Evidence from two or more "High" quality studies with consistent findings for recommending for or against the intervention.

B. Strong evidence supports that a heterogenous signal in a contrast-enhanced MRI can assist in determining if a soft tissue tumor is benign or malignant.

Strength of Recommendation: Strong ★★★★

Description: Evidence from two or more "High" quality studies with consistent findings for recommending for or against the intervention.

C. In the absence of reliable evidence, it is the opinion of the work group that IV contrast does not offer any advantages for detecting tumor presence over a non-contrast study.

Strength of Recommendation: Consensus ★☆☆☆

Description: There is no supporting evidence. In the absence of reliable evidence, the work group is making a recommendation based on their clinical opinion.

RATIONALE

Although it is clear from the available literature and meta-analysis (2 high quality and 5 moderate quality studies) that the use of IV contrast assists in the differentiation between benign and malignant entities, a substantial amount of discussion was dedicated to the issue of how MRIs should be used as an initial imaging modality by referring practitioners. In most circumstances, a non-contrast study will provide adequate information to determine the underlying identity of a mass, specifically if the lesion is clearly consistent with a common benign entity, such as a lipoma or synovial cyst, or if there are abnormal characteristics consistent with a possible sarcoma, in which case referral to a specialty center is warranted and strongly recommended. The work group did not feel that a universal recommendation to perform contrast enhanced MRI in every patient was a judicious use of resources, but rather if contrast was deemed necessary by the treating cancer specialists, a limited contrast enhanced study could be performed at the discretion of the treating team on an individualized basis. Meta-analysis of 1 high quality and 4 moderate quality studies also showed that heterogeneous signal on contrast MRI has some value in determining whether a soft tissue tumor is malignant or benign.

RISKS AND HARMS OF IMPLEMENTING THIS RECOMMENDATION

MRI or CT with IV contrast both pose radiation-related risks and contrast-material related risks including allergic type reaction, nephrogenic systemic fibrosis, and unknown effects of heavy metal (gadolinium) deposition in the brain tissue. However, for patients without risk factors their use may outweigh their potential problems.

FUTURE RESEARCH

Currently no literature specifically investigates contrast vs non-contrast MRI or CT and a prospective comparison would add to the current scientific knowledge. The creation of more specific indications on whether to use contrast for initial imaging in bone and soft tissue tumors would require additional investigation, possibly with decision analysis methodology, to consider guidelines with more strength than our current consensus opinion. In some institutions, there may be a role for monitored MRIs to determine if the addition of contrast would be of benefit for each individual patient, and would certainly lead to the most judicious use of contrast in the setting of bone and soft tissue tumors.

RESULTS

STUDY QUALITY TABLE 2: CONTRAST IMAGING

Study	Representative Population	Clear Selection Criteria	Detailed Enough to Replicate	Reference Standard Identifies Target Condition	Blinding	Other Bias?	Inclusion	Strength
Alexandrakis,M.G., 2001	●	●	●	●	◑	◑	Include	Moderate Quality
Amini,B., 2014	●	●	●	○	●	○	Include	Low Quality
Aoki,J., 2001	●	◑	●	●	◑	◑	Include	Moderate Quality
Aoki,J., 2003	●	◑	●	●	◑	◑	Include	Moderate Quality
Bakir,B., 2014	●	◑	●	●	○	◑	Include	Low Quality
Barile,A., 2007	●	◑	●	●	◑	◑	Include	Moderate Quality
Berquist,T.H., 1990	●	●	●	○	●	◑	Include	Moderate Quality
Bohndorf,K., 1986	●	◑	●	●	●	◑	Include	Moderate Quality
Bonarelli,C., 2015	●	◑	●	●	●	◑	Include	Moderate Quality
Brenner,W., 2004	●	◑	●	●	○	◑	Include	Low Quality
Catalano,L., 1999	●	●	●	◑	◑	◑	Include	Moderate Quality
Charest,M., 2009	●	●	●	●	○	◑	Include	Moderate Quality
Choi,B.B., 2013	●	◑	●	●	○	◑	Include	Low Quality
Chung,W.J., 2012	●	●	●	●	○	◑	Include	Moderate Quality
Crombe,A., 2016	●	●	●	●	●	●	Include	High Quality

Study	Representative Population	Clear Selection Criteria	Detailed Enough to Replicate	Reference Standard Identifies Target Condition	Blinding	Other Bias?	Inclusion	Strength
Daniel,A.,Jr., 2009	●	●	●	●	◑	◑	Include	Moderate Quality
Dimitrakopoulou-Strauss,A., 2001	●	◑	●	●	◑	◑	Include	Moderate Quality
Einarsdottir,H., 1999	●	◑	●	●	●	◑	Include	Moderate Quality
Fendler,W.P., 2015	●	●	●	●	●	●	Include	High Quality
Furuta,T., 2017	●	◑	●	●	◑	◑	Include	Moderate Quality
Galant,J., 1998	●	◑	●	●	●	◑	Include	Moderate Quality
Gondim Teixeira,P.A., 2016	●	●	●	●	●	◑	Include	High Quality
Gruber,L., 2017	●	●	●	●	●	◑	Include	High Quality
Hamada,K., 2006	●	◑	●	●	●	◑	Include	Moderate Quality
Harish,S., 2006	●	●	●	●	●	◑	Include	High Quality
Haussler,M.D., 1999	●	◑	●	●	◑	◑	Include	Moderate Quality
Hendel,H.W., 2002	●	○	●	●	○	●	Include	Low Quality
Henninger,B., 2013	●	●	●	●	●	◑	Include	High Quality
Higuchi,T., 2002	●	◑	●	●	○	◑	Include	Low Quality
Hoshi,M., 2014	●	◑	●	●	●	◑	Include	Moderate Quality
Imaeda,T., 1991	●	◑	●	●	◑	◑	Include	Moderate Quality
Inai,R., 2015	●	●	●	○	●	○	Include	Low Quality

Study	Representative Population	Clear Selection Criteria	Detailed Enough to Replicate	Reference Standard Identifies Target Condition	Blinding	Other Bias?	Inclusion	Strength
Jabeen,A., 2016	●	◑	●	●	●	◑	Include	Moderate Quality
Jackson,T., 2015	●	●	●	●	●	◑	Include	High Quality
Jee,W.H., 2004	●	◑	●	●	●	◑	Include	Moderate Quality
Jiang,L., 2013	●	◑	●	●	○	●	Include	Moderate Quality
Kalayanarooj,S., 2008	●	◑	●	●	◑	◑	Include	Moderate Quality
Keller,S., 2017	●	◑	●	●	●	◑	Include	Moderate Quality
Kobayashi,H., 1994	●	◑	●	●	◑	◑	Include	Moderate Quality
Koga,H., 2007	●	◑	●	●	●	◑	Include	Moderate Quality
Kotb,S.Z., 2014	●	◑	●	●	◑	◑	Include	Moderate Quality
Kransdorf,M.J., 1989	●	◑	●	○	●	◑	Include	Low Quality
Lahat,G., 2009	●	◑	●	●	●	◑	Include	Moderate Quality
Leal,A.L., 2014	●	◑	●	●	◑	●	Include	Moderate Quality
Lee,F.Y., 2004	●	●	●	●	○	◑	Include	Moderate Quality
Lisle,J.W., 2009	●	●	●	●	◑	◑	Include	Moderate Quality
Liu,L., 2011	●	●	●	●	●	◑	Include	High Quality

Study	Representative Population	Clear Selection Criteria	Detailed Enough to Replicate	Reference Standard Identifies Target Condition	Blinding	Other Bias?	Inclusion	Strength
Lu,J., 2014	●	◑	●	●	●	◑	Include	Moderate Quality
Lucas,J.D., 1999	●	●	●	●	●	◑	Include	High Quality
Matsumoto,Y., 2016	●	●	●	●	●	◑	Include	High Quality
Meng,X.-X., 2016	●	◑	●	●	●	●	Include	High Quality
Moog,F., 1998	●	●	●	●	●	◑	Include	High Quality
Mori,T., 2005	●	●	●	●	○	◑	Include	Moderate Quality
Moulton,J.S., 1995	●	●	●	○	●	○	Include	Low Quality
Nakajo,M., 2015	●	●	●	●	●	◑	Include	High Quality
Negendank,W.G., 1989	●	●	●	●	◑	◑	Include	Moderate Quality
Nose,H., 2013	●	◑	●	●	◑	◑	Include	Moderate Quality
Ohguri,T., 2003	●	◑	●	●	●	◑	Include	Moderate Quality
Okazumi,S., 2009	●	◑	●	●	◑	◑	Include	Moderate Quality
Otsuka,H., 2009	●	●	●	○	◑	○	Include	Low Quality
Park,S.Y., 2016	●	◑	●	○	●	○	Include	Low Quality
Pinkas,L., 2001	●	◑	●	◑	●	◑	Include	Moderate Quality
Rougraff,B.T., 1997	●	●	●	●	●	◑	Include	High Quality
Russo,F., 2012	●	◑	●	●	●	◑	Include	Moderate Quality

Study	Representative Population	Clear Selection Criteria	Detailed Enough to Replicate	Reference Standard Identifies Target Condition	Blinding	Other Bias?	Inclusion	Strength
Sacchi,S., 1987	●	◑	●	●	◑	◑	Include	Moderate Quality
Samuels,L.D., 1971	●	◑	●	○	◑	◑	Include	Low Quality
Schulte,M., 1999	●	◑	●	●	●	●	Include	High Quality
Schulte,M., 2000	●	◑	●	●	●	●	Include	High Quality
Schwartz,H.S., 1990	●	◑	●	●	◑	◑	Include	Moderate Quality
Sen,J., 2010	●	●	●	●	◑	◑	Include	Moderate Quality
Shin,D.S., 2008	●	◑	●	●	●	○	Include	Moderate Quality
Sneppen,O., 1978	●	◑	●	●	◑	◑	Include	Moderate Quality
Strobel,K., 2008	●	●	●	○	●	○	Include	Low Quality
Tacikowska,M., 2002	●	◑	●	●	◑	◑	Include	Moderate Quality
Tacikowska,M., 2002	●	◑	●	●	◑	◑	Include	Moderate Quality
Teo,E.L., 2000	●	◑	●	○	●	◑	Include	Low Quality
Tian,M., 2004	●	●	●	●	◑	◑	Include	Moderate Quality
Tian,M., 2011	●	●	●	●	○	●	Include	Moderate Quality
Van der Woude,H.J., 1998	●	●	●	●	◑	◑	Include	Moderate Quality
Verga,L., 2015	●	◑	●	●	●	◑	Include	Moderate Quality

Study	Representative Population	Clear Selection Criteria	Detailed Enough to Replicate	Reference Standard Identifies Target Condition	Blinding	Other Bias?	Inclusion	Strength
Wang,D., 2015	●	◑	●	●	○	◑	Include	Low Quality
Wanken,J.J., 1973	●	◑	●	●	●	◑	Include	Moderate Quality
Wasa,J., 2010	●	◑	●	●	○	◑	Include	Low Quality
Watanabe,H., 2000	●	●	●	○	◑	◑	Include	Low Quality
Wells,R.G., 1987	●	◑	●	◑	○	◑	Include	Low Quality
Wu,H., 2001	●	◑	●	●	◑	◑	Include	Moderate Quality
Xu,R., 2014	●	◑	●	●	◑	◑	Include	Moderate Quality
Yadav,S.S., 1979	●	◑	●	●	◑	◑	Include	Moderate Quality
Yapar,Z., 2002	●	◑	●	●	●	◑	Include	Moderate Quality
Yildirim,A., 2016	●	◑	●	○	●	◑	Include	Low Quality
Yoo,H.J., 2009	●	●	●	●	●	◑	Include	High Quality
Zhang,Y., 2011	●	◑	●	●	●	●	Include	High Quality
Zhang,Y., 2015	●	◑	●	●	●	●	Include	High Quality
Zhao,F., 2014	●	●	●	●	○	◑	Include	Moderate Quality

SUMMARY OF DATA FINDINGS

SUMMARY TABLE 2: PICO 2 - MRI OR CT VS HISTOPATHOLOGY FOR DIAGNOSING TUMOR PRESENCE

DIAGNOSING TUMOR PRESENCE			Moderate				
Tumor Type	**Imaging Method**	**Diagnostic Threshold**	**Furuta,T., 2017***	**Haussler,M.D., 1999***	**Koga,H., 2007***	**Lahat,G., 2009***	**Lu,J., 2014***
Bone Tumors	CE MRI(1.0-1.5T; gadopentetate dimeglumine; T1/T2)	Heterogeneous signal		**87.1** 46.67			
Soft tissue tumors	CE MRI(magnet unspecified; gadolinium)	Contrast enhancement	**100** 28.1				
		Flow void present	**81.25** **96.6**				
		Fluid-fluid levels present	18.75 **100**				
	CE MRI(magnet unspecified; gadolinium, T1w/T2w)	Hyperintense signal	75 **88.76**				
		Biphasic pattern, peripherally high intensity on T2w, and centrally high intensity on gad T1w			59.3 **100**		
	CE CT(omnipaque; 60s post IV)	No calcifications				**84.85** 28.8	
		No cystic/necrotic area				48.48 **86.6**	
		No focal nodular/water density				51.52 **97.7**	
		No hypervascularity				63.64 **95.5**	
		No organ infiltration on imaging				48.48 75.5	
	CE CT(oral contrast unspecified or water and IV omnipaque)	Fatty or large ST density mass with small satellite nodules, uniform density, integrity margin					75.86 **88.8**
		Satellite nodules, hypervascular focus, and infiltration					**81.82** 77.7

SUMMARY TABLE 3: PICO 2 - MRI OR CT VS HISTOPATHOLOGY FOR DIAGNOSING MALIGNANCY OF BONE TUMORS

DIAGNOSING MALIGNANCY OF BONE TUMORS ON MRI AND/OR CT		High			Moderate
Imaging Method	**Diagnostic Threshold**	**Henninger,B., 2013***	**Matsumoto,Y., 2016****	**Meng,X.-X., 2016****	**Van der Woude,H.J., 1998**
DCE MRI(3.0 T; 5-10 s before gadoterate meglumine IV; T1 only)	Maximum enhancement <=807.47			76.92 61.5	
	Relative maximum enhancement <177.45			76.92 46.1	
CE MRI(0.5 T; gd-DTPA or gadoteridol)	Early enhancement(6sec or less after arterial enhancement)				66.2 56
	Peripheral tumor enhancement				63.38 76
	Type I(rapidly progressing enhancement)				70.42 50
CE MRI(1.5T; gadoterate meglumine or gadobutrol)	Tracer uptake(avg of 2 radiologists)	**100** **94.44**			
CE MRI(3.0 T; gadoterate dimeglumine; 3-5 min post IV; T1 & T2)	Radiologist interpretation(grade 3 or 2, degree of tumor vascularity)			**92.31** 7.6	
CE MRI(magnet unspecified; gadolinium)	Heterogeneous contrast enhancement		**80** 15.38		
	Presence of cyst		35 79.49		
CE MRI(magnet unspecified; gadolinium) and CT(no contrast)	DSS score >=3		**90** **84.62**		

SUMMARY TABLE 4: PICO 2 - MRI OR CT VS HISTOPATHOLOGY FOR DIAGNOSING MALIGNANCY OF SOFT TISSUE TUMORS

DIAGNOSING MALIGNANCY OF SOFT TISSUE TUMORS ON MRI		High				Moderate										Low
Imaging Method	Diagnostic Threshold	Crombe,A., 2016**	Gondim Teixeira,P.A., 2016	Gruber,L., 2017	Liu,L., 2011	Barile,A., 2007	Bonarelli,C., 2015	Chung,W.J., 2012	Daniel,A.,Jr., 2009	Kalayanarooj,S., 2008	Ohguri,T., 2003*	Russo,F., 2012	Sen,J., 2010	Tacikowska,M., 2002(a)	Tacikowska,M., 2002(b)	Van der Woude,H.J., 1998	Bakir,B., 2014*
CE MRI(0.5 T; gd-DTPA or gadoteridol)	Early enhancement(6sec or less after arterial enhancement)															**90.91** 75	
	Early enhancement(6sec or less after arterial enhancement) and peripheral enhancement															**95.45** 71.8	
	Early enhancement(6sec or less after arterial enhancement) and type I(rapid progressing enhancement)															**90.91** 71.8	
	Peripheral enhancement and type I(rapidly progressing enhancement)															**90.91** 78.1	
	Peripheral tumor enhancement															72.73 **96.8**	
	Type I(rapidly progressing enhancement)															**86.36** **81.2**	
CE MRI(1.0T & 1.5T; gadolinium-DTPA)	Rapid initial contrast enhancement					63.64 58.3											
CE MRI(1.5 T; contrast unspecified) and DWI	Postcontrast quotient greater than 1.19																**100** **100**
CE MRI(1.5T; gadolinium)	Manual method ADC avg of 1.65 or more						62.5 53.66										
	Manual method ADC min of 1.28 or more						79.17 60.9										
	Semiautomatic method ADC avg of 1.68 or more						62.5 56.1										
	Semiautomatic method ADC min of 0.91 or more						62.5 63.41										
	Heterogeneous contrast enhancement								**100** 7.69								
	Ill-defined margins, intra-tumoral fat, hemorrhagic component, fibrosis, or tail sign	**92.75** **92.3**															
	Presence of bone changes								**83.33** **84.6**								
	Radiologist interpretation(size, shape, margins, enhancement)								**95.83** **84.6**								
	Tumor surface with more than 50% enhancement	52.17 76.9															
CE MRI(1.5T; gadolinium; T1w only)	Heterogeneous signal									51.43 59.5							
	Isointensity signal								70.83 76.9								
	Absence of hyperintense tracts								**100** 11.54								
CE MRI(1.5 T; gadolinium; T2w only)	Heterogeneous signal									**82.86** 34							
	Hyperintensity signal								**95.83** 38.4								
CE MRI(1.5 T; Gd-DPTA)	Bone involvement												8.7 **100**				
	Heterogeneous contrast enhancement												**91.3** 37.5				
	3 or more thick septa or nodular/patchy non-adipose component										65.22 **90.6**						
CE MRI(1.5 T; Gd-DPTA; T1w only)	Heterogeneous signal												30.43 78.1				
CE MRI(1.5 T; Gd-DPTA; T2w only)	Heterogeneous signal												**86.96** 31.2				
CE MRI(1.5T minimum; gadobutol, gadobenate dimeglumine, or gadoterate meglumine)	P2/P3(inhomogenous or peripheral CE with confluent areas of CE sparing)			**88.71** 59.7													
CE MRI(1.5T or 3T; contrast unspecified; T2 only)	Heterogeneous signal							**87.25** 44.5									
CE MRI(1.5T; gadolinium; DWI)	ADC ratio of 0.915 or more		60 67.39														
	ADC ratio of 1.32 or more		**90** 30.43														
	ADC value of 1.19 or more		53.33 65.2														
	ADC value of 1.68 or more		**96.67** 30.4														
CE MRI(2T; gadolinium-DTPA)	Tissue enhancement rate(Erc%/min) greater than 25													**93.33** 66.6			
	Total contrast enhancement(Tec%) more than 80%													**83.33** 73.3			
CE MRI(3T; gadolinium; T1 only)	Marked and heterogeneous enhancement				**100** 15.38												
CE MRI(dynamic 2.0 T; Gd-DTPA)	Periphery-centre or whole tumor enhancement														**92.86** 42.8		
	Tissue enhancement rate(erc%) greater than 0.6														**93.33** 73.3		
1H-MRS(1.5 T; gadobutrol paramagnetic)	Choline peak present(signal/noise ratio >3)											**94.44** **83.3**					

SUMMARY TABLE 5: PICO 2 - MRI OR CT VS HISTOPATHOLOGY FOR DIAGNOSING MALIGNANCY OF BONE/SOFT TISSUE TUMORS

DIAGNOSING MALIGNANCY OF BONE/SOFT TISSUE TUMORS ON MRI OR CT		Moderate					Low	
Imaging Method	**Diagnostic Threshold**	**Barile,A., 2007**	**Mori,T., 2005**	**Negendank,W.G., 1989**	**Verga,L., 2015**	**Xu,R., 2014**	**Choi,B.B., 2013***	**Wasa,J., 2010***
CE CT(IV iomeron iodinated contrast)	Heterogeneous enhancement(>20HU)				**90.74 82.3**			
CE CT(multidetector; nonionic iodine contrast, arterial phase 40-50s and venous phase 90-100s post IV)	Tracer uptake and radiologist interpretation		47.06 49.0					
CT(no contrast)	Texture parameters (CAD interpreted)					**81.36** 61.3		
CE MRI(0.5-1.5 T; w/ or w/o gadolinium; T1 & T2)	2+ points(1 point per statistically significant MRI feature, 4 possible pts)							60.98 **90**
	Presence of cystic change							39.02 **90**
	Presence of perilesional edema							29.27 **100**
CE MRI(0.5-1.5 T; gadolinium; T1 & T2)	Presence of peripheral enhancement							56 **91.67**
CE MRI(0.5-1.5 T; gadolinium; T1)	Heterogeneous							51.22 70
CE MRI(0.5-1.5 T; gadolinium; T2)	Heterogeneous							78.05 30
CE MRI(1.0T & 1.5T; gadolinium-DTPA)	Rapid initial contrast enhancement	70.59 63.6						
CE MRI(1.5T; IV gadopentetate dimeglumine)	Multilocular diffuse contrast enhancement						**83.33** 56.2	
CE MRI(1.5T; IV gadopentetate dimeglumine; T1w only)	Intermediate signal intensity						72.22 75	
CE MRI(1.5T; IV gadopentetate dimeglumine; T2w only)	Heterogeneous signal						**100** 18.75	
	High/Intermediate signal intensity						**100** 12.5	
CE MRI(1T or 1.5T; gadolinium) AND plain radiograph	Tracer uptake and radiologist interpretation		**94.12 92.1**					
MR spectroscopy(1.5T; phosphorus-31)	Higher ratios of PME/NTP and phosphodiester/NTP, lower phosphocreatine/NTP ratio, higher mean pH			**100 94.12**				

SUMMARY TABLE 6: PICO 2 - MRI OR CT VS HISTOPATHOLOGY FOR DIAGNOSING TUMOR STAGE

DIAGNOSING STAGE OF TUMOR			High	Moderate	
Tumor Type	**Imaging Method**	**Diagnostic Threshold**	**Yoo,H.J., 2009***	**Van der Woude,H.J., 1998**	**Zhao,F., 2014**
Bone tumors	CE MRI(0.5 T; gd-DTPA or gadoteridol)	Early enhancement(6sec or less after arterial enhancement)		**95.56 84.6**	
		Peripheral tumor enhancement		77.78 61.5	
		Type I(rapidly progressing enhancement)		**97.78** 76.9	
Soft tissue tumors	CE MRI(contrast unspecified; magnet unspecified)	Contrast enhancement(25 percent or more)			**89.71** 14.2
		Peritumoral enhancement			**91.18** 57.1
	MRI(magnet unspecified; no contrast, T1w only)	Heterogeneous			72.15 37.5
	MRI(magnet unspecified; no contrast, T2w only)	Heterogeneous			**94.94** 26.6
Other tumors	CE MRI(1.5 T or 1.0 T; gadolinium)	Presence of cortical bone destruction with associated soft tissue mass	71.43 **96.4**		
		Presence of entrapped fat within tumor	**92.86 92.8**		
		Presence of soft tissue mass formation	78.57 **96.4**		
	CE MRI(1.5 T or 1.0 T; gadolinium; T1w only)	Presence of central high signal intensity	42.86 **100**		

DATA TABLE 3: PICO 2 - BONE TUMOR DIAGNOSIS

Quality	Author	N	Study Notes	Tumor Type	Imaging VS. Reference	Index Cutoff	Sens|Spec	LR+|LR-	Rule In Test	Rule Out Test
High Quality	Moog,F., 1998	78	abnormal lymphoid cells(Ann Arbor classification system)	Lymphomatous (HD/NHL) bone marrow	PET(18F-FDG; 50-60 min post IV) VS. Histopathology(Bone marrow biopsy)	Tracer uptake	0.6364|0.850	4.26|0.43	WEAK	WEAK
Moderate Quality	Catalano,L., 1999	23	untreated pts	bone or marrow lesions (MM, MGUS, and solitary plasmacytoma)	BS(Tc99m-sestaMIBI; 10min post IV) VS. radiograph	radiologist interpretation from tracer uptake	0.7|0.7692	3.03|0.39	WEAK	WEAK
Moderate Quality	Haussler,M.D., 1999	46		malignant bone tumor (osteosarcoma/ ewing sarcoma vs bone lymphoma)	MRI(1.0-1.5T; gadopentetate dimeglumine; T1/T2) VS. Histopathology(biopsy)	heterogeneous signal	0.871|0.4667	1.63|0.28	POOR	WEAK
Low Quality	Wells,R.G., 1987	54	pediatric	bone tumors(osteoid osteoma/osteoblastoma) or spondylolysis	BS(contrast unspecified; delayed image, time unspecified) VS. x-ray	positive tracer uptake	1|0.1163	1.13|0.00	POOR	**STRONG**
Low Quality	Wells,R.G., 1987	54	pediatric	bone tumors(osteoid osteoma/osteoblastoma) or spondylolysis	BS(contrast unspecified; immediate image, time unspecified) VS. x-ray	positive tracer uptake	1|1	100.00|0.00	**STRONG**	**STRONG**
Low Quality	Wang,D., 2015	41	avg of 3 readers	costal bone tumors or tumor-like	CT(multidetector; w/ or w/o nonionic contrast) VS. pathology(biopsy or surgery)	clinician interpretation	1|1	100.00|0.00	**STRONG**	**STRONG**

Quality	Author	N	Study Notes	Tumor Type	Imaging VS. Reference	Index Cutoff	Sens|Spec	LR+|LR-	Rule In Test	Rule Out Test
Low Quality	Charest,M., 2009	25	suspected of recurrence (previously treated); pts received oral and IV contrast simultaneously	recurrent bone tumors	PET/CT(oral barium sulfate and IV FDG; 60min post IV) VS. histopathology and/or CFU(13pts; no time given)	radiologist interpretation (tracer uptake)	0.9167|1	91.67|0.08	**STRONG**	**STRONG**

DATA TABLE 4: PICO 2 - BONE/SOFT TISSUE TUMOR DIAGNOSIS

Quality	Author	N	Study Notes	Tumor Type	Imaging VS. Reference	Index Cutoff	Sens|Spec	LR+|LR-	Rule In Test	Rule Out Test
Low Quality	Charest,M., 2009	126	newly diagnosed; pts received oral and IV contrast simultaneously	bone and soft tissue tumors	PET/CT(oral barium sulfate and IV FDG; 60min post IV) VS. histopathology and/or CFU(17pts; no time given)	radiologist interpretation (tracer uptake)	0.9633|1	96.33|0.04	**STRONG**	**STRONG**
Low Quality	Charest,M., 2009	86	suspected of recurrence (previously treated); pts received oral and IV contrast simultaneously	recurrent bone and soft tissue tumors	PET/CT(oral barium sulfate and IV FDG; 60min post IV) VS. histopathology and/or CFU(32pts; no time given)	radiologist interpretation (tracer uptake)	0.8889|1	88.89|0.11	**STRONG**	**MODERATE**

DATA TABLE 5: PICO 2 - MALIGNANCY

Quality	Author	N	Study Notes	Tumor Type	Imaging VS. Reference	Index Cutoff	Sens|Spec	LR+|LR-	Rule In Test	Rule Out Test
High Quality	Schulte,M., 2000	202	biopsy by needle, excision, or incision	Bone tumors (whole body)	PET(FDG; 45-60min post IV) VS. Histopathology(biopsy)	tumor-to-background ratio of 3 or more	0.9304|0.666	2.79|0.10	WEAK	**STRONG**
High Quality	Rougraff,B.T., 1997	46		Lipomatous masses	MRI(magnet unspecified; contrast not mentioned; T1, T2, & STIR) VS. pathology(resection and biopsy)	Heterogeneous	0.6111|0.892	5.70|0.44	**MODERATE**	WEAK
High Quality	Henninger,B., 2013	28	avg of 2 readers	bone lesion (ewing sarcoma vs osteomyelitis)	MRI(1.5T; gadoterate meglumine or gadobutrol) VS. Histopathology(biopsy; open or guided)	Tracer uptake(avg of 2 radiologists)	1|0.9444	18.00|0.00	**STRONG**	**STRONG**
High Quality	Zhang,Y., 2015	48		bone tumor	BS(99mTc-MDP; 3-6hr post IV; angiographic, soft-tissue, & delayed phases) VS. pathology(surgical resection or biopsy)	increased blood supply, uptake in flow, pool, and delayed phases	0.9688|0.312	1.41|0.10	POOR	**STRONG**
High Quality	Zhang,Y., 2015	48		bone tumors (whole body)	SPECT/CT and BS(99mTc-MDP; 3-6hr post IV; angiographic, soft-tissue, & delayed phases) VS. pathology(surgical resection or biopsy)	osteolytic/osteoblastic changes in abnormal uptake areas	1|0.8125	5.33|0.00	**MODERATE**	**STRONG**
High Quality	Nakajo,M., 2015	63	Subset of only PET pos pts from original 85 suspects	musculoskeletal tumors	PET/CT(18F-FDG PET 1hr post IV; CT no contrast mentioned) VS. pathology(surgical resection or biopsy)	AUC-cumulative SUV-volume histogram of 0.42 or more	0.6071|0.857	4.25|0.46	WEAK	WEAK

Quality	Author	N	Study Notes	Tumor Type	Imaging VS. Reference	Index Cutoff	Sens|Spec	LR+|LR-	Rule In Test	Rule Out Test
High Quality	Nakajo,M., 2015	85		musculoskeletal tumors	PET/CT(18F-FDG PET 1hr post IV; CT no contrast mentioned) VS. pathology(surgical resection or biopsy)	mild uptake or similar/greater than liver uptake	0.7368|0.255	0.99|1.03	POOR	POOR
High Quality	Nakajo,M., 2015	63	Subset of only PET pos pts from original 85 suspects	musculoskeletal tumors	PET/CT(18F-FDG PET 1hr post IV; CT no contrast mentioned) VS. pathology(surgical resection or biopsy)	SUVmax greater than 6.9	0.6071|0.657	1.77|0.60	POOR	POOR
High Quality	Nakajo,M., 2015	63	Subset of only PET pos pts from original 85 suspects	musculoskeletal tumors	PET/CT(18F-FDG PET 1hr post IV; CT no contrast mentioned) VS. pathology(surgical resection or biopsy)	SUVmean greater than 3	0.5357|0.6	1.34|0.77	POOR	POOR
High Quality	Gondim Teixeira,P.A., 2016	76		non-fatty soft tissue tumors	MRI(1.5T; gadolinium; DWI) VS. histology	ADC ratio of 0.915 or more	0.6|0.6739	1.84|0.59	POOR	POOR
High Quality	Gondim Teixeira,P.A., 2016	76		non-fatty soft tissue tumors	MRI(1.5T; gadolinium; DWI) VS. histology	ADC ratio of 1.32 or more	0.9|0.3043	1.29|0.33	POOR	WEAK
High Quality	Gondim Teixeira,P.A., 2016	76		non-fatty soft tissue tumors	MRI(1.5T; gadolinium; DWI) VS. histology	ADC value of 1.19 or more	0.5333|0.652	1.53|0.72	POOR	POOR
High Quality	Gondim Teixeira,P.A., 2016	76		non-fatty soft tissue tumors	MRI(1.5T; gadolinium; DWI) VS. histology	ADC value of 1.68 or more	0.9667|0.304	1.39|0.11	POOR	**MODERATE**
High Quality	Zhang,Y., 2011	36		non-metastatic spinal tumors	SPECT/CT(Tc-99m-MDP SPECT 3-6hr post IV; CT no contrast mentioned) VS. pathology(surgical resection or biopsy)	Tracer uptake and discrete lytic/sclerotic lesions	0.8947|0.705	3.04|0.15	WEAK	**MODERATE**

Quality	Author	N	Study Notes	Tumor Type	Imaging VS. Reference	Index Cutoff	Sens|Spec	LR+|LR-	Rule In Test	Rule Out Test
High Quality	Zhang,Y., 2011	36		non-metastatic spinal tumors	SPECT(Tc-99m-MDP; 3-6hr post IV) VS. pathology(surgical resection or biopsy)	tracer uptake(vertebral body or pedicles)	0.8421|0.647	2.39|0.24	WEAK	WEAK
High Quality	Crombe,A., 2016	95		peripheral soft tissue tumors with myxoid stroma	MRI(1.5T; gadolinium) VS. histopathology(surgery)	ill-defined margins, intra-tumoral fat, hemorrhagic component, fibrosis, or tail sign	0.9275|0.923	12.06|0.08	**STRONG**	**STRONG**
High Quality	Crombe,A., 2016	95		peripheral soft tissue tumors with myxoid stroma	MRI(1.5T; gadolinium) VS. histopathology(surgery)	tumor surface with more than 50% enhancement	0.5217|0.769	2.26|0.62	WEAK	POOR
High Quality	Harish,S., 2006	40	gadolinium contrast used in only 13 pts	soft tissue tumors	MRI(magnet unspecified; w/ or w/o gadolinium) VS. Histopathology	heterogeneous signal	0.7692|0.666	2.31|0.35	WEAK	WEAK
High Quality	Harish,S., 2006	40	gadolinium contrast used in only 13 pts	soft tissue tumors	MRI(magnet unspecified; w/ or w/o gadolinium) VS. Histopathology	heterogeneous signal	0.7692|0.518	1.60|0.45	POOR	WEAK
High Quality	Lucas,J.D., 1999	31		soft tissue tumors	PET(18F-FDG; 40 min post IV) VS. histology(open biopsy)	high uptake(greater than the liver uptake or photopenic area)	0.9474|0.583	2.27|0.09	WEAK	**STRONG**
High Quality	Lucas,J.D., 1999	31		soft tissue tumors	PET(18F-FDG; 40 min post IV) VS. histology(open biopsy)	SUV of 2 or more	0.9474|0.75	3.79|0.07	WEAK	**STRONG**

Quality	Author	N	Study Notes	Tumor Type	Imaging VS. Reference	Index Cutoff	Sens|Spec	LR+|LR-	Rule In Test	Rule Out Test
High Quality	Schulte,M., 1999	102		soft tissue tumors	PET(18F-FDG; 45min post IV) VS. Histology(resection or needle biopsy)	Tumor to background ratio (TBR) of 3 or more	0.9701|0.657	2.83|0.05	WEAK	**STRONG**
High Quality	Liu,L., 2011	31		soft tissue tumors (lower limbs)	MRI(3T; gadolinium; T1 only) VS. histopathology(biopsy or excision)	marked and heterogeneous enhancement	1|0.1538	1.18|0.00	POOR	**STRONG**
High Quality	Gruber,L., 2017	211		soft tissue tumors (malignant vs benign/intermediate)	MRI(1.5T minimum; gadobutol, gadobenate dimeglumine, or gadoterate meglumine) VS. histopathology(biopsy, US-guided biopsy, or resection)	P2/P3(inhomogenous or peripheral CE with confluent areas of CE sparing)	0.8871|0.597	2.20|0.19	WEAK	**MODERATE**
High Quality	Matsumoto,Y., 2016	59	Dumbbell score system from 0-6 points includes tumor size, boundary, and shape on MRI and presence of bone destruction on CT	spinal dumbbell tumors	MRI(magnet unspecified; gadolinium) and CT(no contrast) VS. histopathology(surgery or biopsy)	DSS score > or =3	0.9|0.8462	5.85|0.12	**MODERATE**	**MODERATE**
High Quality	Matsumoto,Y., 2016	59		spinal dumbbell tumors	MRI(magnet unspecified; gadolinium) VS. histopathology(surgery or biopsy)	heterogeneous contrast enhancement	0.8|0.1538	0.95|1.30	POOR	POOR
High Quality	Matsumoto,Y., 2016	59		spinal dumbbell tumors	MRI(magnet unspecified; gadolinium) VS. histopathology(surgery or biopsy)	presence of cyst	0.35|0.7949	1.71|0.82	POOR	POOR

Quality	Author	N	Study Notes	Tumor Type	Imaging VS. Reference	Index Cutoff	Sens|Spec	LR+|LR-	Rule In Test	Rule Out Test
High Quality	Meng,X.-X., 2016	26		spinal tumors	DCE-MRI(3.0 T; 5-10 s before gadoterate meglumine IV; T1 only) VS. histopathology	Maximum enhancement <=807.47	0.7692|0.615	2.00|0.38	POOR	WEAK
High Quality	Meng,X.-X., 2016	26		spinal tumors	MRI(3.0 T; gadoterate dimeglumine; 3-5 min post IV; T1 & T2) VS. histopathology	radiologist interpretation (grade 3 or 2, degree of tumor vascularity)	0.9231|0.076	1.00|1.00	POOR	POOR
High Quality	Meng,X.-X., 2016	26		spinal tumors	DCE-MRI(3.0 T; 5-10 s before gadoterate meglumine IV; T1 only) VS. histopathology	relative maximum enhancement <177.45	0.7692|0.461	1.43|0.50	POOR	POOR
Moderate Quality	Verga,L., 2015	88		Aggressive vs Active bone/soft tissue tumors	CT(IV iomeron iodinated contrast) VS. Histopathology(resection)	Heterogeneous enhancement (>20HU)	0.9074|0.823	5.14|0.11	**MODERATE**	**MODERATE**
Moderate Quality	Kotb,S.Z., 2014	100	71% pain pts	Bone tumors and tumor-like lesions	MRI(magnet unspecified; contrast not mentioned; DWI) VS. pathology(surgery or needle biopsy)	Restricted diffusion(high SI)	0.5098|0.898	5.00|0.55	**MODERATE**	POOR
Moderate Quality	Okazumi,S., 2009	71	suspected of recurrent STT post-surgery	Soft tissue tumors	PET(18F-FDG; 60min post IV) VS. Histopathology(surgical or biopsy)	SUV >4	0.5745|0.958	13.79|0.44	**STRONG**	WEAK
Moderate Quality	Okazumi,S., 2009	46		Soft tissue tumors	PET(18F-FDG; 60min post IV) VS. Histopathology(surgical or biopsy)	SUV >4	0.4375|0.857	3.06|0.66	WEAK	POOR
Moderate Quality	Okazumi,S., 2009	46		Soft tissue tumors	PET(18F-FDG; 60min post IV) VS. Histopathology(surgical or biopsy)	SUV >4 and FD >1.25	0.5313|0.857	3.72|0.55	WEAK	POOR

Quality	Author	N	Study Notes	Tumor Type	Imaging VS. Reference	Index Cutoff	Sens|Spec	LR+|LR-	Rule In Test	Rule Out Test
Moderate Quality	Okazumi,S., 2009	71	suspected of recurrent STT post-surgery	Soft tissue tumors	PET(18F-FDG; 60min post IV) VS. Histopathology(surgical or biopsy)	SUV >4, FD >1.25, and Ki >0.03	0.8085|0.875	6.47|0.22	**MODERATE**	WEAK
Moderate Quality	Keller,S., 2017	43	atypical requires absence of massive calcification, periosteal reaction, or Codman triangles	atypical osteosarcoma vs. giant cell tumor	BS(thallium-201; 120min post IV, delayed phase only) VS. histopathology	tumor-to-background ratio of 1.64 or more	0.5|0.7826	2.30|0.64	WEAK	POOR
Moderate Quality	Keller,S., 2017	43	atypical requires absence of massive calcification, periosteal reaction, or Codman triangles	atypical osteosarcoma vs. giant cell tumor	BS(thallium-201; 15min post IV, early phase only) VS. histopathology	tumor-to-background ratio of 3.9 or more	0.5|0.7826	2.30|0.64	WEAK	POOR
Moderate Quality	Wu,H., 2001	31	2 cases of bone metastases	bone tumors	PET(18F-FDG; 55-60min post IV) VS. histology	metabolic rate of FDG 9 or more(micro mol per min per 0.1kg)	0.8235|0.928	11.53|0.19	**STRONG**	**MODERATE**
Moderate Quality	Wu,H., 2001	37	2 cases of bone metastases	bone tumors	PET(18F-FDG; 55-60min post IV) VS. histology	SUV avg of 1.8 or more	0.85|0.8235	4.82|0.18	WEAK	**MODERATE**
Moderate Quality	Wu,H., 2001	31	AUTHOR REPORTED RESULTS; 2 cases of bone metastases	bone tumors	PET(18F-FDG; 55-60min and 60-to-30min ratio post IV) VS. histology	SUV avg of 1.8 or more and SUV avg ratio of 1.1 or more	0.813|0.933	12.13|0.20	**STRONG**	**MODERATE**
Moderate Quality	Wu,H., 2001	31	2 cases of bone metastases	bone tumors	PET(18F-FDG; 60-to-30min post IV ratio) VS. histology	SUV avg ratio of 1.1 or more	0.9375|0.6	2.34|0.10	WEAK	**STRONG**

Quality	Author	N	Study Notes	Tumor Type	Imaging VS. Reference	Index Cutoff	Sens|Spec	LR+|LR-	Rule In Test	Rule Out Test
Moderate Quality	Wu,H., 2001	33	2 cases of bone metastases	bone tumors	PET(18F-FDG; 55-60min post IV) VS. histology	SUV max of 3 or more	0.8333|0.8	4.17|0.21	WEAK	WEAK
Moderate Quality	Wu,H., 2001	31	2 cases of bone metastases	bone tumors	PET(18F-FDG; 60-to-30min post IV ratio) VS. histology	SUV max ratio of 1.14 or more	0.875|0.6	2.19|0.21	WEAK	WEAK
Moderate Quality	Wu,H., 2001	35	2 cases of bone metastases	bone tumors	PET(18F-FDG; 55-60min post IV) VS. histology	tumor-to-muscle avg SUV ratio of 3.5 or more	0.7368|0.75	2.95|0.35	WEAK	WEAK
Moderate Quality	Yadav,S.S., 1979	91	excluded 11 secondary tumors	bone tumors	Arteriography(meglumine iothalamate) VS. histopathology(biopsy)	clinician interpretation of visualized arterial, capillary, and venous drainage of lesion	0.8947|0.933	13.42|0.11	**STRONG**	**MODERATE**
Moderate Quality	Aoki,J., 2001	52		bone tumors or tumor-like	PET(18F-FDG; 40-50min post IV) VS. Pathology(biopsy or surgical resection)	SUV of 2 or more	0.7895|0.575	1.86|0.37	POOR	WEAK
Moderate Quality	Bohndorf,K., 1986	67		bone tumors or tumor-like	MRI(1.5, 1.0, 0.5, 0.35, T; no contrast mentioned) VS. histopathology(surgical findings or pathological specimen)	heterogeneous signal	0.9583|0.263	1.30|0.16	POOR	**MODERATE**
Moderate Quality	Sneppen,O., 1978	54		bone tumors or tumor-like	BS(Tc-99m polyphosphate) VS. Histology	tracer uptake of 1.5 or more	0.931|0.52	1.94|0.13	POOR	**MODERATE**
Moderate Quality	Wanken,J.J., 1973	30	pediatric pts	bone tumors or tumor-like	BS(87mSr; 1hr min post IV) VS. Pathology	active uptake	1|0.8947	9.50|0.00	**MODERATE**	**STRONG**

Quality	Author	N	Study Notes	Tumor Type	Imaging VS. Reference	Index Cutoff	Sens|Spec	LR+|LR-	Rule In Test	Rule Out Test
Moderate Quality	Mori,T., 2005	68		bone/soft tissue lesions	CT(multidetector; nonionic iodine contrast, arterial phase 40-50s and venous phase 90-100s post IV) VS. Histology(surgery or biopsy)	tracer uptake and radiologist interpretation	0.4706|0.490	0.92|1.08	POOR	POOR
Moderate Quality	Mori,T., 2005	68		bone/soft tissue lesions	MRI(1T or 1.5T; gadolinium) and plain radiograph VS. Histology(surgery or biopsy)	tracer uptake and radiologist interpretation	0.9412|0.921	12.00|0.06	**STRONG**	**STRONG**
Moderate Quality	Barile,A., 2007	39		bone/soft tissue tumors	MRI(1.0T & 1.5T; gadolinium-DTPA) VS. Histopathology(biopsy or surgical resection)	rapid initial contrast enhancement	0.7059|0.636	1.94|0.46	POOR	WEAK
Moderate Quality	Jabeen,A., 2016	48	BS(MIBI) based on BS(99mTc-MDP; 3hr post IV; 3 phase) ROI	bone/soft tissue tumors	BS(99mTc-MIBI; 30min post IV) VS. Histopathology(biopsy)	Tracer uptake(moderate/severe)	0.8333|0.866	6.25|0.19	**MODERATE**	**MODERATE**
Moderate Quality	Xu,R., 2014	103	18 of 59 are bone mets with unspecified primary tumors	bone/soft tissue tumors	PET/CT(18F-FDG PET 60 min post IV; CT no contrast) VS. histology	SUV max of 5.4 or more (CAD interpreted)	0.6441|0.613	1.67|0.58	POOR	POOR
Moderate Quality	Xu,R., 2014	103	18 of 59 are bone mets with unspecified primary tumors	bone/soft tissue tumors	PET(18F-FDG; 60min post IV) VS. histology	Texture parameters (CAD interpreted)	0.8305|0.636	2.28|0.27	WEAK	WEAK
Moderate Quality	Xu,R., 2014	103	18 of 59 are bone mets with unspecified primary tumors	bone/soft tissue tumors	PET/CT(18F-FDG PET 60 min post IV; CT no contrast) VS. histology	Texture parameters (CAD interpreted)	0.8644|0.772	3.80|0.18	WEAK	**MODERATE**

Quality	Author	N	Study Notes	Tumor Type	Imaging VS. Reference	Index Cutoff	Sens|Spec	LR+|LR-	Rule In Test	Rule Out Test
Moderate Quality	Xu,R., 2014	103	18 of 59 are bone mets with unspecified primary tumors	bone/soft tissue tumors	CT(no contrast) VS. histology	Texture parameters (CAD interpreted)	0.8136|0.613	2.11|0.30	WEAK	WEAK
Moderate Quality	Yadav,S.S., 1979	123	excluded 11 secondary tumors	bone/soft tissue tumors	Arteriography(meglumine iothalamate) VS. histopathology(biopsy)	clinician interpretation of visualized arterial, capillary, and venous drainage of lesion	0.9072|0.846	5.90|0.11	**MODERATE**	**MODERATE**
Moderate Quality	Negendank,W.G., 1989	34		bone/soft tissue tumors (extremities)	MR spectroscopy(1.5T; phosphorus-31) VS. histology(biopsy)	higher ratios of PME/NTP and phosphodiester/NTP, lower phosphocreatine/NTP ratio, higher mean pH	1|0.9412	17.00|0.00	**STRONG**	**STRONG**
Moderate Quality	Yapar,Z., 2002	39		bone/soft tissue tumors/conditions	BS(99mTc-tetrofosmin; 30min post IV) VS. Histopathology(biopsy and/or surgical resection)	any visual perfusion increase(mild/moderate/marked)	1|0.5	2.00|0.00	POOR	**STRONG**
Moderate Quality	Yapar,Z., 2002	39		bone/soft tissue tumors/conditions	BS(99mTc-tetrofosmin; 30min post IV) VS. Histopathology(biopsy and/or surgical resection)	moderate/marked visual perfusion increase	0.88|0.9286	12.32|0.13	**STRONG**	**MODERATE**

Quality	Author	N	Study Notes	Tumor Type	Imaging VS. Reference	Index Cutoff	Sens|Spec	LR+|LR-	Rule In Test	Rule Out Test
Moderate Quality	Yapar,Z., 2002	39		bone/soft tissue tumors/conditions	BS(99mTc-tetrofosmin; 30min post IV) VS. Histopathology(biopsy and/or surgical resection)	moderate/strong visual update and mild/moderate/marked visual perfusion increase	0.88|0.9286	12.32|0.13	**STRONG**	**MODERATE**
Moderate Quality	Yapar,Z., 2002	39		bone/soft tissue tumors/conditions	BS(99mTc-tetrofosmin; 30min post IV) VS. Histopathology(biopsy and/or surgical resection)	moderate/strong visual update and moderate/marked visual perfusion increase	0.8|1	80.00|0.20	**STRONG**	**MODERATE**
Moderate Quality	Yapar,Z., 2002	39		bone/soft tissue tumors/conditions	BS(99mTc-tetrofosmin; 30min post IV) VS. Histopathology(biopsy and/or surgical resection)	moderate/strong visual uptake	0.88|0.8571	6.16|0.14	**MODERATE**	**MODERATE**
Moderate Quality	Yapar,Z., 2002	39		bone/soft tissue tumors/conditions	BS(99mTc-tetrofosmin; 30min post IV) VS. Histopathology(biopsy and/or surgical resection)	uptake ratio greater than 1.76	0.92|0.8571	6.44|0.09	**MODERATE**	**STRONG**
Moderate Quality	Yapar,Z., 2002	39		bone/soft tissue tumors/conditions	BS(99mTc-tetrofosmin; 30min post IV) VS. Histopathology(biopsy and/or surgical resection)	uptake ratio greater than 1.76 and mild/moderate/marked visual perfusion increase	0.92|0.9286	12.88|0.09	**STRONG**	**STRONG**

Quality	Author	N	Study Notes	Tumor Type	Imaging VS. Reference	Index Cutoff	Sens|Spec	LR+|LR-	Rule In Test	Rule Out Test
Moderate Quality	Yapar,Z., 2002	39		bone/soft tissue tumors/conditions	BS(99mTc-tetrofosmin; 30min post IV) VS. Histopathology(biopsy and/or surgical resection)	uptake ratio greater than 1.76 and moderate/marked visual perfusion increase	0.84|1	84.00|0.16	**STRONG**	**MODERATE**
Moderate Quality	Lee,F.Y., 2004	35	tumor counts	cartilage tumors of bone (chondrosarcoma vs osteochondroma/enchondroma)	PET(18F-FDG; 50min post IV) VS. Histopathology	SUV of 2.33 or more	0.5|0.9231	6.50|0.54	**MODERATE**	POOR
Moderate Quality	Lee,F.Y., 2004	35	tumor counts	cartilage tumors of bone (chondrosarcoma vs osteochondroma/enchondroma)	BS(99mTc) VS. Histopathology	tracer uptake(more)	0.6364|0.076	0.69|4.73	POOR	POOR
Moderate Quality	Van der Woude,H.J., 1998	121	4 cases of bone metastases	musculoskeletal bone tumors	MRI(0.5 T; gd-DTPA or gadoteridol) VS. histology(trocar biopsy or resection)	early enhancement (6sec or less after arterial enhancement)	0.662|0.56	1.50|0.60	POOR	POOR
Moderate Quality	Van der Woude,H.J., 1998	121	4 cases of bone metastases	musculoskeletal bone tumors	MRI(0.5 T; gd-DTPA or gadoteridol) VS. histology(trocar biopsy or resection)	peripheral tumor enhancement	0.6338|0.76	2.64|0.48	WEAK	WEAK
Moderate Quality	Van der Woude,H.J., 1998	121	4 cases of bone metastases	musculoskeletal bone tumors	MRI(0.5 T; gd-DTPA or gadoteridol) VS. histology(trocar biopsy or resection)	type I(rapidly progressing enhancement)	0.7042|0.5	1.41|0.59	POOR	POOR

Quality	Author	N	Study Notes	Tumor Type	Imaging VS. Reference	Index Cutoff	Sens|Spec	LR+|LR-	Rule In Test	Rule Out Test
Moderate Quality	Van der Woude,H.J., 1998	54		musculoskeletal soft tissue tumors	MRI(0.5 T; gd-DTPA or gadoteridol) VS. histology(trocar biopsy or resection)	early enhancement (6sec or less after arterial enhancement)	0.9091|0.75	3.64|0.12	WEAK	**MODERATE**
Moderate Quality	Van der Woude,H.J., 1998	54		musculoskeletal soft tissue tumors	MRI(0.5 T; gd-DTPA or gadoteridol) VS. histology(trocar biopsy or resection)	early enhancement (6sec or less after arterial enhancement) and peripheral enhancement	0.9545|0.718	3.39|0.06	WEAK	**STRONG**
Moderate Quality	Van der Woude,H.J., 1998	54		musculoskeletal soft tissue tumors	MRI(0.5 T; gd-DTPA or gadoteridol) VS. histology(trocar biopsy or resection)	early enhancement (6sec or less after arterial enhancement) and type I(rapid progressing enhancement)	0.9091|0.718	3.23|0.13	WEAK	**MODERATE**
Moderate Quality	Van der Woude,H.J., 1998	54		musculoskeletal soft tissue tumors	MRI(0.5 T; gd-DTPA or gadoteridol) VS. histology(trocar biopsy or resection)	peripheral enhancement and type I(rapidly progressing enhancement)	0.9091|0.781	4.16|0.12	WEAK	**MODERATE**
Moderate Quality	Van der Woude,H.J., 1998	54		musculoskeletal soft tissue tumors	MRI(0.5 T; gd-DTPA or gadoteridol) VS. histology(trocar biopsy or resection)	peripheral tumor enhancement	0.7273|0.968	23.27|0.28	**STRONG**	WEAK

Quality	Author	N	Study Notes	Tumor Type	Imaging VS. Reference	Index Cutoff	Sens|Spec	LR+|LR-	Rule In Test	Rule Out Test
Moderate Quality	Van der Woude,H.J., 1998	54		musculoskeletal soft tissue tumors	MRI(0.5 T; gd-DTPA or gadoteridol) VS. histology(trocar biopsy or resection)	type I(rapidly progressing enhancement)	0.8636|0.812	4.61|0.17	WEAK	**MODERATE**
Moderate Quality	Pinkas,L., 2001	72		musculoskeletal tumors	Scintigraphy(Tc-MIBI IV; immediate and 20-30min post injection) VS. histology(biopsy) and clinical outcome(unspecified)	MIBI uptake(high)	0.7895|0.867	5.98|0.24	**MODERATE**	WEAK
Moderate Quality	Tian,M., 2011	34		musculoskeletal tumors	PET(18F-FAMT; 40 min post IV) VS. Histopathology(biopsy or surgical resection)	SUV of 1.26 or more	0.6667|0.818	3.67|0.41	WEAK	WEAK
Moderate Quality	Tian,M., 2011	36		musculoskeletal tumors	PET(11C-choline; 5min post IV) VS. Histopathology(biopsy or surgical resection)	SUV of 2.69 or more	0.8462|0.695	2.78|0.22	WEAK	WEAK
Moderate Quality	Tian,M., 2011	36		musculoskeletal tumors	PET(18F-FDG; 40 min post IV) VS. Histopathology(biopsy or surgical resection)	SUV of 2.77 or more	0.6923|0.695	2.28|0.44	WEAK	WEAK
Moderate Quality	Tian,M., 2004	21		myeloma, bone, or soft tissue tumors	PET(11C-choline; 5min post IV) VS. Histopathology(biopsy or surgical specimen)	SUV of 2.65 or more	1|0.8182	5.50|0.00	**MODERATE**	**STRONG**
Moderate Quality	Tian,M., 2004	21		myeloma, bone, or soft tissue tumors	PET(18F-FDG; 40min post IV) VS. Histopathology(biopsy or surgical specimen)	SUV of 2.88 or more	0.9|0.8182	4.95|0.12	WEAK	**MODERATE**
Moderate Quality	Nose,H., 2013	22	tumor counts	peripheral nerve sheath tumor vs schwannoma/neurofibroma	PET/CT(18F-FDG PET 1hr post IV; CT no contrast mentioned) VS. pathology(biopsy and/or surgery)	SUV max of 4.8 or more	0.9|0.9167	10.80|0.11	**STRONG**	**MODERATE**

Quality	Author	N	Study Notes	Tumor Type	Imaging VS. Reference	Index Cutoff	Sens|Spec	LR+|LR-	Rule In Test	Rule Out Test
Moderate Quality	Aoki,J., 2003	114		soft tissue tumors	PET(18F-FDG; 40-50min post IV) VS. pathology(biopsy or resection)	SUV of 2 or more	0.7059|0.712	2.46|0.41	WEAK	WEAK
Moderate Quality	Aoki,J., 2003	114		soft tissue tumors	PET(18F-FDG; 40-50min post IV) VS. pathology(biopsy or resection)	SUV of 2.5 or more	0.5882|0.737	2.24|0.56	WEAK	POOR
Moderate Quality	Aoki,J., 2003	114		soft tissue tumors	PET(18F-FDG; 40-50min post IV) VS. pathology(biopsy or resection)	SUV of 3 or more	0.5588|0.837	3.44|0.53	WEAK	POOR
Moderate Quality	Aoki,J., 2003	114		soft tissue tumors	PET(18F-FDG; 40-50min post IV) VS. pathology(biopsy or resection)	SUV of 3.5 or more	0.5588|0.9	5.59|0.49	**MODERATE**	WEAK
Moderate Quality	Aoki,J., 2003	114		soft tissue tumors	PET(18F-FDG; 40-50min post IV) VS. pathology(biopsy or resection)	SUV of 4 or more	0.4412|0.912	5.04|0.61	**MODERATE**	POOR
Moderate Quality	Barile,A., 2007	23		soft tissue tumors	MRI(1.0T & 1.5T; gadolinium-DTPA) VS. Histopathology(biopsy or surgical resection)	rapid initial contrast enhancement	0.6364|0.583	1.53|0.62	POOR	POOR
Moderate Quality	Berquist,T.H., 1990	95		soft tissue tumors	MRI(0.15T or 1.5T; no contrast mentioned; T1 and T2) VS. Histopathology(surgery) or clinical follow-up(n=9)	mostly/completely homogeneous	0.7111|0.76	2.96|0.38	WEAK	WEAK
Moderate Quality	Daniel,A.,Jr., 2009	50		soft tissue tumors	MRI(1.5T; gadolinium; T1w only) VS. Histopathology	absence of hyperintense tracts	1|0.1154	1.13|0.00	POOR	**STRONG**

Quality	Author	N	Study Notes	Tumor Type	Imaging VS. Reference	Index Cutoff	Sens|Spec	LR+|LR-	Rule In Test	Rule Out Test
Moderate Quality	Daniel,A.,Jr., 2009	50		soft tissue tumors	MRI(1.5T; gadolinium) VS. Histopathology	heterogeneous contrast enhancement	1|0.0769	1.08|0.00	POOR	**STRONG**
Moderate Quality	Daniel,A.,Jr., 2009	50		soft tissue tumors	MRI(1.5 T; gadolinium; T2w only) VS. Histopathology	hyperintensity signal	0.9583|0.384	1.56|0.11	POOR	**MODERATE**
Moderate Quality	Daniel,A.,Jr., 2009	50		soft tissue tumors	MRI(1.5 T; gadolinium; T1w only) VS. Histopathology	isointensity signal	0.7083|0.769	3.07|0.38	WEAK	WEAK
Moderate Quality	Daniel,A.,Jr., 2009	50		soft tissue tumors	MRI(1.5T; gadolinium) VS. Histopathology	presence of bone changes	0.8333|0.846	5.42|0.20	**MODERATE**	**MODERATE**
Moderate Quality	Daniel,A.,Jr., 2009	50		soft tissue tumors	MRI(1.5T; gadolinium) VS. Histopathology	radiologist interpretation (size, shape, margins, enhancement)	0.9583|0.846	6.23|0.05	**MODERATE**	**STRONG**
Moderate Quality	Hamada,K., 2006	56		soft tissue tumors	PET(18F-FDG; 1 and 2hr post IV, early and delayed phases) VS. Histopathology(surgical resection)	presence of tracer uptake	0.8421|0.324	1.25|0.49	POOR	WEAK
Moderate Quality	Hamada,K., 2006	56	optimal SUV cut-off determined for maximal sensitivity	soft tissue tumors	PET(18F-FDG; 2hr post IV, delayed phase only) VS. Histopathology(surgical resection)	SUV of 1.4 or more	0.8421|0.324	1.25|0.49	POOR	WEAK
Moderate Quality	Hamada,K., 2006	56	optimal SUV cut-off determined for maximal sensitivity	soft tissue tumors	PET(18F-FDG; 1hr post IV, early phase only) VS. Histopathology(surgical resection)	SUV of 1.59 or more	0.9474|0.324	1.40|0.16	POOR	**MODERATE**

Quality	Author	N	Study Notes	Tumor Type	Imaging VS. Reference	Index Cutoff	Sens|Spec	LR+|LR-	Rule In Test	Rule Out Test
Moderate Quality	Hoshi,M., 2014	113		soft tissue tumors	PET/CT(18F-FDG PET 60min post IV; CT no contrast mentioned) and tumor size VS. Histopathology(surgical or biopsy)	Size 5cm or more AND SUV of 2 or more	0.5532|0.473	1.05|0.94	POOR	POOR
Moderate Quality	Hoshi,M., 2014	113		soft tissue tumors	PET/CT(18F-FDG PET 60 min post IV; CT no contrast mentioned) VS. Histopathology(surgical or biopsy)	SUV of 2 or more	0.883|0.3684	1.40|0.32	POOR	WEAK
Moderate Quality	Kalayanarooj,S., 2008	82	MOD QUAL; weak ref pts removed from this group	soft tissue tumors	MRI(1.5 T; gadolinium; T2w only) VS. histopathology(biopsy)	heterogeneous signal	0.8286|0.340	1.26|0.50	POOR	POOR
Moderate Quality	Kalayanarooj,S., 2008	82	MOD QUAL; weak ref pts removed from this group	soft tissue tumors	MRI(1.5 T; gadolinium; T1w only) VS. histopathology(biopsy)	heterogeneous signal	0.5143|0.595	1.27|0.82	POOR	POOR
Moderate Quality	Nose,H., 2013	54	tumor counts	soft tissue tumors	PET/CT(18F-FDG PET 1hr post IV; CT no contrast mentioned) VS. pathology(biopsy and/or surgery)	SUV max of 4.5 or more	0.6452|0.826	3.71|0.43	WEAK	WEAK
Moderate Quality	Russo,F., 2012	36	Excluding 1 metastases and 6 undetermined	soft tissue tumors	1H-MRS(1.5 T; gadobutrol paramagnetic) VS. pathology(surgical resection or biopsy)	choline peak present(signal/noise ratio >3)	0.9444|0.833	5.67|0.07	**MODERATE**	**STRONG**
Moderate Quality	Schwartz,H.S., 1990	55	STT diameters 1in or more	soft tissue tumors	BS(gallium-67 citrate; 24/48hr, and 72hr post IV) VS. histology	clinician interpretation	0.9583|0.871	7.43|0.05	**MODERATE**	**STRONG**

Quality	Author	N	Study Notes	Tumor Type	Imaging VS. Reference	Index Cutoff	Sens|Spec	LR+|LR-	Rule In Test	Rule Out Test
Moderate Quality	Sen,J., 2010	55		soft tissue tumors	MRI(1.5 T; Gd-DPTA) VS. Histopathology(surgical resection)	bone involvement	0.087|1	8.70|0.91	**MODERATE**	POOR
Moderate Quality	Sen,J., 2010	55		soft tissue tumors	MRI(1.5 T; Gd-DPTA) VS. Histopathology(surgical resection)	heterogeneous contrast enhancement	0.913|0.375	1.46|0.23	POOR	WEAK
Moderate Quality	Sen,J., 2010	55		soft tissue tumors	MRI(1.5 T; Gd-DPTA; T1w only) VS. Histopathology(surgical resection)	heterogeneous signal	0.3043|0.781	1.39|0.89	POOR	POOR
Moderate Quality	Sen,J., 2010	55		soft tissue tumors	MRI(1.5 T; Gd-DPTA; T2w only) VS. Histopathology(surgical resection)	heterogeneous signal	0.8696|0.312	1.27|0.42	POOR	WEAK
Moderate Quality	Shin,D.S., 2008	44	MOD QUAL; weak ref pts removed from this group	soft tissue tumors	PET/CT(18F-FDG PET 60 min post IV; CT no contrast mentioned) VS. surgical biopsy	SUVmax of 3.8 or more	0.8|0.6842	2.53|0.29	WEAK	WEAK
Moderate Quality	Tacikowska,M., 2002(a)	45		soft tissue tumors	MRI(2T; gadolinium-DTPA) VS. Histology(biopsy)	tissue enhancement rate(Erc%/min) greater than 25	0.9333|0.666	2.80|0.10	WEAK	**STRONG**
Moderate Quality	Tacikowska,M., 2002(a)	33		soft tissue tumors	MRI(2T; gadolinium-DTPA) VS. Histology(biopsy)	total contrast enhancement (Tec%) more than 80%	0.8333|0.733	3.13|0.23	WEAK	WEAK
Moderate Quality	Tacikowska,M., 2002(b)	42		soft tissue tumors	MRI(dynamic 2.0 T; Gd-DTPA) VS. Histology(biopsy)	periphery-centre or whole tumor enhancement	0.9286|0.428	1.63|0.17	POOR	**MODERATE**

Quality	Author	N	Study Notes	Tumor Type	Imaging VS. Reference	Index Cutoff	Sens|Spec	LR+|LR-	Rule In Test	Rule Out Test
Moderate Quality	Tacikowska,M., 2002(b)	45		soft tissue tumors	MRI(dynamic 2.0 T; Gd-DTPA) VS. Histology(biopsy)	tissue enhancement rate(erc%) greater than 0.6	0.9333|0.733	3.50|0.09	WEAK	**STRONG**
Moderate Quality	Yadav,S.S., 1979	32	excluded 11 secondary tumors	soft tissue tumors	Arteriography(meglumine iothalamate) VS. histopathology(biopsy)	clinician interpretation of visualized arterial, capillary, and venous drainage of lesion	0.7143|0.25	0.95|1.14	POOR	POOR
Moderate Quality	Bonarelli,C., 2015	65	avg of 2 readers	soft tissue tumors (extremities or trunk)	MRI(1.5 T; gadolinium) VS. histology	manual method ADC avg of 1.65 or more	0.625|0.5366	1.35|0.70	POOR	POOR
Moderate Quality	Bonarelli,C., 2015	65	avg of 2 readers	soft tissue tumors (extremities or trunk)	MRI(1.5 T; gadolinium) VS. histology	manual method ADC min of 1.28 or more	0.7917|0.609	2.03|0.34	WEAK	WEAK
Moderate Quality	Bonarelli,C., 2015	65	avg of 2 readers	soft tissue tumors (extremities or trunk)	MRI(1.5 T; gadolinium) VS. histology	semiautomatic method ADC avg of 1.68 or more	0.625|0.561	1.42|0.67	POOR	POOR
Moderate Quality	Bonarelli,C., 2015	65	avg of 2 readers	soft tissue tumors (extremities or trunk)	MRI(1.5 T; gadolinium) VS. histology	semiautomatic method ADC min of 0.91 or more	0.625|0.6341	1.71|0.59	POOR	POOR
Moderate Quality	Chung,W.J., 2012	266		soft tissue tumors (extremities)	MRI(1.5T or 3T; contrast unspecified; T2 only) VS. Histopathology(biopsy or surgical resection)	heterogeneous signal	0.8725|0.445	1.57|0.29	POOR	WEAK

Quality	Author	N	Study Notes	Tumor Type	Imaging VS. Reference	Index Cutoff	Sens|Spec	LR+|LR-	Rule In Test	Rule Out Test
Moderate Quality	Imaeda,T., 1991	74	avg of 2 readers	soft tissue tumors (extremities)	BS(gallium-67 citrate; 48hr and 72hr post IV) VS. histology(surgical resection)	positive intensity(intensity more than normal/equal to liver intensity)	0.7895|0.745	3.10|0.28	WEAK	WEAK
Moderate Quality	Leal,A.L., 2014	44		soft tissue tumors (limbs or abdominal wall)	PET/CT(18F-FDG PET 1hr post IV; CT oral pielograf) VS. Histopathology(US-guided core needle or excision biopsy)	SUV max of 3 or more	1|0.8462	6.50|0.00	**MODERATE**	**STRONG**
Moderate Quality	Einarsdottir,H., 1999	110	tumor counts	soft tissue tumors (liposarcoma/atypical lipomatous vs lipoma)	MRI(1.0 & 1.5 T; no contrast mentioned) or CT(no contrast mentioned) VS. histopathology	less than 75% of fat within lesion	0.8|1	80.00|0.20	**STRONG**	**MODERATE**
Moderate Quality	Galant,J., 1998	64	29 pts with contrast	soft tissue tumors (musculoskeletal-subcutaneous space)	MRI(0.5 T & 1.5 T; w/ or w/o gd-DTPA or gd-DTPA-BMA) VS. Histology(surgery)	STT that crosses the superficial fascia	0.9091|0.419	1.57|0.22	POOR	WEAK
Moderate Quality	Dimitrakopoulou-Strauss,A., 2001	56	70% suspected of recurrence (previous surgery/radiotherapy)	soft tissue tumors or tumor-like	PET(18F-FDG; 60min post IV) VS. Histology(surgery)	radiologist interpretation of parameters(SUV, K1, k3, vascular fraction, fractal dimension)	1|0.2308	1.30|0.00	POOR	**STRONG**
Moderate Quality	Dimitrakopoulou-Strauss,A., 2001	56	70% suspected of recurrence (previous surgery/radiotherapy)	soft tissue tumors or tumor-like	PET(18F-FDG; 55-60min post IV) VS. Histology(surgery)	SUV value	1|0	1.00|0.00	POOR	**STRONG**

Quality	Author	N	Study Notes	Tumor Type	Imaging VS. Reference	Index Cutoff	Sens|Spec	LR+|LR-	Rule In Test	Rule Out Test
Moderate Quality	Dimitrakopoulou-Strauss,A., 2001	56	70% suspected of recurrence (previous surgery/radiotherapy)	soft tissue tumors or tumor-like	PET(18F-FDG; 60min post IV) VS. Histology(surgery)	visual evaluation by radiologist	0.7674|0.384	1.25|0.61	POOR	POOR
Moderate Quality	Kobayashi,H., 1994	64	masses of 3cm or more in diameter	soft tissue tumors or tumor-like	BS(99mTc-DMS; 2 hr post IV) VS. histology(surgical specimen or needle biopsy)	positive uptake	1|0.3556	1.55|0.00	POOR	**STRONG**
Moderate Quality	Kobayashi,H., 1994	46	masses of 5cm or more in diameter	soft tissue tumors or tumor-like	BS(99mTc-DMS; 2 hr post IV) VS. histology(surgical specimen or needle biopsy)	positive uptake	1|0.3929	1.65|0.00	POOR	**STRONG**
Moderate Quality	Kobayashi,H., 1994	71	masses of 2cm or more in diameter	soft tissue tumors or tumor-like	BS(99mTc-DMS; 2 hr post IV) VS. histology(surgical specimen or needle biopsy)	positive uptake	1|0.3846	1.63|0.00	POOR	**STRONG**
Moderate Quality	Kobayashi,H., 1994	47	masses of 3cm or more in diameter	soft tissue tumors or tumor-like	BS(Ga-67 citrate; 72hr post IV) VS. histology(surgical specimen or needle biopsy)	positive uptake	0.5714|0.697	1.89|0.62	POOR	POOR
Moderate Quality	Kobayashi,H., 1994	34	masses of 5cm or more in diameter	soft tissue tumors or tumor-like	BS(Ga-67 citrate; 72hr post IV) VS. histology(surgical specimen or needle biopsy)	positive uptake	0.5714|0.65	1.63|0.66	POOR	POOR
Moderate Quality	Kobayashi,H., 1994	52	masses of 2cm or more in diameter	soft tissue tumors or tumor-like	BS(Ga-67 citrate; 72hr post IV) VS. histology(surgical specimen or needle biopsy)	positive uptake	0.5714|0.736	2.17|0.58	WEAK	POOR

Quality	Author	N	Study Notes	Tumor Type	Imaging VS. Reference	Index Cutoff	Sens|Spec	LR+|LR-	Rule In Test	Rule Out Test
Moderate Quality	Jiang,L., 2013	39		spinal tumors	SPECT/CT(Tc99m-MDP SPECT 3-4hr post IV; CT no contrast mentioned) VS. Pathology	CT tracer uptake(centrum and/or pedicle of vertebral arch)	0.9524|0.5	1.91|0.10	POOR	**STRONG**
Moderate Quality	Jiang,L., 2013	39		spinal tumors	SPECT(Tc99m-MDP; 3-4hr post IV) VS. Pathology	tracer uptake(vertebral body and/or pedicles)	0.9524|0.333	1.43|0.14	POOR	**MODERATE**
Moderate Quality	Ohguri,T., 2003	55	tumor counts; excluded 3 infiltrating lipomas	well-differentiated liposarcoma vs lipoma	MRI(1.5T; gadopentetate dimeglumine) VS. histopathology(surgical resection)	3 or more thick septa or nodular/patchy non-adipose component	0.6522|0.906	6.96|0.38	**MODERATE**	WEAK
Low Quality	Teo,E.L., 2000	32		ST masses vs hemangiomas	MRI(1.5T; WITH gadolinium) VS. Histology, angiography, or CFU(6pts; no time given)	Enhancement present	0.952380952|	0.95|4.76	POOR	POOR
Low Quality	Shin,D.S., 2008	91	LOW QUAL DOWNGRADE FOR REF; 8/46 benign pts with clinical FU as ref	bone and soft tissue tumors	PET/CT(18F-FDG PET 60 min post IV; CT no contrast mentioned) VS. surgical biopsy(83/91 pts) or clinical FU(8/91 pts)	SUVmax of 3.8 or more	0.8|0.6522	2.30|0.31	WEAK	WEAK
Low Quality	Shin,D.S., 2008	47	LOW QUAL DOWNGRADE FOR REF; 8/27 benign pts with clinical FU as ref	bone tumors	PET/CT(18F-FDG PET 60 min post IV; CT no contrast mentioned) VS. surgical biopsy(39/47 pts) or clinical FU(8/47 pts)	SUVmax of 3.7 or more	0.8|0.6296	2.16|0.32	WEAK	WEAK

Quality	Author	N	Study Notes	Tumor Type	Imaging VS. Reference	Index Cutoff	Sens|Spec	LR+|LR-	Rule In Test	Rule Out Test
Low Quality	Strobel,K., 2008	50		bone tumors	PET(18F-FDG; 60min after IV injection) VS. histology(US or CT-guided biopsy or resection) or CFU(4pts; 12mo)	SUVmax>=2.5	0.8485|0.352	1.31|0.43	POOR	WEAK
Low Quality	Strobel,K., 2008	50		bone tumors	PET/CT(18F-FDG; 60min after IV injection) VS. histology(US or CT-guided biopsy or resection) or CFU(4pts; 12mo)	SUVmax>=2.5 and radiologist interpretation of CT	0.9091|0.764	3.86|0.12	WEAK	**MODERATE**
Low Quality	Higuchi,T., 2002	32		bone tumors (OS or chordoma vs Giant cell tumor)	bone scan (TI-chloride; early phase 15min post IV) VS. Histopathology	T1-chloride uptake ratio >3	0.3571|0.277	0.50|2.31	POOR	POOR
Low Quality	Higuchi,T., 2002	32		bone tumors (OS or chordoma vs Giant cell tumor)	bone scan (TI-chloride; delayed 3hr post IV) VS. Histopathology	T1-chloride uptake ratio >3	0|0.5333	0.00|1.88	POOR	POOR
Low Quality	Hendel,H.W., 2002	22		bone tumors (chondrosarcoma vs osteochondroma)	BS(Tc-99m HDP; planar) VS. histopathology	increased tracer uptake	0.7273|0.272	1.00|1.00	POOR	POOR
Low Quality	Samuels,L.D., 1971	51	pts aged 3-24 suspected of malignant bone tumors	bone tumors or tumor-like	scintigraphy(strontium-87m; 0.5-2hr after IV contrast) VS. pathology(40 malignant pts) or clinical FU(11 benign pts)	intense/moderate uptake	1|0.7273	3.67|0.00	WEAK	**STRONG**

Quality	Author	N	Study Notes	Tumor Type	Imaging VS. Reference	Index Cutoff	Sens|Spec	LR+|LR-	Rule In Test	Rule Out Test
Low Quality	Inai,R., 2015	279		bone tumors(extremities and trunk)	BS(Thallium-201; 2hrs post IV) VS. histology or CFU(102 pts; 12mo including CT or MRI)	greater than 0.38 TBC pixels	0.8039|0.763	3.39|0.26	WEAK	WEAK
Low Quality	Inai,R., 2015	279		bone tumors(extremities and trunk)	BS(Thallium-201; 15min post IV) VS. histology or CFU(102 pts; 12mo including CT or MRI)	greater than 0.68 TBC pixels	0.7647|0.745	3.01|0.32	WEAK	WEAK
Low Quality	Choi,B.B., 2013	34		low grade chondrosarcoma vs enchondroma	MRI(1.5T; IV gadopentetate dimeglumine; T2w only) VS. histopathology	heterogeneous signal	1|0.1875	1.23|0.00	POOR	**STRONG**
Low Quality	Choi,B.B., 2013	34		low grade chondrosarcoma vs enchondroma	MRI(1.5T; IV gadopentetate dimeglumine; T2w only) VS. histopathology	High/Intermediate signal intensity	1|0.125	1.14|0.00	POOR	**STRONG**
Low Quality	Choi,B.B., 2013	34		low grade chondrosarcoma vs enchondroma	MRI(1.5T; IV gadopentetate dimeglumine; T1w only) VS. histopathology	Intermediate signal intensity	0.7222|0.75	2.89|0.37	WEAK	WEAK
Low Quality	Choi,B.B., 2013	34		low grade chondrosarcoma vs enchondroma	MRI(1.5T; IV gadopentetate dimeglumine) VS. histopathology	Multilocular diffuse contrast enhancement	0.8333|0.562	1.91|0.30	POOR	WEAK
Low Quality	Wasa,J., 2010	61	gadolinium only in 37 pts	malignant peripheral nerve sheath tumor vs benign neurofibroma	MRI(0.5-1.5 T; gadolinium; T1 & T2) VS. pathology	2+ points(1 point per statistically significant MRI feature, 4 possible pts)	0.6098|0.9	6.10|0.43	**MODERATE**	WEAK

Quality	Author	N	Study Notes	Tumor Type	Imaging VS. Reference	Index Cutoff	Sens|Spec	LR+|LR-	Rule In Test	Rule Out Test
Low Quality	Wasa,J., 2010	61	gadolinium only in 37 pts	malignant peripheral nerve sheath tumor vs benign neurofibroma	MRI(0.5-1.5 T; gadolinium; T1 & T2) VS. pathology	heterogeneous	0.5122|0.7	1.71|0.70	POOR	POOR
Low Quality	Wasa,J., 2010	61	gadolinium only in 37 pts	malignant peripheral nerve sheath tumor vs benign neurofibroma	MRI(0.5-1.5 T; gadolinium; T1 & T2) VS. pathology	heterogeneous	0.7805|0.3	1.12|0.73	POOR	POOR
Low Quality	Wasa,J., 2010	61	gadolinium only in 37 pts	malignant peripheral nerve sheath tumor vs benign neurofibroma	MRI(0.5-1.5 T; gadolinium; T1 & T2) VS. pathology	presence of cystic change	0.3902|0.9	3.90|0.68	WEAK	POOR
Low Quality	Wasa,J., 2010	61	gadolinium only in 37 pts	malignant peripheral nerve sheath tumor vs benign neurofibroma	MRI(0.5-1.5 T; gadolinium; T1 & T2) VS. pathology	presence of perilesional edema	0.2927|1	29.27|0.71	**STRONG**	POOR
Low Quality	Wasa,J., 2010	37	all received gadolinium contrast	malignant peripheral nerve sheath tumor vs benign neurofibroma	MRI(0.5-1.5 T; gadolinium; T1 & T2) VS. pathology	presence of peripheral enhancement	0.56|0.9167	6.72|0.48	**MODERATE**	WEAK
Low Quality	Watanabe,H., 2000	27	FOLLOW-UP AUTOPSY diagnosis for some pts	musculoskeletal bone tumors or tumor-like	PET(FMT; 40 min post IV) VS. histopathology(biopsy, surgical excision, and autopsy)	moderate/intense visual uptake	1|0.0625	1.07|0.00	POOR	**STRONG**

Quality	Author	N	Study Notes	Tumor Type	Imaging VS. Reference	Index Cutoff	Sens|Spec	LR+|LR-	Rule In Test	Rule Out Test
Low Quality	Watanabe,H., 2000	27	FOLLOW-UP AUTOPSY diagnosis for some pts	musculoskeletal bone tumors or tumor-like	PET(FDG; 40 min post IV) VS. histopathology(biopsy, surgical excision, and autopsy)	moderate/intense visual uptake	1|0	1.00|0.00	POOR	**STRONG**
Low Quality	Watanabe,H., 2000	27	FOLLOW-UP AUTOPSY diagnosis for some pts	musculoskeletal bone tumors or tumor-like	PET(FMT; 40 min post IV) VS. histopathology(biopsy, surgical excision, and autopsy)	SUV of 1.2 or more	0.8182|0.75	3.27|0.24	WEAK	WEAK
Low Quality	Watanabe,H., 2000	27	FOLLOW-UP AUTOPSY diagnosis for some pts	musculoskeletal bone tumors or tumor-like	PET(FDG; 40 min post IV) VS. histopathology(biopsy, surgical excision, and autopsy)	SUV of 1.9 or more	0.7273|0.375	1.16|0.73	POOR	POOR
Low Quality	Watanabe,H., 2000	75	FOLLOW-UP AUTOPSY diagnosis for some pts	musculoskeletal bone/soft tissue tumors	PET(FDG; 40 min post IV) VS. histopathology(biopsy, surgical excision, and autopsy)	moderate/intense visual uptake	1|0.1509	1.18|0.00	POOR	**STRONG**
Low Quality	Watanabe,H., 2000	75	FOLLOW-UP AUTOPSY diagnosis for some pts	musculoskeletal bone/soft tissue tumors	PET(FMT; 40 min post IV) VS. histopathology(biopsy, surgical excision, and autopsy)	moderate/intense visual uptake	1|0.2642	1.36|0.00	POOR	**STRONG**
Low Quality	Watanabe,H., 2000	75	FOLLOW-UP AUTOPSY diagnosis for some pts	musculoskeletal bone/soft tissue tumors	PET(FMT; 40 min post IV) VS. histopathology(biopsy, surgical excision, and autopsy)	SUV of 1.2 or more	0.7273|0.849	4.82|0.32	WEAK	WEAK
Low Quality	Watanabe,H., 2000	75	FOLLOW-UP AUTOPSY diagnosis for some pts	musculoskeletal bone/soft tissue tumors	PET(FDG; 40 min post IV) VS. histopathology(biopsy, surgical excision, and autopsy)	SUV of 1.9 or more	0.7273|0.660	2.14|0.41	WEAK	WEAK

Quality	Author	N	Study Notes	Tumor Type	Imaging VS. Reference	Index Cutoff	Sens|Spec	LR+|LR-	Rule In Test	Rule Out Test
Low Quality	Watanabe,H., 2000	48	FOLLOW-UP AUTOPSY diagnosis for some pts	musculoskeletal soft tissue tumors or tumor-like	PET(FMT; 40 min post IV) VS. histopathology(biopsy, surgical excision, and autopsy)	moderate/intense visual uptake	1|0.3514	1.54|0.00	POOR	**STRONG**
Low Quality	Watanabe,H., 2000	48	FOLLOW-UP AUTOPSY diagnosis for some pts	musculoskeletal soft tissue tumors or tumor-like	PET(FDG; 40 min post IV) VS. histopathology(biopsy, surgical excision, and autopsy)	moderate/intense visual uptake	1|0.2162	1.28|0.00	POOR	**STRONG**
Low Quality	Watanabe,H., 2000	48	FOLLOW-UP AUTOPSY diagnosis for some pts	musculoskeletal soft tissue tumors or tumor-like	PET(FMT; 40 min post IV) VS. histopathology(biopsy, surgical excision, and autopsy)	SUV of 1.2 or more	0.6364|0.891	5.89|0.41	**MODERATE**	WEAK
Low Quality	Watanabe,H., 2000	48	FOLLOW-UP AUTOPSY diagnosis for some pts	musculoskeletal soft tissue tumors or tumor-like	PET(FDG; 40 min post IV) VS. histopathology(biopsy, surgical excision, and autopsy)	SUV of 1.9 or more	0.7273|0.783	3.36|0.35	WEAK	WEAK
Low Quality	Bakir,B., 2014	41		retroperitoneal soft tissue-tumors(malignant RPF and chronic RPF)	MRI(1.5 T; contrast unspecified) and DWI VS. pathology	postcontrast quotient greater than 1.19	1|1	100.00|0.00	**STRONG**	**STRONG**
Low Quality	Amini,B., 2014	100	avg of 4 readers	soft tissue sarcoma vs benign fluid collection (extremities)	PET/CT(18F-FDG PET 60min post IV; CT no contrast) VS. biopsy, clinical imaging follow up >6 months	radiologist interpretation	0.9286|0.772	4.09|0.09	WEAK	**STRONG**
Low Quality	Amini,B., 2014	100		soft tissue sarcoma vs benign fluid collection (extremities)	PET/CT(18F-FDG PET 60min post IV; CT no contrast) VS. biopsy, clinical imaging follow up >6 months	SUVmax >5.15	0.8393|0.886	7.39|0.18	**MODERATE**	**MODERATE**

Quality	Author	N	Study Notes	Tumor Type	Imaging VS. Reference	Index Cutoff	Sens|Spec	LR+|LR-	Rule In Test	Rule Out Test
Low Quality	Amini,B., 2014	100	avg of 4 readers	soft tissue sarcoma vs benign fluid collection (extremities)	PET/CT(18F-FDG PET 60min post IV; CT no contrast) VS. biopsy, clinical imaging follow up >6 months	thick/solid spatial pattern of contrast avidity	0.6964|0.977	30.64|0.31	**STRONG**	WEAK
Low Quality	Kransdorf,M.J., 1989	112	xray, CT, arteriogram, or CFU in 16 cases	soft tissue tumors	MRI(0.5 or 1.5 T; T2w only; no contrast mentioned) VS. pathology(biopsy) or CFU(16pts; time not given)	>=25% of mass showing inhomogeneous signal	0.4074|0.6	1.02|0.99	POOR	POOR
Low Quality	Kransdorf,M.J., 1989	112	xray, CT, arteriogram, or CFU in 16 cases	soft tissue tumors	MRI(0.5 or 1.5 T; T1w only; no contrast mentioned) VS. pathology(biopsy) or CFU(16pts; time not given)	>=25% of mass showing inhomogeneous signal	0.1852|0.717	0.66|1.14	POOR	POOR
Low Quality	Moulton,J.S., 1995	225		soft tissue tumors	MRI(1.5T, no contrast) VS. Histopathology or CFU(41pts; 2yrs)	Bone abnormality	0.1739|0.927	2.40|0.89	WEAK	POOR
Low Quality	Moulton,J.S., 1995	225		soft tissue tumors	MRI(1.5T, no contrast; T1 only) VS. Histopathology or CFU(41pts; 2yrs)	Heterogeneous signal	0.4565|0.536	0.99|1.01	POOR	POOR
Low Quality	Moulton,J.S., 1995	225		soft tissue tumors	MRI(1.5T, no contrast; T2 only) VS. Histopathology or CFU(41pts; 2yrs)	Heterogeneous signal	0.8696|0.352	1.34|0.37	POOR	WEAK

Quality	Author	N	Study Notes	Tumor Type	Imaging VS. Reference	Index Cutoff	Sens|Spec	LR+|LR-	Rule In Test	Rule Out Test
Low Quality	Moulton,J.S., 1995	225		soft tissue tumors	MRI(1.5T, no contrast) VS. Histopathology or CFU(41pts; 2yrs)	radiologist interpretation (size, homogeneity, margins, signal intensity, edema, involvement)	0.587|0.9441	10.51|0.44	**STRONG**	WEAK
Low Quality	Otsuka,H., 2009	91		soft tissue tumors	scintigraphy(Thallium-201 chloride; 15min and 3hrs post IV) VS. Pathology or CFU (26pts; 6mo)	high uptake in both phases(early and delayed)	0.7895|0.708	2.71|0.30	WEAK	WEAK
Low Quality	Yildirim,A., 2016	35	4 metastases pts	soft tissue tumors	MRI(1.5T; no contrast) VS. histology(32/35 pts) or clinical FU(3/35 pts)	bone involvement	0.3684|1	36.84|0.63	**STRONG**	POOR
Low Quality	Yildirim,A., 2016	35	4 metastases pts	soft tissue tumors	MRI(1.5T; gadopentetate dimeglumine or gadodiamide) VS. histology(32/35 pts) or clinical FU(3/35 pts)	heterogeneous or peripheral contrast enhancement	0.7368|0.125	0.84|2.11	POOR	POOR
Low Quality	Yildirim,A., 2016	35	4 metastases pts	soft tissue tumors	MRI(1.5T; no contrast; T1 only) VS. histology(32/35 pts) or clinical FU(3/35 pts)	heterogeneous signal	0.4737|0.75	1.90|0.70	POOR	POOR
Low Quality	Yildirim,A., 2016	35	4 metastases pts	soft tissue tumors	MRI(1.5T; no contrast; T2 only) VS. histology(32/35 pts) or clinical FU(3/35 pts)	heterogeneous signal	0.7895|0.187	0.97|1.12	POOR	POOR
Low Quality	Yildirim,A., 2016	34	3 metastases pts	soft tissue tumors	MRI(1.5T; gadopentetate dimeglumine or gadodiamide) VS. histology(32/35 pts) or clinical FU(3/35 pts)	rapid initial contrast enhancement followed by washout/plateau phase	1|0.75	4.00|0.00	WEAK	**STRONG**

DATA TABLE 6: PICO 2 - SOFT TISSUE TUMOR DIAGNOSIS

Quality	Author	N	Study Notes	Tumor Type	Imaging VS. Reference	Index Cutoff	Sens|Spec	LR+|LR-	Rule In Test	Rule Out Test
Moderate Quality	Lu,J., 2014	47	Histo/Radiology diagnostic matching	Dedifferentiated liposarcoma vs other liposarcomas	CT(oral contrast unspecified or water and IV omnipaque) VS. Histopathology	satellite nodules, hypervascular focus, and infiltration	0.8182|0.777	3.68|0.23	WEAK	WEAK
Moderate Quality	Koga,H., 2007	981		Schwannoma vs other soft tissue tumors (malignant/benign)	MRI(magnet unspecified; T2w and gadolinium enhanced T1w) VS. Histology(surgical resection)	Biphasic pattern, peripherally high intensity on T2w, and centrally high intensity on gad T1w	0.593|1	59.30|0.41	**STRONG**	WEAK
Moderate Quality	Lahat,G., 2009	78		Well differentiated (WD/ALT) vs Dedifferentiated Liposarcoma	CT(omnipaque; 60s post IV) VS. Histopathology(surgical biopsy)	No calcifications	0.8485|0.288	1.19|0.52	POOR	POOR
Moderate Quality	Lahat,G., 2009	78		Well differentiated (WD/ALT) vs Dedifferentiated Liposarcoma	CT(omnipaque; 60s post IV) VS. Histopathology(surgical biopsy)	No cystic/necrotic area	0.4848|0.866	3.64|0.59	WEAK	POOR
Moderate Quality	Lahat,G., 2009	78		Well differentiated (WD/ALT) vs Dedifferentiated Liposarcoma	CT(omnipaque; 60s post IV) VS. Histopathology(surgical biopsy)	No focal nodular/water density	0.5152|0.977	23.18|0.50	**STRONG**	POOR
Moderate Quality	Lahat,G., 2009	78		Well differentiated (WD/ALT) vs Dedifferentiated Liposarcoma	CT(omnipaque; 60s post IV) VS. Histopathology(surgical biopsy)	No hypervascularity	0.6364|0.955	14.32|0.38	**STRONG**	WEAK

Quality	Author	N	Study Notes	Tumor Type	Imaging VS. Reference	Index Cutoff	Sens|Spec	LR+|LR-	Rule In Test	Rule Out Test
Moderate Quality	Lahat,G., 2009	78		Well differentiated (WD/ALT) vs Dedifferentiated Liposarcoma	CT(omnipaque; 60s post IV) VS. Histopathology(surgical biopsy)	No organ infiltration on imaging	0.4848|0.755	1.98|0.68	POOR	POOR
Moderate Quality	Lu,J., 2014	47	Histo/Radiology diagnostic matching	Well differentiated (WD/ALT) vs other liposarcomas	CT(oral contrast unspecified or water and IV omnipaque) VS. Histopathology	fatty or large ST density mass with small satellite nodules, uniform density, integrity margin	0.7586|0.888	6.83|0.27	**MODERATE**	WEAK
Moderate Quality	Jee,W.H., 2004	52	5 pts no contrast	extra-axial neurofibroma vs neurilemmoma	MRI(1.0 or 1.5 T; w/ or w/o gadopentetate dimeglumine; T2 only) VS. pathology	absence of fascicular appearance(small ringlike structures with peripheral higher signal intensity)	0.75|0.625	2.00|0.40	POOR	WEAK
Moderate Quality	Jee,W.H., 2004	52	5 pts no contrast	extra-axial neurofibroma vs neurilemmoma	MRI(1.0 or 1.5 T; w/ or w/o gadopentetate dimeglumine; T2 only) VS. pathology	heterogeneous signal intensity	0.9167|0.225	1.18|0.37	POOR	WEAK
Moderate Quality	Jee,W.H., 2004	52	5 pts no contrast	extra-axial neurofibroma vs neurilemmoma	MRI(1.0 or 1.5 T; w/ or w/o gadopentetate dimeglumine; T2 only) VS. pathology	presence of a "split-fat" sign	1|0.025	1.03|0.00	POOR	**STRONG**
Moderate Quality	Jee,W.H., 2004	52	5 pts no contrast	extra-axial neurofibroma vs neurilemmoma	MRI(1.0 or 1.5 T; w/ or w/o gadopentetate dimeglumine; T2 only) VS. pathology	target sign present (peripheral high SI; central low SI)	0.5833|0.85	3.89|0.49	WEAK	WEAK

Quality	Author	N	Study Notes	Tumor Type	Imaging VS. Reference	Index Cutoff	Sens|Spec	LR+|LR-	Rule In Test	Rule Out Test
Moderate Quality	Furuta,T., 2017	105	AUTHOR REPORTED RESULTS; no gadolinium only if allergic	hemangioma vs other STT	MRI(magnet unspecified; gadolinium) VS. pathology(biopsy or surgery)	contrast enhancement	1|0.281	1.39|0.00	POOR	**STRONG**
Moderate Quality	Furuta,T., 2017	105	no gadolinium only if allergic	hemangioma vs other STT	MRI(magnet unspecified; gadolinium) VS. pathology(biopsy or surgery)	flow void present	0.8125|0.966	24.10|0.19	**STRONG**	**MODERATE**
Moderate Quality	Furuta,T., 2017	105	no gadolinium only if allergic	hemangioma vs other STT	MRI(magnet unspecified; gadolinium) VS. pathology(biopsy or surgery)	fluid-fluid levels present	0.1875|1	18.75|0.81	**STRONG**	POOR
Moderate Quality	Furuta,T., 2017	105	no gadolinium only if allergic	hemangioma vs other STT	MRI(magnet unspecified; gadolinium, T1/T2) VS. pathology(biopsy or surgery)	hyperintense signal	0.75|0.8876	6.68|0.28	**MODERATE**	WEAK
Low Quality	Park,S.Y., 2016	152	suspected of recurrent STS	recurrent soft tissue sarcoma	PET/CT(18F-FDG; 60min post IV; CT no contrast) VS. histopathology or CFU(4pts; 2yrs)	radiologist interpretation (abnormal focal contrast uptake above background)	0.95|0.9545	20.90|0.05	**STRONG**	**STRONG**
Low Quality	Charest,M., 2009	61	suspected of recurrence (previously treated); pts received oral and IV contrast simultaneously	recurrent soft tissue tumors	PET/CT(oral barium sulfate and IV FDG; 60min post IV) VS. histopathology and/or CFU(19pts; no time given)	radiologist interpretation (tracer uptake)	0.881|1	88.10|0.12	**STRONG**	**MODERATE**

DATA TABLE 7: PICO 2 - STAGE OF TUMOR

Quality	Author	N	Study Notes	Tumor Type	Imaging VS. Reference	Index Cutoff	Sens|Spec	LR+|LR-	Rule In Test	Rule Out Test
High Quality	Fendler,W.P., 2015	78	primary soft tissue tumors	Soft tissue tumors (high grade vs low grade)	PET/CT(18F-FDG, furosemide, and butylscopolamine PET 90 min post IV; CT w/ or w/o iodine contrast) VS. Histopathology(biopsy)	SUVpeak 6.6	0.77|0.88	6.42|0.26	**MODERATE**	WEAK
High Quality	Fendler,W.P., 2015	78	primary soft tissue tumors	Soft tissue tumors (high grade vs low grade)	PET/CT(18F-FDG, furosemide, and butylscopolamine PET 90 min post IV; CT w/ or w/o iodine contrast) VS. Histopathology(biopsy)	SUVpeak/SUVliver 2.4	0.79|0.81	4.16|0.26	WEAK	WEAK
High Quality	Jackson,T., 2015	21		bone/soft tissue sarcomas (high grade/metastatic vs low grade/non-metastatic)	PET/CT(18F-NaF and 18F-FDG; 56-213 min post IV) VS. pathology(biopsy)	metastic grade(focal tracer uptake with CT evidence of malignancy)	0.8182|0.6	2.05|0.30	WEAK	WEAK
High Quality	Yoo,H.J., 2009	42		chondrosarcoma (high grade vs low grade)	MRI(1.5 T or 1.0 T; gadolinium; T1w only) VS. pathology(curettage, intralesion or wide excision, or biopsy)	presence of central high signal intensity	0.4286|1	42.86|0.57	**STRONG**	POOR
High Quality	Yoo,H.J., 2009	42		chondrosarcoma (high grade vs low grade)	MRI(1.5 T or 1.0 T; gadolinium) VS. pathology(curettage, intralesion or wide excision, or biopsy)	presence of cortical bone destruction with associated soft tissue mass	0.7143|0.964	20.00|0.30	**STRONG**	WEAK

Quality	Author	N	Study Notes	Tumor Type	Imaging VS. Reference	Index Cutoff	Sens|Spec	LR+|LR-	Rule In Test	Rule Out Test
High Quality	Yoo,H.J., 2009	42		chondrosarcoma (high grade vs low grade)	MRI(1.5 T or 1.0 T; gadolinium) VS. pathology(curettage, intralesion or wide excision, or biopsy)	presence of entrapped fat within tumor	0.9286|0.928	13.00|0.08	**STRONG**	**STRONG**
High Quality	Yoo,H.J., 2009	42		chondrosarcoma (high grade vs low grade)	MRI(1.5 T or 1.0 T; gadolinium) VS. pathology(curettage, intralesion or wide excision, or biopsy)	presence of soft tissue mass formation	0.7857|0.964	22.00|0.22	**STRONG**	WEAK
Moderate Quality	Alexandrakis,M. G., 2001	28	Stage 3 (Salmon and Durie criteria)	Multiple myeloma (stage 3 vs stage 1)	BS(Tc-99m MIBI; 3hr post IV) VS. Histopathology(blood, aspiration, serum, aspiration, biopsy)	2 or 3(uptake equal to or greater than myocardium)	0.3529|0.818	1.94|0.79	POOR	POOR
Moderate Quality	Alexandrakis,M. G., 2001	28	Stage 3 (Salmon and Durie criteria)	Multiple myeloma (stage 3 vs stage 1)	BS(Tc-99 MDP; 72hr post IV) VS. Histopathology(blood, aspiration, serum, aspiration, biopsy)	Tracer uptake	0.4706|0.363	0.74|1.46	POOR	POOR
Moderate Quality	Charest,M., 2009	109	MOD QUAL-NO CFU pts received oral and IV contrast simultaneously	bone and soft tissue sarcomas (high grade vs low grade)	PET/CT(oral barium sulfate and IV FDG; 60min post IV) VS. histopathology	SUVmax>=6.5	0.6768|1	67.68|0.32	**STRONG**	WEAK
Moderate Quality	Lee,F.Y., 2004	35	tumor counts	chondrosarcomas (high grade 2/3) vs chondrosarcoma (low grade 1), osteochondromas, enchondromas	PET(18F-FDG; 50min post IV) VS. Histopathology	SUV of 2.33 or more	0.9|0.92	11.25|0.11	**STRONG**	**MODERATE**

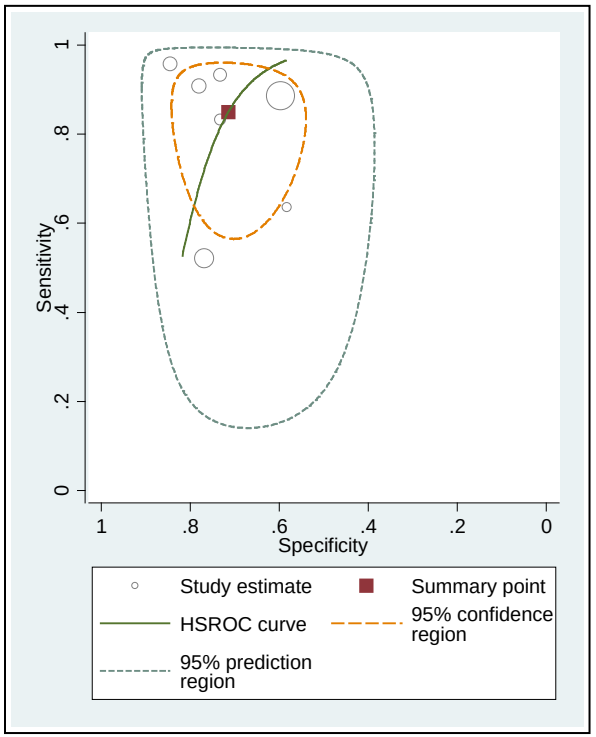
Quality	Author	N	Study Notes	Tumor Type	Imaging VS. Reference	Index Cutoff	Sens|Spec	LR+|LR-	Rule In Test	Rule Out Test
Moderate Quality	Lee,F.Y., 2004	35	tumor counts	chondrosarcomas (high grade 2/3) vs chondrosarcoma (low grade 1), osteochondromas, enchondromas	BS(99mTc) VS. Histopathology	tracer uptake(more)	0.9|0.32	1.32|0.31	POOR	WEAK
Moderate Quality	Bohndorf,K., 1986	48		malignant bone tumors (high grade 2 vs low grade 1)	MRI(1.5, 1.0, 0.5, 0.35, T; no contrast mentioned) VS. histopathology(surgical findings or pathological specimen)	heterogeneous signal	1|0.1333	1.15|0.00	POOR	**STRONG**
Moderate Quality	Sacchi,S., 1987	22	Durie and Salmon criteria	multiple myeloma (high grade stage 2/3 vs low grade stage 1)	bone marrow scintigraphy(99mTc-Nanocoll; 3-4hrs post IV) VS. histology	advanced or moderate marrow expansion	0.8|0.6667	2.40|0.30	WEAK	WEAK
Moderate Quality	Van der Woude,H.J., 1998	71	4 cases of bone metastases	musculoskeletal malignant bone tumors (high grade vs low grade)	MRI(0.5 T; gd-DTPA or gadoteridol) VS. histology(trocar biopsy or resection)	early enhancement (6sec or less after arterial enhancement)	0.9556|0.846	6.21|0.05	**MODERATE**	**STRONG**
Moderate Quality	Van der Woude,H.J., 1998	71	4 cases of bone metastases	musculoskeletal malignant bone tumors (high grade vs low grade)	MRI(0.5 T; gd-DTPA or gadoteridol) VS. histology(trocar biopsy or resection)	peripheral tumor enhancement	0.7778|0.615	2.02|0.36	WEAK	WEAK
Moderate Quality	Van der Woude,H.J., 1998	71	4 cases of bone metastases	musculoskeletal malignant bone tumors (high grade vs low grade)	MRI(0.5 T; gd-DTPA or gadoteridol) VS. histology(trocar biopsy or resection)	type I(rapidly progressing enhancement)	0.9778|0.769	4.24|0.03	WEAK	**STRONG**

Quality	Author	N	Study Notes	Tumor Type	Imaging VS. Reference	Index Cutoff	Sens|Spec	LR+|LR-	Rule In Test	Rule Out Test
Moderate Quality	Dimitrakopoulou-Strauss,A., 2001	43	60% suspected of recurrence (previous surgery/radiotherapy)	soft tissue sarcomas (high grade 2/3 vs low grade 1)	PET(18F-FDG; 60min post IV) VS. Histology(surgery)	radiologist interpretation of parameters(SUV, K1, k3, vascular fraction, fractal dimension)	0.8788|0.8	4.39|0.15	WEAK	**MODERATE**
Moderate Quality	Dimitrakopoulou-Strauss,A., 2001	43	60% suspected of recurrence (previous surgery/radiotherapy)	soft tissue sarcomas (high grade 2/3 vs low grade 1)	PET(18F-FDG; 55-60min post IV) VS. Histology(surgery)	SUV value	0.8485|0.5	1.70|0.30	POOR	WEAK
Moderate Quality	Zhao,F., 2014	82	given contrast; FNCLCC criteria for high and low grade	soft tissue sarcomas (high grade 2/3 vs low grade 1)	MRI(contrast unspecified; magnet unspecified) VS. Histology(surgical resection)	Contrast enhancement (25 percent or more)	0.8971|0.142	1.05|0.72	POOR	POOR
Moderate Quality	Zhao,F., 2014	94	FNCLCC criteria for high and low grade	soft tissue sarcomas (high grade 2/3 vs low grade 1)	MRI(magnet unspecified; no contrast, T2w only) VS. Histology(surgical resection)	Heterogeneous	0.9494|0.266	1.30|0.19	POOR	**MODERATE**
Moderate Quality	Zhao,F., 2014	95	FNCLCC criteria for high and low grade	soft tissue sarcomas (high grade 2/3 vs low grade 1)	MRI(magnet unspecified; no contrast, T1w only) VS. Histology(surgical resection)	Heterogeneous	0.7215|0.375	1.15|0.74	POOR	POOR
Moderate Quality	Zhao,F., 2014	82	given contrast; FNCLCC criteria for high and low grade	soft tissue sarcomas (high grade 2/3 vs low grade 1)	MRI(contrast unspecified; magnet unspecified) VS. Histology(surgical resection)	Peritumoral enhancement	0.9118|0.571	2.13|0.15	WEAK	**MODERATE**
Moderate Quality	Lisle,J.W., 2009	41	FNCLCC grading system	synovial sarcomas (high vs intermediate grade)	PET(18F-FDG; 45min post IV) VS. Histology(surgical resection)	SUVmax greater than 4.35	0.8462|0.642	2.37|0.24	WEAK	WEAK

Quality	Author	N	Study Notes	Tumor Type	Imaging VS. Reference	Index Cutoff	Sens|Spec	LR+|LR-	Rule In Test	Rule Out Test
Low Quality	Brenner,W., 2004	31		chondrosarcomas (high grade vs low grade)	PET(18F-FDG; 45 mins post IV) VS. histopathology(surgical excision)	SUVmax>4	0.625|0.7333	2.34|0.51	WEAK	POOR
Low Quality	Watanabe,H., 2000	22	FOLLOW-UP AUTOPSY diagnosis for some pts	musculoskeletal malignant bone/soft tissue tumors (high grade 3 vs low grade 1/2)	PET(FMT; 40 min post IV) VS. histopathology(biopsy, surgical excision, and autopsy)	SUV of 1.6 or more	0.7273|0.909	8.00|0.30	**MODERATE**	WEAK
Low Quality	Watanabe,H., 2000	22	FOLLOW-UP AUTOPSY diagnosis for some pts	musculoskeletal malignant bone/soft tissue tumors (high grade 3 vs low grade 1/2)	PET(FDG; 40 min post IV) VS. histopathology(biopsy, surgical excision, and autopsy)	SUV of 3.3 or more	0.9091|0.818	5.00|0.11	**MODERATE**	**MODERATE**

DETAILED DATA FINDINGS

FIGURE 2: PICO 2 HSROC META-ANALYSIS - ENHANCEMENT ON CE MRI VS HISTOPATHOLOGY FOR DETERMINING MALIGNANCY OF SOFT TISSUE TUMORS



Meta-analysis of diagnostic accuracy

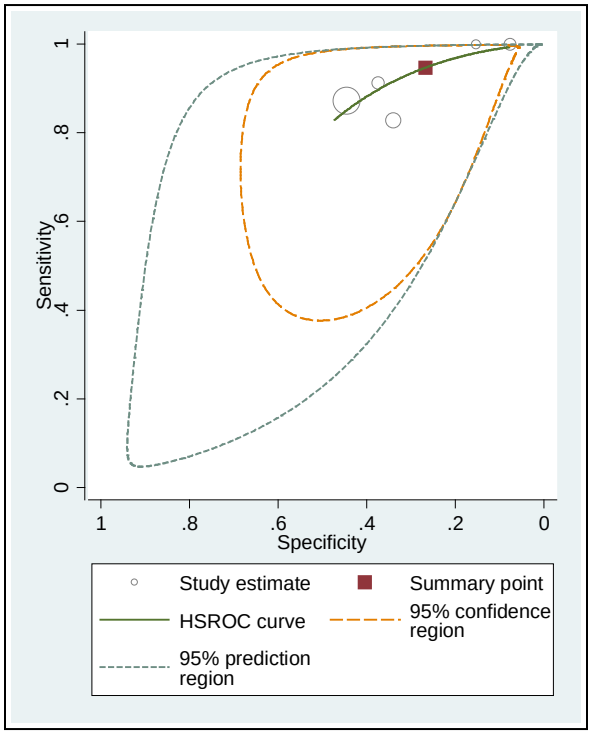
Log likelihood = -35.105292 Number of studies = 7

	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
Bivariate						
E(logitSe)	1.730464	.43218			.883407	2.577521
E(logitSp)	.9185391	.2227626			.4819324	1.355146
Var(logitSe)	.9001318	.6530144			.2171645	3.730983
Var(logitSp)	.115841	.1286706			.0131337	1.021729
Corr(logits)	.1710953	.7303185			-.8621779	.9284943
HSROC						
Lambda	2.570045	.4687372			1.651338	3.488753
Theta	-.2485648	.4063201			-1.044938	.5478079
beta	-1.025161	.6463385	-1.59	0.113	-2.291961	.2416389
s2alpha	.7563215	.7988364			.0954238	5.994547
s2theta	.1338317	.1244708			.0216219	.8283678
Summary pt.						
Se	.8494718	.0552626			.7075277	.9294008
Sp	.7147443	.0454179			.6182041	.7949696
DOR	14.13994	7.093105			5.289979	37.79558
LR+	2.977931	.5261922			2.106249	4.210364
LR-	.2106043	.0795043			.1004926	.4413676
1/LR-	4.748242	1.792487			2.265685	9.950985

Covariance between estimates of E(logitSe) & E(logitSp) .0076181

Reference	Quality	Sens | Spec	LR+ | LR-
Crombe,A., 2016	High Quality	0.52174|0.7692	2.26|0.622
Gruber,L., 2017	High Quality	0.8871|0.5973	2.20|0.189
Barile,A., 2007	Moderate Quality	0.6364|0.5833	1.53|0.623
Daniel,A.,Jr., 2009	Moderate Quality	0.9583|0.8462	6.23|0.049
Tacikowska,M., 2002(a)	Moderate Quality	0.8333|0.7333	3.12|0.227
Tacikowska,M., 2002(b)	Moderate Quality	0.9333|0.7333	3.5|0.091
Van der Woude,H.J., 1998	Moderate Quality	0.909|0.7812	4.16|0.116

FIGURE 3: PICO 2 HSROC META-ANALYSIS - HETEROGENEOUS SIGNAL ON CE MRI VS HISTOPATHOLOGY FOR DETERMINING MALIGNANCY OF SOFT TISSUE TUMORS



Meta-analysis of diagnostic accuracy

Log likelihood = -23.483961 Number of studies = 5

	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
Bivariate						
E(logitSe)	2.882999	.7750806			1.363869	4.40213
E(logitSp)	-1.005923	.407841			-1.805277	-.2065698
Var(logitSe)	1.220149	1.791487			.068649	21.68662
Var(logitSp)	.578037	.5422151			.09194	3.634184
Corr(logits)	-1	.			.	.
HSROC						
Lambda	1.179337	.75279			-.2961048	2.654778
Theta	1.802161	.4817149			.8580175	2.746305
beta	-.3735452	.6608381	-0.57	0.572	-1.668764	.9216737
s2alpha	0	.			.	.
s2theta	.8398163	.873217			.1094282	6.445244
Summary pt.						
Se	.9469996	.0389023			.7963878	.9878971
Sp	.2677784	.0799667			.1412099	.4485404
DOR	6.53437	4.152192			1.88069	22.70336
LR+	1.293324	.1189469			1.079996	1.548789
LR-	.1979263	.1213692			.0595036	.6583603
1/LR-	5.052385	3.098142			1.518925	16.8057

Covariance between estimates of E(logitSe) & E(logitSp) -.1816509

Reference	Quality	Sens | Spec	LR+ | LR-
Liu,L., 2011	High Quality	1|0.1538	1.18|0
Chung,W.J., 2012	Moderate Quality	0.8725|0.4451	1.57|0.286
Daniel,A.,Jr., 2009	Moderate Quality	1|0.0769	1.08|0
Kalayanarooj,S., 2008	Moderate Quality	0.8286|0.3404	1.26|0.504
Sen,J., 2010	Moderate Quality	0.913|0.375	1.46|0.232

MRI: MAGNET STRENGTH

In the absence of reliable evidence, it is the opinion of the work group that a magnet of at least 1.5 Tesla should be used when imaging musculoskeletal neoplasms.

Strength of Recommendation: Consensus 

Description: There is no supporting evidence. In the absence of reliable evidence, the work group is making a recommendation based on their clinical opinion.

RATIONALE

No investigations directly compare the diagnostic performance of different magnet strengths on the same tumors, limiting the statements that can be made regarding whether increasing strength of the magnet improves diagnostic performance. However, strong evidence including several high and moderate quality investigations (Henninger, Crombe, Thornhill, Daniel, and Negendank) have demonstrated a strong sensitivity and specificity for differentiating between benign and malignant etiologies when imaging the tumor with a 1.5T magnet strength (1.5T magnets are widely available and are known to provide good quality images), when compared with the gold standard of histologic diagnosis. 1.5T was the most commonly used magnet strength in the literature, however, these several moderate strength studies demonstrated less accurate diagnostic results for 1.5T magnet strength compared to stronger magnets (Chen, Kalayanarooj).

RISKS AND HARMS OF IMPLEMENTING THIS RECOMMENDATION

Increasing magnet strength of MRI poses no substantial risk to the patient who qualifies for MRI.

FUTURE RESEARCH

While the recommendation to evaluate the mass with the highest strength magnet is logical, future investigations directly comparing the diagnostic yield of varying strengths of magnets would be helpful in solidifying this recommendation and determining the minimum acceptable magnet strength to provide the detail needed for clinical decision-making.

RESULTS

STUDY QUALITY TABLE 3: MRI MAGNET STRENGTH

Study	Representative Population	Clear Selection Criteria	Detailed Enough to Replicate	Reference Standard Identifies Target Condition	Blinding	Other Bias?	Inclusion	Strength
Bakir,B., 2014	●	◑	●	●	○	◑	Include	Low Quality
Bonarelli,C., 2015	●	◑	●	●	●	◑	Include	Moderate Quality
Chen,C.K., 2009	●	◑	●	●	●	◑	Include	Moderate Quality
Choi,B.B., 2013	●	◑	●	●	○	◑	Include	Low Quality
Crombe,A., 2016	●	●	●	●	●	●	Include	High Quality
Daniel,A.,Jr., 2009	●	●	●	●	◑	◑	Include	Moderate Quality
Davies,A.M., 2004	●	●	●	●	○	◑	Include	Moderate Quality
Gondim Teixeira,P.A., 2016	●	●	●	●	●	◑	Include	High Quality
Henninger,B., 2013	●	●	●	●	●	◑	Include	High Quality
Jeon,J.Y., 2016	●	●	●	●	●	◑	Include	High Quality
Kalayanarooj,S., 2008	●	◑	●	●	◑	◑	Include	Moderate Quality
Lee,S.Y., 2016	●	●	●	●	●	◑	Include	High Quality
Liu,L., 2011	●	●	●	●	●	◑	Include	High Quality
Meng,X.-X., 2016	●	◑	●	●	●	●	Include	High Quality
Moulton,J.S., 1995	●	●	●	○	●	○	Include	Low Quality
Negendank,W.G., 1989	●	●	●	●	◑	◑	Include	Moderate Quality
Ohguri,T., 2003	●	◑	●	●	●	◑	Include	Moderate Quality
Pang,K.K., 2003	●	◑	●	●	●	◑	Include	Moderate Quality

Study	Representative Population	Clear Selection Criteria	Detailed Enough to Replicate	Reference Standard Identifies Target Condition	Blinding	Other Bias?	Inclusion	Strength
Pereira,H.M., 2014	●	◑	●	●	◑	◑	Include	Moderate Quality
Pozzi,G., 2012	●	◑	●	●	○	◑	Include	Low Quality
Qi,Z.H., 2009	●	◑	●	●	◑	●	Include	Moderate Quality
Rupp,R.E., 1995	●	○	●	●	○	◑	Include	Low Quality
Russo,F., 2012	●	◑	●	●	●	◑	Include	Moderate Quality
Sen,J., 2010	●	●	●	●	◑	◑	Include	Moderate Quality
Tacikowska,M., 2002	●	◑	●	●	◑	◑	Include	Moderate Quality
Tacikowska,M., 2002	●	◑	●	●	◑	◑	Include	Moderate Quality
Teo,E.L., 2000	●	◑	●	○	●	◑	Include	Low Quality
Thornhill,R.E., 2014	●	●	●	●	●	◑	Include	High Quality
Van der Woude,H.J., 1998	●	●	●	●	◑	◑	Include	Moderate Quality
van Rijswijk,C.S., 2002	●	◑	●	●	●	◑	Include	Moderate Quality
Yildirim,A., 2016	●	◑	●	○	●	◑	Include	Low Quality

SUMMARY OF DATA FINDINGS

SUMMARY TABLE 7: PICO 3 - 1.5T MRI VS HISTOPATHOLOGY FOR DIAGNOSING MALIGNANCY OF BONE OR BONE/SOFT TISSUE TUMORS

DIAGNOSING MALIGNANCY OF BONE OR BONE/SOFT TISSUE TUMORS ON MRI 1.5 T MAGNET STRENGTH			High	Moderate	Low
Tumor Type	**Imaging Method**	**Diagnostic Threshold**	**Henninger,B., 2013***	**Negendank,W.G., 1989**	**Choi,B.B., 2013***
Bone tumors	CE MRI(1.5T; gadoterate meglumine or gadobutrol)	Tracer uptake(avg of 2 radiologists)	**100** **94.44**		
Bone/Soft tissue tumors	CE MR spectroscopy(1.5T; phosphorus-31)	Higher ratios of PME/NTP and phosphodiester/NTP, lower phosphocreatine/NTP ratio, higher mean pH		**100** **94.12**	
	CE MRI(1.5T; IV gadopentetate dimeglumine)	Multilocular diffuse contrast enhancement			**83.33** 56.2
	CE MRI(1.5T; IV gadopentetate dimeglumine; T1w only)	Intermediate signal intensity			72.22 75
	CE MRI(1.5T; IV gadopentetate dimeglumine; T2w only)	Heterogeneous signal			**100** 18.75
		High/Intermediate signal intensity			**100** 12.5

SUMMARY TABLE 8: PICO 3 - 1.5T MRI VS HISTOPATHOLOGY FOR DIAGNOSING MALIGNANCY OF SOFT TISSUE TUMORS

DIAGNOSING MALIGNANCY OF SOFT TISSUE TUMORS ON MRI 1.5 T MAGNET STRENGTH		High			Moderate								Low
Imaging Method	Diagnostic Threshold	Crombe,A., 2016**	Gondim Teixeira,P.A., 2016	Thornhill,R.E., 2014*	Bonarelli,C., 2015	Chen,C.K., 2009(c)	Daniel,A.,Jr., 2009	Kalayanarooj,S., 2008	Ohguri,T., 2003*	Russo,F., 2012	Sen,J., 2010	van Rijswijk,C.S., 2002	Bakir,B., 2014*
1H-MRS(1.5 T; gadobutrol paramagnetic)	Choline peak present(signal/noise ratio >3)									**94.44** **83.3**			
CE MRI(1.5T; contrast unspecified) and DWI	DWI quotient greater than 1.99												**92** **100**
	Postcontrast quotient greater than 1.19												**100** **100**
	ADC value of 1.05 or less												**96** **100**
CE MRI(1.5 T; gadolinium)	Manual method ADC avg of 1.65 or more				62.5 53.66								
	Manual method ADC min of 1.28 or more				79.17 60.9								
	Semiautomatic method ADC avg of 1.68 or more				62.5 56.1								
	Semiautomatic method ADC min of 0.91 or more				62.5 63.41								
	Heterogeneous contrast enhancement						**100** 7.69						
	Ill-defined margins, intra-tumoral fat, hemorrhagic component, fibrosis, or tail sign	**92.75** **92.3**											
	Presence of bone changes						**83.33** **84.6**						
	Radiologist interpretation(size, shape, margins, enhancement)						**95.83** **84.6**						
	Tumor surface with more than 50% enhancement	52.17 76.9											
CE MRI(1.5 T; gadolinium; T1w only)	Heterogeneous signal							51.43 59.5					
	Isointensity signal						70.83 76.9						
	Absence of hyperintense tracts						**100** 11.54						
CE MRI(1.5 T; gadolinium; T2w only)	Heterogeneous signal							**82.86** 34					
	Hyperintensity signal						**95.83** 38.4						
CE MRI(1.5 T; Gd-DPTA)	Bone involvement										8.7 **100**		
	Heterogeneous contrast enhancement										**91.3** 37.5		
	3 or more thick septa or nodular/patchy non-adipose component								65.22 **90.6**				
CE MRI(1.5 T; Gd-DPTA; T1w only)	Heterogeneous signal										30.43 78.1		
CE MRI(1.5 T; Gd-DPTA; T2w only)	Heterogeneous signal										**86.96** 31.2		
CE MRI(1.5T; contrast unspecified), T2w, and DWI	T2-weighted quotient greater than 2.61												40 **87.5**
CE MRI(1.5T; gadolinium; DWI)	ADC ratio of 0.915 or more		60 67.39										
	ADC ratio of 1.32 or more		**90** 30.43										
	ADC value of 1.19 or more		53.33 65.2										
	ADC value of 1.68 or more		**96.67** 30.4										
MRI(1.5 T; w/ or w/o gadolinium)	Bone involvement					35.48 75							
	Presence of fat rim sign					4.84 78.5							
MRI(1.5 T; w/ or w/o gadolinium; T1 only)	High signal matrix					43.55 69.6							
MRI(1.5 T; w/ or w/o gadolinium; T2 only)	High signal matrix					**85.48** 41							
MRI(1.5T; w/ or w/o gadolinium)	Radiologist interpretation			**80** 79.17									
MRI(1.5T; no contrast mentioned; DWI)	True diffusion coefficient of 1.13 or less											70 75	
MRI(1.5T; no contrast)	CAD(cross validated 2 shape and 2 texture features)			**85** **95.83**									

SUMMARY TABLE 9: PICO 3 - MRI (VARYING MAGNET STRENGTH) VS HISTOPATHOLOGY FOR DIAGNOSING MALIGNANCY OF BONE AND/OR SOFT TISSUE TUMORS

DIAGNOSING MALIGNANCY USING VARIOUS MRI MAGNET STRENGTHS			High				Moderate					
Tumor Type	Imaging Method	Diagnostic Threshold	Jeon,J.Y., 2016	Lee,S.Y., 2016	Liu,L., 2011	Meng,X.-X., 2016**	Davies,A.M., 2004	Pang,K.K., 2003	Qi,Z.H., 2009	Tacikowska,M., 2002(a)	Tacikowska,M., 2002(b)	Van der Woude,H.J., 1998
Bone tumors	CE MRI(0.5 T; gd-DTPA or gadoteridol)	Early enhancement(6sec or less after arterial enhancement)										66.2 56
		Peripheral tumor enhancement										63.38 76
		Type I(rapidly progressing enhancement)										70.42 50
	CE MRI(3.0 T; gadoterate dimeglumine; 3-5 min post IV; T1 & T2)	Radiologist interpretation(grade 3 or 2, degree of tumor vascularity)				**92.31** 7.6						
	DCE-MRI(3.0 T; 5-10 s before gadoterate meglumine IV; T1 only)	Maximum enhancement <=807.47				76.92 61.5						
		Relative maximum enhancement <177.45				76.92 46.1						
Bone/Soft tissue tumors	MR spectroscopy(3T; no contrast mentioned)	Radiologist interpretation(Choline/creatine ratio)							**94.44** **83.3**			
Soft tissue tumors	CE MRI(0.5 T; gd-DTPA or gadoteridol)	Early enhancement(6sec or less after arterial enhancement)										**90.91** 75
		Early enhancement(6sec or less after arterial enhancement) and peripheral enhancement										**95.45** 71.8
		Early enhancement(6sec or less after arterial enhancement) and type I(rapid progressing enhancement)										**90.91** 71.8
		Peripheral enhancement and type I(rapidly progressing enhancement)										**90.91** 78.1
		Peripheral tumor enhancement										72.73 **96.8**
		Type I(rapidly progressing enhancement)										**86.36** **81.2**
	MRI(0.5 T; no contrast mentioned; T1w only)	Heterogeneous signal						68.75 71.4				
	MRI(0.5 T; no contrast mentioned; T2w only)	Heterogeneous signal						**87.5** 64.29				
	MRI(1.0 T; w/ and w/o gadolinium chelate)	Radiologist interpretation					60.32 **87.5**					
	CE MRI(2T; gadolinium-DTPA)	Tissue enhancement rate(Erc%/min) greater than 25								**93.33** 66.6		
		Total contrast enhancement(Tec%) more than 80%								**83.33** 73.3		
	CE MRI(dynamic 2.0 T; Gd-DTPA)	Periphery-centre or whole tumor enhancement									**92.86** 42.8	
		Tissue enhancement rate(erc%) greater than 0.6									**93.33** 73.3	
	CE MRI(3T; contrast unspecified)	ADC score of 2-4(malignant)		**97.06** 72.4								
	CE MRI(3T; contrast unspecified) and DWI	ADC score of 2-4(malignant)		**97.06** **89.6**								
	CE MRI(3T; gadolinium; T1 only)	Marked and heterogeneous enhancement			**100** 15.38							
	MRI(3T; w/ or w/o gadopentetate dimeglumine)	Destruction of deep fascia			**93.1** **100**							
	MRI(3T; w/ or w/o gadopentetate dimeglumine; T1 only)	Heterogeneous signal			65.52 68.4							
	MRI(3T; w/ or w/o gadopentetate dimeglumine; T2 only)	Heterogeneous/iso/low signal intensity			**96.55** 31.5							
	DWI-MRI(3.0 T; no contrast mentioned; T1 & T2)	Radiologist interpretation(lobulation, fascial oedema, skin thickening, hemorrhage or necrosis)	**96** **85.71**									
	MRI(3.0 T; no contrast mentioned; T1 & T2)	Mean ADC value from enhancing solid portion <1090.2	66.67 74.2									
		Mean ADC value from entire mass on axial plane <1496.7	**100** 51.43									
		Radiologist interpretation(lobulation, fascial oedema, skin thickening, hemorrhage or necrosis)	**80** **88.57**									

SUMMARY TABLE 10: PICO 3 - MRI (VARYING MAGNET STRENGTH) VS HISTOPATHOLOGY FOR DIAGNOSING STAGE OR PRESENCE OF BONE TUMORS

			Moderate		Low	
Tumor Type	**Imaging Method**	**Diagnostic Threshold**	**Pereira,H.M., 2014***	**Van der Woude,H.J., 1998**	**Pozzi,G., 2012***	**Rupp,R.E., 1995****
Bone tumors	MRI(0.5 T; gd-DTPA or gadoteridol)	Early enhancement(6sec or less after arterial enhancement)		**95.56 84.6**		
		Peripheral tumor enhancement		77.78 61.5		
		Type I(rapidly progressing enhancement)		**97.78** 76.9		
Bone tumors	MRI(1.5 T; w/ or w/o gadolinium)	Involving 50% or more of lesion	71.43 56.2			
		Radiologist interpretation				**83.33** 25
	MRI(1.5T; w/ or w/o gadolinium; T1 and T2)	Low T1 and high T2 signals				**94.44** 62.5
	MRI(1.5T; w/ or w/o gadolinium; T1 only)	Complete/incomplete replacement of bone marrow				**94.44** 31.2
	MRI(1.5 T; no contrast mentioned; DWI)	Radiologist interpretation(hyper or isointense signal)			**95.65 90**	

DATA TABLE 8: PICO 3 - BONE TUMOR DIAGNOSIS

Quality	Author	N	Study Notes	Tumor Type	Imaging VS. Reference	Index Cutoff	Sens|Spec	LR+|LR-	Rule In Test	Rule Out Test
Moderate Quality	Pereira,H.M., 2014	30	confirmed giant cell bone tumor pts; 86% present pain	secondary aneurysmal bone cyst	MRI(1.5 T; w/ or w/o gadolinium) VS. Histopathology	involving 50% or more of lesion	0.7143|0.562	1.63|0.51	POOR	POOR
Low Quality	Pozzi,G., 2012	33	confirmed vertebral fractures	neoplastic or osteoporotic vertebral fractures	MRI(1.5 T; no contrast mentioned; DWI) VS. histology(biopsy)	radiologist interpretation (hyper or isointense signal)	0.9565|0.9	9.57|0.05	**MODERATE**	**STRONG**
Low Quality	Rupp,R.E., 1995	34	confirmed compression spine fractures	vertebral tumors or osteoporosis	MRI(1.5T; w/ or w/o gadolinium) VS. histology(CT-guided percutaneous biopsy)	radiologist interpretation	0.8333|0.25	1.11|0.67	POOR	POOR
Low Quality	Rupp,R.E., 1995	34	confirmed compression spine fractures	vertebral tumors or osteoporosis	MRI(1.5T; w/ or w/o gadolinium; T1 and T2) VS. histology(CT-guided percutaneous biopsy)	low T1 and high T2 signals	0.9444|0.625	2.52|0.09	WEAK	**STRONG**
Low Quality	Rupp,R.E., 1995	34	confirmed compression spine fractures	vertebral tumors or osteoporosis	MRI(1.5T; w/ or w/o gadolinium; T1 only) VS. histology(CT-guided percutaneous biopsy)	complete/incomplete replacement of bone marrow	0.9444|0.312	1.37|0.18	POOR	**MODERATE**

DATA TABLE 9: PICO 3 - MALIGNANCY

Quality	Author	N	Study Notes	Tumor Type	Imaging VS. Reference	Index Cutoff	Sens|Spec	LR+|LR-	Rule In Test	Rule Out Test
High Quality	Henninger,B., 2013	28	avg of 2 readers	bone lesion (ewing sarcoma vs osteomyelitis)	MRI(1.5T; gadoterate meglumine or gadobutrol) VS. Histopathology(biopsy ; open or guided)	Tracer uptake(avg of 2 radiologists)	1|0.9444	18.00|0.00	**STRONG**	**STRONG**
High Quality	Thornhill,R.E., 2014	44	computer assisted image reading	liposarcoma vs lipoma	MRI(1.5T; no contrast) VS. Pathology(biopsy or excision)	CAD(cross validated 2 shape and 2 texture features)	0.85|0.9583	20.40|0.16	**STRONG**	**MODERATE**
High Quality	Thornhill,R.E., 2014	44	avg sens and spec of 2 radiologists	liposarcoma vs lipoma	MRI(1.5T; w/ or w/o gadolinium) VS. Pathology(biopsy or excision)	radiologist interpretation	0.8|0.7917	3.84|0.25	WEAK	WEAK
High Quality	Gondim Teixeira,P.A., 2016	76		non-fatty soft tissue tumors	MRI(1.5T; gadolinium; DWI) VS. histology	ADC ratio of 0.915 or more	0.6|0.6739	1.84|0.59	POOR	POOR
High Quality	Gondim Teixeira,P.A., 2016	76		non-fatty soft tissue tumors	MRI(1.5T; gadolinium; DWI) VS. histology	ADC ratio of 1.32 or more	0.9|0.3043	1.29|0.33	POOR	WEAK
High Quality	Gondim Teixeira,P.A., 2016	76		non-fatty soft tissue tumors	MRI(1.5T; gadolinium; DWI) VS. histology	ADC value of 1.19 or more	0.5333|0.652	1.53|0.72	POOR	POOR
High Quality	Gondim Teixeira,P.A., 2016	76		non-fatty soft tissue tumors	MRI(1.5T; gadolinium; DWI) VS. histology	ADC value of 1.68 or more	0.9667|0.304	1.39|0.11	POOR	**MODERATE**
High Quality	Crombe,A., 2016	95		peripheral soft tissue tumors with myxoid stroma	MRI(1.5T; gadolinium) VS. histopathology(surgery)	ill-defined margins, intra-tumoral fat, hemorrhagic component, fibrosis, or tail sign	0.9275|0.923	12.06|0.08	**STRONG**	**STRONG**

Quality	Author	N	Study Notes	Tumor Type	Imaging VS. Reference	Index Cutoff	Sens|Spec	LR+|LR-	Rule In Test	Rule Out Test
High Quality	Crombe,A., 2016	95		peripheral soft tissue tumors with myxoid stroma	MRI(1.5T; gadolinium) VS. histopathology(surgery)	tumor surface with more than 50% enhancement	0.5217|0.769	2.26|0.62	WEAK	POOR
High Quality	Lee,S.Y., 2016	63		soft tissue tumors	MRI(3T; contrast unspecified) VS. Pathology	ADC score of 2-4(malignant)	0.9706|0.724	3.52|0.04	WEAK	**STRONG**
High Quality	Lee,S.Y., 2016	63		soft tissue tumors	MRI(3T; contrast unspecified) and DWI VS. Pathology	ADC score of 2-4(malignant)	0.9706|0.896	9.38|0.03	**MODERATE**	**STRONG**
High Quality	Liu,L., 2011	48	31 patients received IV contrast	soft tissue tumors (lower limbs)	MRI(3T; w/ or w/o gadopentetate dimeglumine; T1 only) VS. histopathology(biopsy or excision)	heterogeneous signal	0.6552|0.684	2.08|0.50	WEAK	POOR
High Quality	Liu,L., 2011	48	31 patients received IV contrast	soft tissue tumors (lower limbs)	MRI(3T; w/ or w/o gadopentetate dimeglumine; T2 only) VS. histopathology(biopsy or excision)	heterogeneous/iso/low signal intensity	0.9655|0.315	1.41|0.11	POOR	**MODERATE**
High Quality	Liu,L., 2011	48	31 patients received IV contrast	soft tissue tumors (lower limbs)	MRI(3T; w/ or w/o gadopentetate dimeglumine) VS. histopathology(biopsy or excision)	Destruction of deep fascia	0.931|1	93.10|0.07	**STRONG**	**STRONG**
High Quality	Liu,L., 2011	31		soft tissue tumors (lower limbs)	MRI(3T; gadolinium; T1 only) VS. histopathology(biopsy or excision)	marked and heterogeneous enhancement	1|0.1538	1.18|0.00	POOR	**STRONG**

Quality	Author	N	Study Notes	Tumor Type	Imaging VS. Reference	Index Cutoff	Sens|Spec	LR+|LR-	Rule In Test	Rule Out Test
High Quality	Jeon,J.Y., 2016	60	includes 13 malignant melanomas, squamous-cell carcinomas, and lymphoma	soft tissue tumors (superficial)	DWI-MRI(3.0 T; no contrast mentioned; T1 & T2) VS. histopathology	radiologist interpretation (lobulation, fascial oedema, skin thickening, hemorrhage or necrosis)	0.96|0.8571	6.72|0.05	**MODERATE**	**STRONG**
High Quality	Jeon,J.Y., 2016	60	includes 13 malignant melanomas, squamous-cell carcinomas, and lymphoma	soft tissue tumors (superficial)	MRI(3.0 T; no contrast mentioned; T1 & T2) VS. histopathology	radiologist interpretation (lobulation, fascial oedema, skin thickening, hemorrhage or necrosis)	0.8|0.8857	7.00|0.23	**MODERATE**	WEAK
High Quality	Jeon,J.Y., 2016	47		soft tissue tumors (superficial)	MRI(3.0 T; no contrast mentioned; T1 & T2) VS. histopathology	mean ADC value from enhancing solid portion <1090.2	0.6667|0.742	2.59|0.45	WEAK	WEAK
High Quality	Jeon,J.Y., 2016	47		soft tissue tumors (superficial)	MRI(3.0 T; no contrast mentioned; T1 & T2) VS. histopathology	mean ADC value from entire mass on axial plane <1496.7	1|0.5143	2.06|0.00	WEAK	**STRONG**
High Quality	Meng,X.-X., 2016	26		spinal tumors	DCE-MRI(3.0 T; 5-10 s before gadoterate meglumine IV; T1 only) VS. histopathology	Maximum enhancement <=807.47	0.7692|0.615	2.00|0.38	POOR	WEAK
High Quality	Meng,X.-X., 2016	26		spinal tumors	MRI(3.0 T; gadoterate dimeglumine; 3-5 min post IV; T1 & T2) VS. histopathology	radiologist interpretation (grade 3 or 2, degree of tumor vascularity)	0.9231|0.076	1.00|1.00	POOR	POOR

Quality	Author	N	Study Notes	Tumor Type	Imaging VS. Reference	Index Cutoff	Sens|Spec	LR+|LR-	Rule In Test	Rule Out Test
High Quality	Meng,X.-X., 2016	26		spinal tumors	DCE-MRI(3.0 T; 5-10 s before gadoterate meglumine IV; T1 only) VS. histopathology	relative maximum enhancement <177.45	0.7692|0.461	1.43|0.50	POOR	POOR
Moderate Quality	Qi,Z.H., 2009	54	1 metastases included	bone/soft tissue tumors	MR spectroscopy(3T; no contrast mentioned) VS. Histology(needle biopsy or surgery)	radiologist interpretation (Choline/creatine ratio)	0.9444|0.833	5.67|0.07	**MODERATE**	**STRONG**
Moderate Quality	Negendank,W.G., 1989	34		bone/soft tissue tumors (extremities)	MR spectroscopy(1.5T; phosphorus-31) VS. histology(biopsy)	higher ratios of PME/NTP and phosphodiester/NTP, lower phosphocreatine/NTP ratio, higher mean pH	1|0.9412	17.00|0.00	**STRONG**	**STRONG**
Moderate Quality	Van der Woude,H.J., 1998	121	4 cases of bone metastases	musculoskeletal bone tumors	MRI(0.5 T; gd-DTPA or gadoteridol) VS. histology(trocar biopsy or resection)	early enhancement (6sec or less after arterial enhancement)	0.662|0.56	1.50|0.60	POOR	POOR
Moderate Quality	Van der Woude,H.J., 1998	121	4 cases of bone metastases	musculoskeletal bone tumors	MRI(0.5 T; gd-DTPA or gadoteridol) VS. histology(trocar biopsy or resection)	peripheral tumor enhancement	0.6338|0.76	2.64|0.48	WEAK	WEAK
Moderate Quality	Van der Woude,H.J., 1998	121	4 cases of bone metastases	musculoskeletal bone tumors	MRI(0.5 T; gd-DTPA or gadoteridol) VS. histology(trocar biopsy or resection)	type I(rapidly progressing enhancement)	0.7042|0.5	1.41|0.59	POOR	POOR

Quality	Author	N	Study Notes	Tumor Type	Imaging VS. Reference	Index Cutoff	Sens|Spec	LR+|LR-	Rule In Test	Rule Out Test
Moderate Quality	Van der Woude,H.J., 1998	54		musculoskeletal soft tissue tumors	MRI(0.5 T; gd-DTPA or gadoteridol) VS. histology(trocar biopsy or resection)	early enhancement (6sec or less after arterial enhancement)	0.9091|0.75	3.64|0.12	WEAK	**MODERATE**
Moderate Quality	Van der Woude,H.J., 1998	54		musculoskeletal soft tissue tumors	MRI(0.5 T; gd-DTPA or gadoteridol) VS. histology(trocar biopsy or resection)	early enhancement (6sec or less after arterial enhancement) and peripheral enhancement	0.9545|0.718	3.39|0.06	WEAK	**STRONG**
Moderate Quality	Van der Woude,H.J., 1998	54		musculoskeletal soft tissue tumors	MRI(0.5 T; gd-DTPA or gadoteridol) VS. histology(trocar biopsy or resection)	early enhancement (6sec or less after arterial enhancement) and type I(rapid progressing enhancement)	0.9091|0.718	3.23|0.13	WEAK	**MODERATE**
Moderate Quality	Van der Woude,H.J., 1998	54		musculoskeletal soft tissue tumors	MRI(0.5 T; gd-DTPA or gadoteridol) VS. histology(trocar biopsy or resection)	peripheral enhancement and type I(rapidly progressing enhancement)	0.9091|0.781	4.16|0.12	WEAK	**MODERATE**
Moderate Quality	Van der Woude,H.J., 1998	54		musculoskeletal soft tissue tumors	MRI(0.5 T; gd-DTPA or gadoteridol) VS. histology(trocar biopsy or resection)	peripheral tumor enhancement	0.7273|0.968	23.27|0.28	**STRONG**	WEAK

Quality	Author	N	Study Notes	Tumor Type	Imaging VS. Reference	Index Cutoff	Sens|Spec	LR+|LR-	Rule In Test	Rule Out Test
Moderate Quality	Van der Woude,H.J., 1998	54		musculoskeletal soft tissue tumors	MRI(0.5 T; gd-DTPA or gadoteridol) VS. histology(trocar biopsy or resection)	type I(rapidly progressing enhancement)	0.8636|0.812	4.61|0.17	WEAK	**MODERATE**
Moderate Quality	Chen,C.K., 2009(c)	118	4 metastases included; 2 pts without IV contrast	soft tissue tumors	MRI(1.5 T; w/ or w/o gadolinium) VS. Histology	bone involvement	0.3548|0.75	1.42|0.86	POOR	POOR
Moderate Quality	Chen,C.K., 2009(c)	118	4 metastases included; 2 pts without IV contrast	soft tissue tumors	MRI(1.5 T; w/ or w/o gadolinium; T1 only) VS. Histology	high signal matrix	0.4355|0.696	1.44|0.81	POOR	POOR
Moderate Quality	Chen,C.K., 2009(c)	118	4 metastases included; 2 pts without IV contrast	soft tissue tumors	MRI(1.5 T; w/ or w/o gadolinium) VS. Histology	presence of fat rim sign	0.0484|0.785	0.23|1.21	POOR	POOR
Moderate Quality	Chen,C.K., 2009(c)	118	4 metastases included; 2 pts without IV contrast	soft tissue tumors	MRI(1.5 T; w/ or w/o gadolinium; T2 only) VS. Histology	high signal matrix	0.8548|0.410	1.45|0.35	POOR	WEAK
Moderate Quality	Daniel,A.,Jr., 2009	50		soft tissue tumors	MRI(1.5T; gadolinium; T1w only) VS. Histopathology	absence of hyperintense tracts	1|0.1154	1.13|0.00	POOR	**STRONG**
Moderate Quality	Daniel,A.,Jr., 2009	50		soft tissue tumors	MRI(1.5T; gadolinium) VS. Histopathology	radiologist interpretation (size, shape, margins, enhancement)	0.9583|0.846	6.23|0.05	**MODERATE**	**STRONG**
Moderate Quality	Daniel,A.,Jr., 2009	50		soft tissue tumors	MRI(1.5T; gadolinium) VS. Histopathology	heterogeneous contrast enhancement	1|0.0769	1.08|0.00	POOR	**STRONG**

Quality	Author	N	Study Notes	Tumor Type	Imaging VS. Reference	Index Cutoff	Sens|Spec	LR+|LR-	Rule In Test	Rule Out Test
Moderate Quality	Daniel,A.,Jr., 2009	50		soft tissue tumors	MRI(1.5 T; gadolinium; T1w only) VS. Histopathology	isointensity signal	0.7083|0.769	3.07|0.38	WEAK	WEAK
Moderate Quality	Daniel,A.,Jr., 2009	50		soft tissue tumors	MRI(1.5 T; gadolinium; T2w only) VS. Histopathology	hyperintensity signal	0.9583|0.384	1.56|0.11	POOR	**MODERATE**
Moderate Quality	Daniel,A.,Jr., 2009	50		soft tissue tumors	MRI(1.5T; gadolinium) VS. Histopathology	presence of bone changes	0.8333|0.846	5.42|0.20	**MODERATE**	**MODERATE**
Moderate Quality	Davies,A.M., 2004	111	previously potentially misdiagnosed as STS	soft tissue tumors	MRI(1.0 T; w/ and w/o gadolinium chelate) VS. histology(surgical re-excision)	radiologist interpretation	0.6032|0.875	4.83|0.45	WEAK	WEAK
Moderate Quality	Kalayanarooj,S., 2008	82	MOD QUAL; weak ref pts removed from this group	soft tissue tumors	MRI(1.5 T; gadolinium; T2w only) VS. histopathology(biopsy)	heterogeneous signal	0.8286|0.340	1.26|0.50	POOR	POOR
Moderate Quality	Kalayanarooj,S., 2008	82	MOD QUAL; weak ref pts removed from this group	soft tissue tumors	MRI(1.5 T; gadolinium; T1w only) VS. histopathology(biopsy)	heterogeneous signal	0.5143|0.595	1.27|0.82	POOR	POOR
Moderate Quality	Russo,F., 2012	36	Excluding 1 metastases and 6 undetermined	soft tissue tumors	1H-MRS(1.5 T; gadobutrol paramagnetic) VS. pathology(surgical resection or biopsy)	choline peak present(signal/noise ratio >3)	0.9444|0.833	5.67|0.07	**MODERATE**	**STRONG**
Moderate Quality	Sen,J., 2010	55		soft tissue tumors	MRI(1.5 T; Gd-DPTA) VS. Histopathology(surgical resection)	bone involvement	0.087|1	8.70|0.91	**MODERATE**	POOR

Quality	Author	N	Study Notes	Tumor Type	Imaging VS. Reference	Index Cutoff	Sens|Spec	LR+|LR-	Rule In Test	Rule Out Test
Moderate Quality	Sen,J., 2010	55		soft tissue tumors	MRI(1.5 T; Gd-DPTA) VS. Histopathology(surgical resection)	heterogeneous contrast enhancement	0.913|0.375	1.46|0.23	POOR	WEAK
Moderate Quality	Sen,J., 2010	55		soft tissue tumors	MRI(1.5 T; Gd-DPTA; T1w only) VS. Histopathology(surgical resection)	heterogeneous signal	0.3043|0.781	1.39|0.89	POOR	POOR
Moderate Quality	Sen,J., 2010	55		soft tissue tumors	MRI(1.5 T; Gd-DPTA; T2w only) VS. Histopathology(surgical resection)	heterogeneous signal	0.8696|0.312	1.27|0.42	POOR	WEAK
Moderate Quality	Tacikowska,M., 2002(a)	45		soft tissue tumors	MRI(2T; gadolinium-DTPA) VS. Histology(biopsy)	tissue enhancement rate(Erc%/min) greater than 25	0.9333|0.666	2.80|0.10	WEAK	**STRONG**
Moderate Quality	Tacikowska,M., 2002(a)	33		soft tissue tumors	MRI(2T; gadolinium-DTPA) VS. Histology(biopsy)	total contrast enhancement (Tec%) more than 80%	0.8333|0.733	3.13|0.23	WEAK	WEAK
Moderate Quality	Tacikowska,M., 2002(b)	42		soft tissue tumors	MRI(dynamic 2.0 T; Gd-DTPA) VS. Histology(biopsy)	periphery-centre or whole tumor enhancement	0.9286|0.428	1.63|0.17	POOR	**MODERATE**
Moderate Quality	Tacikowska,M., 2002(b)	45		soft tissue tumors	MRI(dynamic 2.0 T; Gd-DTPA) VS. Histology(biopsy)	tissue enhancement rate(erc%) greater than 0.6	0.9333|0.733	3.50|0.09	WEAK	**STRONG**
Moderate Quality	van Rijswijk,C.S., 2002	22		soft tissue tumors	MRI(1.5T; no contrast mentioned; DWI) VS. histology(biopsy and/or resected specimen)	true diffusion coefficient of 1.13 or less	0.7|0.75	2.80|0.40	WEAK	WEAK

Quality	Author	N	Study Notes	Tumor Type	Imaging VS. Reference	Index Cutoff	Sens|Spec	LR+|LR-	Rule In Test	Rule Out Test
Moderate Quality	Bonarelli,C., 2015	65	avg of 2 readers	soft tissue tumors (extremities or trunk)	MRI(1.5 T; gadolinium) VS. histology	manual method ADC avg of 1.65 or more	0.625|0.5366	1.35|0.70	POOR	POOR
Moderate Quality	Bonarelli,C., 2015	65	avg of 2 readers	soft tissue tumors (extremities or trunk)	MRI(1.5 T; gadolinium) VS. histology	manual method ADC min of 1.28 or more	0.7917|0.609	2.03|0.34	WEAK	WEAK
Moderate Quality	Bonarelli,C., 2015	65	avg of 2 readers	soft tissue tumors (extremities or trunk)	MRI(1.5 T; gadolinium) VS. histology	semiautomatic method ADC avg of 1.68 or more	0.625|0.561	1.42|0.67	POOR	POOR
Moderate Quality	Bonarelli,C., 2015	65	avg of 2 readers	soft tissue tumors (extremities or trunk)	MRI(1.5 T; gadolinium) VS. histology	semiautomatic method ADC min of 0.91 or more	0.625|0.6341	1.71|0.59	POOR	POOR
Moderate Quality	Pang,K.K., 2003	30		soft tissue tumors and tumor-like conditions	MRI(0.5 T; no contrast mentioned; T2w only) VS. pathology	heterogeneous signal	0.875|0.6429	2.45|0.19	WEAK	**MODERATE**
Moderate Quality	Pang,K.K., 2003	30		soft tissue tumors and tumor-like conditions	MRI(0.5 T; no contrast mentioned; T1w only) VS. pathology	heterogeneous signal	0.6875|0.714	2.41|0.44	WEAK	WEAK
Moderate Quality	Ohguri,T., 2003	55	tumor counts; excluded 3 infiltrating lipomas	well-differentiated liposarcoma vs lipoma	MRI(1.5T; gadopentetate dimeglumine) VS. histopathology(surgical resection)	3 or more thick septa or nodular/patchy non-adipose component	0.6522|0.906	6.96|0.38	**MODERATE**	WEAK
Low Quality	Teo,E.L., 2000	32		ST masses vs hemangiomas	MRI(1.5T; WITH gadolinium) VS. Histology, angiography, or CFU(6pts; no time given)	Enhancement present	0.952380952|	0.95|4.76	POOR	POOR

Quality	Author	N	Study Notes	Tumor Type	Imaging VS. Reference	Index Cutoff	Sens|Spec	LR+|LR-	Rule In Test	Rule Out Test
Low Quality	Teo,E.L., 2000	44		ST masses vs hemangiomas	MRI(1.5T; w/wo gadolinium) VS. Histology, angiography, or CFU(6pts; no time given)	Absent lobulation, septation, and cental low SI dots	1|0.90909090	11.00|0.00	**STRONG**	**STRONG**
Low Quality	Teo,E.L., 2000	44		ST masses vs hemangiomas	MRI(1.5T; w/wo gadolinium) VS. Histology, angiography, or CFU(6pts; no time given)	Isointense, mild, or moderate T2 signal intensity	0.772727273|	17.00|0.24	**STRONG**	WEAK
Low Quality	Choi,B.B., 2013	34		low grade chondrosarcoma vs enchondroma	MRI(1.5T; IV gadopentetate dimeglumine; T2w only) VS. histopathology	heterogeneous signal	1|0.1875	1.23|0.00	POOR	**STRONG**
Low Quality	Choi,B.B., 2013	34		low grade chondrosarcoma vs enchondroma	MRI(1.5T; IV gadopentetate dimeglumine; T2w only) VS. histopathology	High/Intermediate signal intensity	1|0.125	1.14|0.00	POOR	**STRONG**
Low Quality	Choi,B.B., 2013	34		low grade chondrosarcoma vs enchondroma	MRI(1.5T; IV gadopentetate dimeglumine; T1w only) VS. histopathology	Intermediate signal intensity	0.7222|0.75	2.89|0.37	WEAK	WEAK
Low Quality	Choi,B.B., 2013	34		low grade chondrosarcoma vs enchondroma	MRI(1.5T; IV gadopentetate dimeglumine) VS. histopathology	Multilocular diffuse contrast enhancement	0.8333|0.562	1.91|0.30	POOR	WEAK
Low Quality	Bakir,B., 2014	41		retroperitoneal soft tissue-tumors(malignant RPF and chronic RPF)	MRI(1.5T; contrast unspecified), T2w, and DWI VS. pathology	T2-weighted quotient greater than 2.61	0.4|0.875	3.20|0.69	WEAK	POOR

Quality	Author	N	Study Notes	Tumor Type	Imaging VS. Reference	Index Cutoff	Sens|Spec	LR+|LR-	Rule In Test	Rule Out Test
Low Quality	Bakir,B., 2014	41		retroperitoneal soft tissue-tumors(malignant RPF and chronic RPF)	MRI(1.5T; contrast unspecified) and DWI VS. pathology	ADC value of 1.05 or less	0.96|1	96.00|0.04	**STRONG**	**STRONG**
Low Quality	Bakir,B., 2014	41		retroperitoneal soft tissue-tumors(malignant RPF and chronic RPF)	MRI(1.5 T; contrast unspecified) and DWI VS. pathology	postcontrast quotient greater than 1.19	1|1	100.00|0.00	**STRONG**	**STRONG**
Low Quality	Bakir,B., 2014	41		retroperitoneal soft tissue-tumors(malignant RPF and chronic RPF)	MRI(1.5T; contrast unspecified) and DWI VS. pathology	DWI quotient greater than 1.99	0.92|1	92.00|0.08	**STRONG**	**STRONG**
Low Quality	Bakir,B., 2014	51		retroperitoneal soft tissue-tumors(malignant RPF and chronic/active RPF)	MRI(1.5 T; contrast unspecified) and DWI VS. pathology	DWI quotient greater than 1.99	0.92|0.6154	2.39|0.13	WEAK	**MODERATE**
Low Quality	Moulton,J.S., 1995	225		soft tissue tumors	MRI(1.5T, no contrast) VS. Histopathology or CFU(41pts; 2yrs)	Bone abnormality	0.1739|0.927	2.40|0.89	WEAK	POOR
Low Quality	Moulton,J.S., 1995	225		soft tissue tumors	MRI(1.5T, no contrast; T1 only) VS. Histopathology or CFU(41pts; 2yrs)	Heterogeneous signal	0.4565|0.536	0.99|1.01	POOR	POOR
Low Quality	Moulton,J.S., 1995	225		soft tissue tumors	MRI(1.5T, no contrast; T2 only) VS. Histopathology or CFU(41pts; 2yrs)	Heterogeneous signal	0.8696|0.352	1.34|0.37	POOR	WEAK

Quality	Author	N	Study Notes	Tumor Type	Imaging VS. Reference	Index Cutoff	Sens|Spec	LR+|LR-	Rule In Test	Rule Out Test
Low Quality	Moulton,J.S., 1995	225		soft tissue tumors	MRI(1.5T, no contrast) VS. Histopathology or CFU(41pts; 2yrs)	radiologist interpretation (size, homogeneity, margins, signal intensity, edema, involvement)	0.587|0.9441	10.51|0.44	**STRONG**	WEAK
Low Quality	Yildirim,A., 2016	35	4 metastases pts	soft tissue tumors	MRI(1.5T; no contrast) VS. histology(32/35 pts) or clinical FU(3/35 pts)	bone involvement	0.3684|1	36.84|0.63	**STRONG**	POOR
Low Quality	Yildirim,A., 2016	35	4 metastases pts	soft tissue tumors	MRI(1.5T; gadopentetate dimeglumine or gadodiamide) VS. histology(32/35 pts) or clinical FU(3/35 pts)	heterogeneous or peripheral contrast enhancement	0.7368|0.125	0.84|2.11	POOR	POOR
Low Quality	Yildirim,A., 2016	34	3 metastases pts	soft tissue tumors	MRI(1.5T; gadopentetate dimeglumine or gadodiamide) VS. histology(32/35 pts) or clinical FU(3/35 pts)	rapid initial contrast enhancement followed by washout/plateau phase	1|0.75	4.00|0.00	WEAK	**STRONG**
Low Quality	Yildirim,A., 2016	35	4 metastases pts	soft tissue tumors	MRI(1.5T; no contrast; T1 only) VS. histology(32/35 pts) or clinical FU(3/35 pts)	heterogeneous signal	0.4737|0.75	1.90|0.70	POOR	POOR
Low Quality	Yildirim,A., 2016	35	4 metastases pts	soft tissue tumors	MRI(1.5T; no contrast; T2 only) VS. histology(32/35 pts) or clinical FU(3/35 pts)	heterogeneous signal	0.7895|0.187	0.97|1.12	POOR	POOR

DATA TABLE 10: PICO 3 - STAGE OF TUMOR

Quality	Author	N	Study Notes	Tumor Type	Imaging VS. Reference	Index Cutoff	Sens|Spec	LR+|LR-	Rule In Test	Rule Out Test
Moderate Quality	Van der Woude,H.J., 1998	71	4 cases of bone metastases	musculoskeletal malignant bone tumors (high grade vs low grade)	MRI(0.5 T; gd-DTPA or gadoteridol) VS. histology(trocar biopsy or resection)	early enhancement (6sec or less after arterial enhancement)	0.9556|0.846	6.21|0.05	**MODERATE**	**STRONG**
Moderate Quality	Van der Woude,H.J., 1998	71	4 cases of bone metastases	musculoskeletal malignant bone tumors (high grade vs low grade)	MRI(0.5 T; gd-DTPA or gadoteridol) VS. histology(trocar biopsy or resection)	peripheral tumor enhancement	0.7778|0.615	2.02|0.36	WEAK	WEAK
Moderate Quality	Van der Woude,H.J., 1998	71	4 cases of bone metastases	musculoskeletal malignant bone tumors (high grade vs low grade)	MRI(0.5 T; gd-DTPA or gadoteridol) VS. histology(trocar biopsy or resection)	type I(rapidly progressing enhancement)	0.9778|0.769	4.24|0.03	WEAK	**STRONG**

MRI AND CT SCANS: AREA TO VISUALIZE

A. In the absence of reliable evidence, it is the opinion of the work group that MRI or CT scans performed to visualize a potentially malignant bone tumor should include a detailed assessment of the tumor and surrounding soft tissue, with additional sequences that visualize the entire bone compartment, from the proximal joint to the distal joint.

Strength of Recommendation: Consensus ★☆☆☆

Description: There is no supporting evidence. In the absence of reliable evidence, the work group is making a recommendation based on their clinical opinion.

B. In the absence of reliable evidence, it is the opinion of the work group that MRI or CT scans performed to visualize a soft tissue tumor should include a detailed assessment of the tumor and surrounding soft tissue, including complete visualization of enhancement along fascial planes and peritumoral edema.

Strength of Recommendation: Consensus ★☆☆☆

Description: There is no supporting evidence. In the absence of reliable evidence, the work group is making a recommendation based on their clinical opinion.

RATIONALE

Although there is a paucity of reliable literature that directly addresses this question, there remains a long history of clinical acumen and associated recommendations from expert panels to justify visualization of the entire bone when performing an MRI to investigate a potentially malignant bone tumor. The American College of Radiology has created practice parameters to guide practitioners on the appropriate execution of MRI in the setting of bone tumors (https://acsearch.acr.org/docs/69421/Narrative/). The field of view should be chosen based on the size of patient and tumor, commonly requiring an adjustment of the field of view to visualize the entire bone to ensure the extent of intramedullary disease and presence of skip lesions are adequately addressed (Kager, 2006). This may require changes to the coil (e.g. a surface coil for a detailed evaluation of the tumor, with a change to a body coil for visualization of the proximal and distal extent of the bone) or possibly performing two separate studies. The sequences should provide multiple perspectives of the tumor and surrounding tissue (axial, coronal, and sagittal) that allow for complete visualization and planning for biopsy execution and operative strategy.

The ordering of advanced imaging for a bone tumor may be an uncommon scenario for many practitioners not specialized in the diagnosis or treatment of neoplastic diseases, and we encourage consultation with or referral to dedicated musculoskeletal radiologists or treating specialists to guarantee the study is performed appropriately. The work group agreed that benign bone tumors and non-neoplastic abnormalities of the bone often do not require extension of the field of view outside of the area of concern, and further supports the recommendation of consultation with specialist practitioners when ordering the study to avoid over-imaging of tumors that are clearly benign.

MRI is the preferred imaging study; however, a CT scan is acceptable when an MRI cannot be performed due to patient-specific contraindications (pacemaker, cerebral aneurysm clips).

RISKS AND HARMS OF IMPLEMENTING THIS RECOMMENDATION

MRI poses minimal risk to the patient. CT scan contains a low to moderate radiation dose, but is acceptable when employed judiciously.

FUTURE RESEARCH

While the recommendation to include the entire bone in advanced axial imaging of a bone tumor is rooted in several decades of clinical observation, and is an accepted practice among treating specialists, a formal evaluation of the incidence of intramedullary extension or skip lesions that would have been missed with a more limited study would provide additional strength to this recommendation.

CT SCANS: STAGING

A. In the absence of reliable evidence, it is the opinion of the work group that CT chest/abdomen/pelvis scans performed in patients with a destructive bone lesion highly suspicious for metastatic disease of bone should use oral and IV contrast.

Strength of Recommendation: Consensus 

Description: There is no supporting evidence. In the absence of reliable evidence, the work group is making a recommendation based on their clinical opinion.

B. In the absence of reliable evidence, it is the opinion of the work group that staging CT scans in the setting of a destructive bone lesion should be ordered by, or in consultation with, an oncology specialist.

Strength of Recommendation: Consensus 

Description: There is no supporting evidence. In the absence of reliable evidence, the work group is making a recommendation based on their clinical opinion.

RATIONALE

We did not find any acceptable investigations that directly addressed this question. However, it is well accepted, that a critical early imaging study is a CT scan that visualizes the chest, abdomen, and pelvis of the patient (Weber, 2010). This allows for assessment of common sites of origin of metastatic carcinoma (lung, breast, prostate, kidney, colon) and common sites of regional (axillary and inguinal lymph nodes) and distant (lung, liver, axial skeleton) disease. Contrast may be helpful to determine true pathologic lesions from other non-neoplastic conditions and should be used if there are no patient contraindications, such as a contrast allergy.

It can be difficult to distinguish between the more common scenarios of metastatic carcinoma and multiple myeloma and the uncommon scenario of a primary sarcoma. However, the treatment of a primary sarcoma is vastly different than the treatment of metastatic carcinoma and multiple myeloma, and the early recognition of the underlying disease is critical for optimal treatment. Therefore, we recommend that a staging CT scan is most appropriately ordered by an oncologic specialist, and encourage non-specialist practitioners to consider an early referral to or consultation with a specialty provider on suspicion of a bone or soft tissue malignancy prior to obtaining a CT chest/abdomen/pelvis. If there is no apparent site of primary carcinoma on the staging CT scan, or if the solitary destructive bone lesion is the only focus of additional disease, a referral to an orthopaedic oncologist is necessary prior to any biopsy or stabilization of the bone lesion to address the potential for a primary sarcoma.

RISKS AND HARMS OF IMPLEMENTING THIS RECOMMENDATION

CT scans contain a low to moderate radiation dose, but is acceptable when employed judiciously.

FUTURE RESEARCH

There is general clinical support for the use of diagnostic CT chest/abdomen/pelvis scans for evaluation of patients suspected of having metastatic carcinoma. However, the utility of IV and oral contrast in CT chest/abdomen/pelvis scans is not specifically investigated and future work could further inform their necessity. Population based investigations could clarify the most appropriate timing and indications for staging CT scans at the time of presentation to a primary care provider. PET/CT scans are an increasingly common imaging study for cancer diagnosis and staging, and their utility in identifying a primary tumor in the setting of a destructive bone lesion should be further defined.

CT SCANS: PRIOR CHEST RADIOGRAPH

In the absence of reliable evidence, it is the opinion of the work group that it is not necessary to perform a chest radiograph prior to a chest CT in the staging of a bone or soft tissue malignancy.

Strength of Recommendation: Consensus 

Description: There is no supporting evidence. In the absence of reliable evidence, the work group is making a recommendation based on their clinical opinion.

RATIONALE

We did not find any acceptable investigations that directly addressed the question of whether performing a chest radiograph prior to a CT scan is warranted or not. The theoretical justification for performing a chest radiograph initially is that the results may influence the decision to obtain a subsequent CT scan. Our work group agreed that when the clinical presentation is concerning enough to justify a CT scan to evaluate for other sites of disease or metastatic spread regardless of the findings on a chest radiograph, as is the case with this scenario, a chest radiograph is of low utility and does not influence the decision to obtain a CT scan. In the clinical setting of a destructive bone lesion or soft tissue mass concerning for malignancy, visualization of the lungs is necessary to determine the presence of distant disease. Chest CT scans provide more detail than chest radiographs and are the study of choice for most practitioners. Because the chest CT and its scout image provide more detailed information, a chest x-ray prior to chest CT is redundant and unnecessary in this situation. If the treating cancer specialists anticipate post-treatment pulmonary surveillance with chest radiographs, a baseline chest radiograph may be useful as a comparison for future studies.

RISKS AND HARMS OF IMPLEMENTING THIS RECOMMENDATION

There is a radiation dose associated with conventional radiographs but it is small enough to pose no real risk to the patient.

FUTURE RESEARCH

Prospective studies could be done to establish how often performing a chest radiograph prior to a CT scan might assist with obtaining a diagnosis or planning further diagnostic studies or treatment.

ULTRASOUND

A. Moderate evidence supports that ultrasound helps to distinguish benign from malignant soft tissue tumors.

Strength of Recommendation: Moderate ★★★☆

Description: Evidence from two or more "Moderate" quality studies with consistent findings, or evidence from a single "High" quality study for recommending for or against the intervention.

B. In the absence of reliable evidence, it is the opinion of the work group that ultrasounds in small (<5 cm), superficial soft tissues tumors can help distinguish between benign lipomas, vascular malformations, cystic structures, and solid tumors that require further characterization.

Strength of Recommendation: Consensus ★☆☆☆

Description: There is no supporting evidence. In the absence of reliable evidence, the work group is making a recommendation based on their clinical opinion.

C. In the absence of reliable evidence, it is the opinion of the work group that ultrasounds in large (>5 cm), deep soft tissues tumors are unlikely to adequately assess the benign or malignant nature of the lesion and should not be the imaging modality of choice.

Strength of Recommendation: Consensus ★☆☆☆

Description: There is no supporting evidence. In the absence of reliable evidence, the work group is making a recommendation based on their clinical opinion.

RATIONALE

Although frequently utilized prior to advanced imaging, standard ultrasound evaluation of concerning masses does not preclude subsequent advanced imaging. As a screening tool, the purpose of an ultrasound evaluation would be to identify which lesions need further imaging and which can be definitively diagnosed as benign. While mostly moderate quality evidence evaluations have shown reasonable psychometrics using advanced techniques in the 80-90% accuracy range (Belli 2000, Chen 2015, Chen 2009a, Lagalla 1998, and Nagano 2015), these studies did not address whether such evaluations could stand alone without an MRI or CT in a prospective manner. Part of the general usefulness of ultrasound is its availability and low cost; if a patient will likely ultimately need an MRI or CT regardless, the rationale for adding additional cost and time for ultrasounds needs further support. A meta-analysis of high and moderate quality studies conducted for this CPG showed a sensitivity of 0.84 and specificity of 0.84 for determining the malignancy of a lesion based on several ultrasound techniques (Chen 2015, Belli 2000, Chen 2009a, Lagalla 1998, Nagano 2015).

Many authors reporting on the utility of ultrasound do so only as an adjunct rather than replacement for other advanced imaging (De Marchi 2003, Furuta 2016, Lagalla 1998, Nagano 2015), in which case the patient-derived value needs to be elucidated. Miller et al (2015) noted that ultrasound studies were generally considered by orthopaedic oncologists to be unhelpful prior to referral. It may be possible in the future that advanced ultrasound techniques could be first line imaging, with MRI ordered by the referral center (De Marchi 2015, Loizides 2012).

It is the consensus recommendation that if a mass is less than 5cm, superficial, and not by critical structures (axilla, groin, popliteal fossa, over a subcutaneous bone) then a principled excisional biopsy without ultrasound evaluation is reasonable. Should a patient not desire removal but reassurance, ultrasound may be able to confirm

cystic nature and allow observation in the absence of growth (Nagano 2015). Wagner et al (2013) noted high accuracy for lipomas with 96.9% specificity for superficial masses. In cases where the size or depth of the lesion cannot be determined by physical examination, ultrasound can provide anatomic location to guide further evaluation and treatment.

It is the consensus recommendation that if a mass is greater than 5cm, or deep, or by critical structures then an ultrasound evaluation is unlikely to obviate the need for advanced imaging and may delay treatment or provide false reassurance. In particular circumstances, such as vascular malformations (Furta 2017), ultrasound can aid in making a diagnosis and avoiding a biopsy, but in this setting ultrasound could be ordered if desired by a referral center.

Moderate and high-quality studies are evaluating means of distinguishing benign versus malignant soft tissue masses by ultrasound (eg., Pass 2017, Chen 2009 a, Chen 2009 b). However, it is the opinion of the work group that there is not yet sufficient sensitivity for malignancy or specificity for benignity for ultrasound evaluations to obviate the need for further advanced imaging for large or deep or precariously located lesions (Nagano 2015). In these suspicious circumstances, an ultrasound should not be required prior to obtaining an MRI.

In other clinical situations, such as evaluating a possible soft tissue sarcoma recurrence, ultrasound may be an effective means of surveillance and directing a biopsy (Arya 2000). We did not find any literature discussing use of ultrasound in bone lesions and suggest that our recommendations apply only to soft tissue tumors.

RISKS AND HARMS OF IMPLEMENTING THIS RECOMMENDATION

Ultrasound is minimal risk as there is no associated radiation dose. There is a possible risk of a false negative study (e.g., a malignant lesion could be incorrectly identified as a benign cyst), which may delay diagnosis and treatment.

FUTURE RESEARCH

Further research on when an ultrasound can provide sufficient evidence of benignity that observation alone is sufficient would help inform on when advanced imaging can be safely avoided. A decision-analysis methodology may be useful to elucidate how and when ultrasound can be useful.

RESULTS

STUDY QUALITY TABLE 4: ULTRASOUND

Study	Representative Population	Clear Selection Criteria	Detailed Enough to Replicate	Reference Standard Identifies Target Condition	Blinding	Other Bias?	Inclusion	Strength
Arya,S., 2000	●	◑	●	●	●	◑	Include	Moderate Quality
Belli,P., 2000	●	●	●	●	◑	◑	Include	Moderate Quality
Bradley,M., 2015	●	●	●	●	◑	◑	Include	Moderate Quality
Chen,C.Y., 2009	●	◑	●	●	●	◑	Include	Moderate Quality
Chen,C.Y., 2009	●	◑	●	●	●	◑	Include	Moderate Quality
Chen,T., 2015	●	●	●	●	●	◑	Include	High Quality
De,Marchi A., 2003	●	◑	●	●	◑	◑	Include	Moderate Quality
De,Marchi A., 2015	●	●	●	○	●	◑	Include	Moderate Quality
Furuta,T., 2017	●	◑	●	●	◑	◑	Include	Moderate Quality
Gruber,L., 2017	●	●	●	●	●	◑	Include	High Quality
Hahn,S., 2017	●	◑	●	●	●	◑	Include	Moderate Quality
Lagalla,R., 1998	●	●	●	●	◑	◑	Include	Moderate Quality
Loizides,A., 2012	●	●	●	●	●	◑	Include	High Quality
Nagano,S., 2015	●	◑	●	●	◑	◑	Include	Moderate Quality
Oebisu,N., 2014	●	●	●	●	◑	◑	Include	Moderate Quality
Pass,B., 2016	●	●	●	●	●	◑	Include	High Quality

Study	Representative Population	Clear Selection Criteria	Detailed Enough to Replicate	Reference Standard Identifies Target Condition	Blinding	Other Bias?	Inclusion	Strength
Pass,B., 2017	●	●	●	○	●	○	Include	Low Quality
Wagner,J.M., 2013	●	◑	●	●	●	◑	Include	Moderate Quality

SUMMARY OF DATA FINDINGS

SUMMARY TABLE 12: PICO 8 - ULTRASOUND VS HISTOPATHOLOGY FOR DIAGNOSING SOFT TISSUE TUMOR PRESENCE

DIAGNOSING SOFT TISSUE TUMOR PRESENCE ON ULTRASOUND		Moderate			
Imaging Method	**Diagnostic Threshold**	**Arya,S., 2000**	**De,Marchi A., 2003**	**Furuta,T., 2017***	**Wagner,J.M., 2013***
US	Poorly reflective, discrete fairly well defined lesion	**91.67** **94.4**			
CE US(echocolor power doppler; 99.9% galactose and 0.01% palmitic acid)	Type III(rapid & irregular peaks/plateau)/type II(between III & I)/type I(regular peaks)		**91.43** 20		
US(grayscale only)	Compressable			**81.25** 65.1	
	Heterogeneous interior			**100** 38.2	
US(power doppler only)	Presence of Doppler flow signal			56.25 64	
	Present sluggish speed sign (SSS)			**93.75** **96.6**	
US(power/color doppler used for 55pts)	Presence of homogeneously hyperechoic or isoechoic/hypoechoic with wavy linear echogenicity				**94.87** **96.9**

SUMMARY TABLE 13: PICO 8 - CONTRAST ENHANCED ULTRASOUND VS HISTOPATHOLOGY FOR DIAGNOSING MALIGNANCY OF SOFT TISSUE TUMORS

DIAGNOSING MALIGNANCY OF SOFT TISSUE TUMORS ON CONTRAST ENHANCED ULTRASOUND		High		Moderate	
Imaging Method	Diagnostic Threshold	Gruber,L., 2017	Loizides,A., 2012	De,Marchi A., 2003	Oebisu,N., 2014
CE US(color doppler; Sonazoid contrast)	Grade 3 and 4(hypervascular)				**86.84** 67.6
CE US(echocolor power doppler; 99.9% galactose and 0.01% palmitic acid)	Type III(rapid & irregular peaks/plateau)			**90.91** **96.5**	
CE US(Sulfur Hexafluoride)	3.3 cm or more, and diffuse enhanced mass		**87.5** **81.48**		
	3.3 cm or more, and diffuse or peripherally enhanced mass		**95.83** 77.7		
	3.3 cm or more, and peripheral enhanced mass		8.33 **96.3**		
	5 cm or more, and diffuse or peripherally enhanced mass		**83.33** **100**		
	5 cm or more, and diffusely enhanced mass		66.67 **88.8**		
	5 cm or more, and peripheral enhanced mass		12.5 **100**		
	6.6 cm or more, and diffusely enhanced mass		54.17 **92.5**		
	6.6 cm or more, and peripheral enhanced mass		8.33 **100**		
	Deep and diffusely enhanced mass		**87.5** **88.89**		
	Deep and diffusely or peripherally enhanced mass		**95.83** **81.4**		
	Deep and peripheral enhanced mass		8.33 **92.5**		
	Deep, 3.3 cm or more, and diffusely enhanced mass		**83.33** **88.8**		
	Deep, 3.3 cm or more, and peripheral or diffusely enhanced mass		**91.67** **85.1**		
	Deep, 5 cm or more, and diffusely enhanced mass		66.67 **92.5**		
	Deep, 5 cm or more, and peripheral or diffusely enhanced mass		66.67 **92.5**		
	Diffusely enhanced mass		**91.67** 77.7		
	Peripheral enhancing mass		8.33 **92.5**		
	Peripheral or diffusely enhanced mass		**100** 70.37		
	P2/P3(inhomogenous or peripheral CE with confluent areas of CE sparing)	**88.33** 66.6			

SUMMARY TABLE 14: PICO 8 - ULTRASOUND VS HISTOPATHOLOGY FOR DIAGNOSING MALIGNANCY OF SOFT TISSUE TUMORS

DIAGNOSING MALIGNANCY OF SOFT TISSUE TUMORS ON ULTRASOUND		High		Moderate							
Imaging Method	Diagnostic Threshold	Chen,T., 2015	Pass,B., 2016	Belli,P., 2000	Bradley,M., 2015	Chen,C.Y., 2009(a)	Chen,C.Y., 2009(b)	Hahn,S., 2017	Lagalla,R., 1998	Nagano,S., 2015	Oebisu,N., 2014
US	2 of infiltrate/mixed tumor growth, irregular margins, hypoechoic pattern, heterogenous texture			60 55.56							
	Consistent blue areas demonstrated on compression elastography				28 **85.05**						
	Heterogeneous textural pattern			65 75					55 **80.77**		
	Presence of irregular margins and heterogeneous textural pattern								75 50		
	USS score of 3 or more(size, echogenesity, texture, doppler pattern)									**85.07** **86.8**	
US(3D automated breast volume scanner)	Radiologist interpretation(margin, shape, internal texture)	**81.82** **93.1**									
US(B-mode)	Hyperechoic or homogeneous		60 77.14								
US(color doppler)	2 of 3 or more afferent vessels, irregular arrangement, abrupt caliber, tortuous/spot flow			**85** **88.89**							
	3 or more vascular hila								**85** **90.48**		
	Presence of 3 or more vascular hila & tortuous/irregular internal vessels								**85** **92.31**		
	Presence of flow signals								**95** 53.85		
	Presence of tortuous vessels								60 **84.62**		
	Grade 3 and 4(hypervascular)										54.84 77.1
US(combined conventional, colored doppler, & pulsed doppler)	Margin, echogenicity, texture, vascularization			**90** **91.67**							
US(computer-aided diagnosis)	Computer generated linear discriminant analysis(16 US characteristics)					**90.63** **89**					
	Computer generated multilayer perception classifier(16 US characteristics)					**90.63** **87.6**					
	Increased presence of zero-crossing, entropy, circularity, rectangularity, and SD						**89.19** **87.1**				
	Presence of increased entropy and zero-crossing						72.97 **91.4**				
	Presence of increased roughness and zero-crossing						64.86 **88.5**				
US(elastography)	Elasticity score >3							75.76 67.5			
US(gray scale)	Heterogeneous textural pattern										62.9 61.86
US(hand held)	Radiologist interpretation(margin, shape, internal texture)	77.27 **88.6**									
US(pulsed doppler only)	Systolic velocity of 0.5 m/s or greater			65 **88.89**							

DATA TABLE 14: PICO 8 - MALIGNANCY

Quality	Author	N	Study Notes	Tumor Type	Imaging VS. Reference	Index Cutoff	Sens|Spec	LR+|LR-	Rule In Test	Rule Out Test
High Quality	Chen,T., 2015	66		soft tissue tumors	US(3D automated breast volume scanner) VS. Pathological diagnosis	radiologist interpretation (margin, shape, internal texture)	0.8182|0.931	12.00|0.20	**STRONG**	**MODERATE**
High Quality	Chen,T., 2015	66		soft tissue tumors	US(hand held) VS. Pathological diagnosis	radiologist interpretation (margin, shape, internal texture)	0.7727|0.886	6.80|0.26	**MODERATE**	WEAK
High Quality	Loizides,A., 2012	51		soft tissue tumors	US(Sono Vue) VS. histology(US-guided biopsy)	3.3 cm or more, and diffuse enhanced mass	0.875|0.8148	4.73|0.15	WEAK	**MODERATE**
High Quality	Loizides,A., 2012	51		soft tissue tumors	US(Sono Vue) VS. histology(US-guided biopsy)	3.3 cm or more, and diffuse or peripherally enhanced mass	0.9583|0.777	4.31|0.05	WEAK	**STRONG**
High Quality	Loizides,A., 2012	51		soft tissue tumors	US(Sono Vue) VS. histology(US-guided biopsy)	3.3 cm or more, and peripheral enhanced mass	0.0833|0.963	2.25|0.95	WEAK	POOR
High Quality	Loizides,A., 2012	51		soft tissue tumors	US(Sono Vue) VS. histology(US-guided biopsy)	5 cm or more, and diffuse or peripherally enhanced mass	0.8333|1	83.33|0.17	**STRONG**	**MODERATE**

Quality	Author	N	Study Notes	Tumor Type	Imaging VS. Reference	Index Cutoff	Sens|Spec	LR+|LR-	Rule In Test	Rule Out Test
High Quality	Loizides,A., 2012	51		soft tissue tumors	US(Sono Vue) VS. histology(US-guided biopsy)	5 cm or more, and diffusely enhanced mass	0.6667|0.888	6.00|0.38	**MODERATE**	WEAK
High Quality	Loizides,A., 2012	51		soft tissue tumors	US(Sono Vue) VS. histology(US-guided biopsy)	5 cm or more, and peripheral enhanced mass	0.125|1	12.50|0.88	**STRONG**	POOR
High Quality	Loizides,A., 2012	51		soft tissue tumors	US(Sono Vue) VS. histology(US-guided biopsy)	6.6 cm or more, and diffusely enhanced mass	0.5417|0.925	7.31|0.50	**MODERATE**	POOR
High Quality	Loizides,A., 2012	51		soft tissue tumors	US(Sono Vue) VS. histology(US-guided biopsy)	6.6 cm or more, and peripheral enhanced mass	0.0833|1	8.33|0.92	**MODERATE**	POOR
High Quality	Loizides,A., 2012	51		soft tissue tumors	US(Sono Vue) VS. histology(US-guided biopsy)	deep and diffusely enhanced mass	0.875|0.8889	7.88|0.14	**MODERATE**	**MODERATE**
High Quality	Loizides,A., 2012	51		soft tissue tumors	US(Sono Vue) VS. histology(US-guided biopsy)	deep and diffusely or peripherally enhanced mass	0.9583|0.814	5.18|0.05	**MODERATE**	**STRONG**
High Quality	Loizides,A., 2012	51		soft tissue tumors	US(Sono Vue) VS. histology(US-guided biopsy)	deep and peripheral enhanced mass	0.0833|0.925	1.13|0.99	POOR	POOR
High Quality	Loizides,A., 2012	51		soft tissue tumors	US(Sono Vue) VS. histology(US-guided biopsy)	deep, 3.3 cm or more, and diffusely enhanced mass	0.8333|0.888	7.50|0.19	**MODERATE**	**MODERATE**

Quality	Author	N	Study Notes	Tumor Type	Imaging VS. Reference	Index Cutoff	Sens|Spec	LR+|LR-	Rule In Test	Rule Out Test
High Quality	Loizides,A., 2012	51		soft tissue tumors	US(Sono Vue) VS. histology(US-guided biopsy)	deep, 3.3 cm or more, and peripheral or diffusely enhanced mass	0.9167|0.851	6.19|0.10	**MODERATE**	**STRONG**
High Quality	Loizides,A., 2012	51		soft tissue tumors	US(Sono Vue) VS. histology(US-guided biopsy)	deep, 5 cm or more, and diffusely enhanced mass	0.6667|0.925	9.00|0.36	**MODERATE**	WEAK
High Quality	Loizides,A., 2012	51		soft tissue tumors	US(Sono Vue) VS. histology(US-guided biopsy)	deep, 5 cm or more, and peripheral or diffusely enhanced mass	0.6667|0.925	9.00|0.36	**MODERATE**	WEAK
High Quality	Loizides,A., 2012	51		soft tissue tumors	US(Sono Vue) VS. histology(US-guided biopsy)	diffusely enhanced mass	0.9167|0.777	4.13|0.11	WEAK	**MODERATE**
High Quality	Loizides,A., 2012	51		soft tissue tumors	US(Sono Vue) VS. histology(US-guided biopsy)	peripheral enhancing mass	0.0833|0.925	1.13|0.99	POOR	POOR
High Quality	Loizides,A., 2012	51		soft tissue tumors	US(Sono Vue) VS. histology(US-guided biopsy)	peripheral or diffusely enhanced mass	1|0.7037	3.38|0.00	WEAK	**STRONG**
High Quality	Pass,B., 2016	45		soft tissue tumors (extremities)	US(B-mode) VS. histology(excision or percutaneous biopsy)	hyperechoic or homogeneous	0.6|0.7714	2.63|0.52	WEAK	POOR
High Quality	Gruber,L., 2017	192		soft tissue tumors (malignant vs benign/intermediate)	US(sulfur hexafluoride) VS. histopathology(biopsy, US-guided biopsy, or resection)	P2/P3(inhomogenous or peripheral CE with confluent areas of CE sparing)	0.8833|0.666	2.65|0.18	WEAK	**MODERATE**

Quality	Author	N	Study Notes	Tumor Type	Imaging VS. Reference	Index Cutoff	Sens|Spec	LR+|LR-	Rule In Test	Rule Out Test
Moderate Quality	Lagalla,R., 1998	41		periskeletal soft tissue tumors	US(color doppler only) VS. histology(percutaneous biopsy or surgery)	3 or more vascular hila	0.85|0.9048	8.93|0.17	**MODERATE**	**MODERATE**
Moderate Quality	Lagalla,R., 1998	46		periskeletal soft tissue tumors	US VS. histology(percutaneous biopsy or surgery)	heterogeneous textural pattern	0.55|0.8077	2.86|0.56	WEAK	POOR
Moderate Quality	Lagalla,R., 1998	46		periskeletal soft tissue tumors	US(color doppler only) VS. histology(percutaneous biopsy or surgery)	presence of 3 or more vascular hila & tortuous/irregular internal vessels	0.85|0.9231	11.05|0.16	**STRONG**	**MODERATE**
Moderate Quality	Lagalla,R., 1998	46		periskeletal soft tissue tumors	US(color doppler only) VS. histology(percutaneous biopsy or surgery)	presence of flow signals	0.95|0.5385	2.06|0.09	WEAK	**STRONG**
Moderate Quality	Lagalla,R., 1998	46		periskeletal soft tissue tumors	US VS. histology(percutaneous biopsy or surgery)	presence of irregular margins and heterogeneous textural pattern	0.75|0.5	1.50|0.50	POOR	POOR
Moderate Quality	Lagalla,R., 1998	46		periskeletal soft tissue tumors	US(color doppler only) VS. histology(percutaneous biopsy or surgery)	presence of tortuous vessels	0.6|0.8462	3.90|0.47	WEAK	WEAK
Moderate Quality	Nagano,S., 2015	189		soft part tumors	US VS. Pathology(surgical excision)	USS score of 3 or more(size, echogenesity, texture, doppler pattern)	0.8507|0.868	6.49|0.17	**MODERATE**	**MODERATE**
Moderate Quality	Oebisu,N., 2014	180		soft tissue masses	US(color doppler) VS. pathology(surgical resection or biopsy)	Grade 3 and 4(hypervascular)	0.5484|0.771	2.40|0.59	WEAK	POOR

Quality	Author	N	Study Notes	Tumor Type	Imaging VS. Reference	Index Cutoff	Sens|Spec	LR+|LR-	Rule In Test	Rule Out Test
Moderate Quality	Oebisu,N., 2014	109		soft tissue masses	US(color doppler; Sonazoid contrast) VS. pathology(surgical resection or biopsy)	Grade 3 and 4(hypervascular)	0.8684|0.676	2.68|0.20	WEAK	**MODERATE**
Moderate Quality	Oebisu,N., 2014	180		soft tissue masses	US(gray scale) VS. pathology(surgical resection or biopsy)	heterogeneous textural pattern	0.629|0.6186	1.65|0.60	POOR	POOR
Moderate Quality	Bradley,M., 2015	157		soft tissue tumors	US VS. pathology(US-guided biopsy)	consistent blue areas demonstrated on compression elastography	0.28|0.8505	1.87|0.85	POOR	POOR
Moderate Quality	Chen,C.Y., 2009(a)	105		soft tissue tumors	US(computer-aided diagnosis) VS. pathology	computer generated linear discriminant analysis(16 US characteristics)	0.9063|0.890	8.27|0.11	**MODERATE**	**MODERATE**
Moderate Quality	Chen,C.Y., 2009(a)	105		soft tissue tumors	US(computer-aided diagnosis) VS. pathology	computer generated multilayer perception classifier(16 US characteristics)	0.9063|0.876	7.35|0.11	**MODERATE**	**MODERATE**
Moderate Quality	Chen,C.Y., 2009(b)	107	included 9 unknown primary metastases pts	soft tissue tumors	US(computer-aided diagnosis) VS. pathology(surgery)	increased presence of zero-crossing, entropy, circularity, rectangularity, and SD	0.8919|0.871	6.94|0.12	**MODERATE**	**MODERATE**

Quality	Author	N	Study Notes	Tumor Type	Imaging VS. Reference	Index Cutoff	Sens|Spec	LR+|LR-	Rule In Test	Rule Out Test
Moderate Quality	Chen,C.Y., 2009(b)	107	included 9 unknown primary metastases pts	soft tissue tumors	US(computer-aided diagnosis) VS. pathology(surgery)	presence of increased entropy and zero-crossing	0.7297|0.914	8.51|0.30	**MODERATE**	WEAK
Moderate Quality	Chen,C.Y., 2009(b)	107	included 9 unknown primary metastases pts	soft tissue tumors	US(computer-aided diagnosis) VS. pathology(surgery)	presence of increased roughness and zero-crossing	0.6486|0.885	5.68|0.40	**MODERATE**	WEAK
Moderate Quality	De,Marchi A., 2015	210	clinical FU only for all benign	soft tissue tumors	US(SonoVue sulphur hexaflouride) VS. histology(biopsy or surgery) or clinical FU(22 pts; benign only; no time given)	presence of heterogeneous pattern and avascular areas	0.5079|0.773	2.25|0.64	WEAK	POOR
Moderate Quality	De,Marchi A., 2015	190	clinical FU only for all benign	soft tissue tumors	US(SonoVue sulphur hexaflouride) VS. histology(biopsy or surgery) or clinical FU(22 pts; benign only; no time given)	vascularisation time up to 11 sec/arterial uptake	0.4522|0.693	1.47|0.79	POOR	POOR
Moderate Quality	Hahn,S., 2017	73		soft tissue tumors	US(elastography) VS. pathology(US-guided core needle biopsy or excisional biopsy)	elasticity score >3	0.7576|0.675	2.33|0.36	WEAK	WEAK
Moderate Quality	De,Marchi A., 2003	80	includes 4 aggressive desmoid fibromatosis (benign)	soft tissue tumors or tumor-like (limbs)	US(echocolor power doppler; 99.9% galactose and 0.01% palmitic acid) VS. histology(biopsy or surgical specimen)	type III(rapid & irregular peaks/plateau)	0.9091|0.965	26.36|0.09	**STRONG**	**STRONG**

Quality	Author	N	Study Notes	Tumor Type	Imaging VS. Reference	Index Cutoff	Sens|Spec	LR+|LR-	Rule In Test	Rule Out Test
Moderate Quality	Belli,P., 2000	56		soft tissue tumors(limbs)	US(color doppler only) VS. Histology(biopsy or surgery)	2 of 3 or more afferent vessels, irregular arrangement, abrupt caliber, tortuous/spot flow	0.85|0.8889	7.65|0.17	**MODERATE**	**MODERATE**
Moderate Quality	Belli,P., 2000	56		soft tissue tumors(limbs)	US VS. Histology(biopsy or surgery)	2 of infiltrate/mixed tumor growth, irregular margins, hypoechoic pattern, heterogenous texture	0.6|0.5556	1.35|0.72	POOR	POOR
Moderate Quality	Belli,P., 2000	56		soft tissue tumors(limbs)	US VS. Histology(biopsy or surgery)	heterogenous texture	0.65|0.75	2.60|0.47	WEAK	WEAK
Moderate Quality	Belli,P., 2000	56		soft tissue tumors(limbs)	US(combined conventional, colored doppler, & pulsed doppler) VS. Histology(biopsy or surgery)	margin, echogenicity, texture, vascularization	0.9|0.9167	10.80|0.11	**STRONG**	**MODERATE**
Moderate Quality	Belli,P., 2000	56		soft tissue tumors(limbs)	US(pulsed doppler only) VS. Histology(biopsy or surgery)	systolic velocity of 0.5 m/s or greater	0.65|0.8889	5.85|0.39	**MODERATE**	WEAK

Quality	Author	N	Study Notes	Tumor Type	Imaging VS. Reference	Index Cutoff	Sens|Spec	LR+|LR-	Rule In Test	Rule Out Test
Low Quality	Pass,B., 2017	105	author received funding from imaging organization	soft tissue tumors (extremities)	US(B-mode) VS. histopathology and/or CFU (6pts; 12mo)	radiologist score 3 or 4(echogenicity, size, power doppler vascularity, depth)	0.7692|0.787	3.63|0.29	WEAK	WEAK

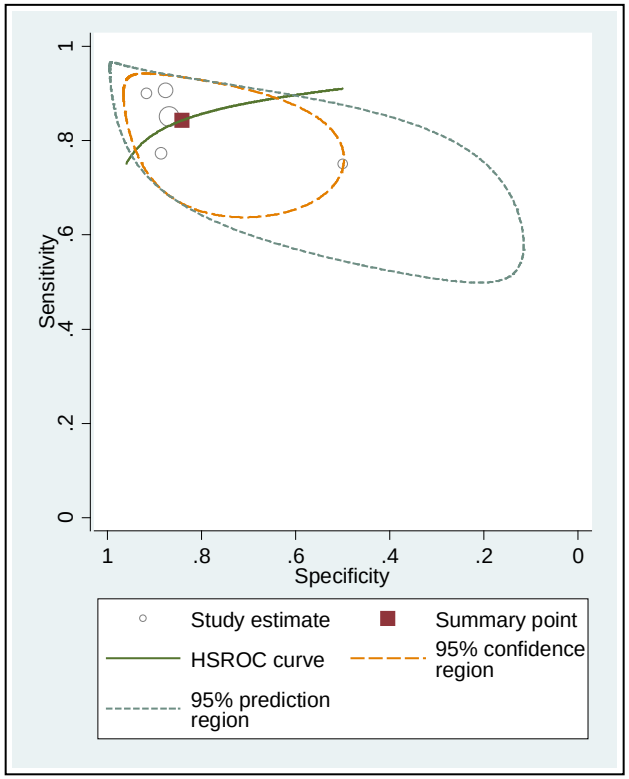
DATA TABLE 15: PICO 8 - SOFT TISSUE TUMOR DIAGNOSIS

Quality	Author	N	Study Notes	Tumor Type	Imaging VS. Reference	Index Cutoff	Sens|Spec	LR+|LR-	Rule In Test	Rule Out Test
Moderate Quality	Wagner,J.M., 2013	72	avg score of 4 examiners	Lipoma vs other soft tissue lesions (superficial)	US(power/color doppler used for 55pts) VS. Histopathology(surgery)	presence of homogeneously hyperechoic or isoechoic/hypoechoic with wavy linear echogenicity	0.9487|0.969	31.31|0.05	**STRONG**	**STRONG**
Moderate Quality	Furuta,T., 2017	105		hemangioma vs other STT	US(grayscale only) VS. pathology(biopsy or surgery)	compressable	0.8125|0.651	2.33|0.29	WEAK	WEAK
Moderate Quality	Furuta,T., 2017	105		hemangioma vs other STT	US(grayscale only) VS. pathology(biopsy or surgery)	heterogeneous interior	1|0.382	1.62|0.00	POOR	**STRONG**
Moderate Quality	Furuta,T., 2017	105		hemangioma vs other STT	US(power doppler only) VS. pathology(biopsy or surgery)	presence of Doppler flow signal	0.5625|0.640	1.56|0.68	POOR	POOR
Moderate Quality	Furuta,T., 2017	105		hemangioma vs other STT	US(power doppler only) VS. pathology(biopsy or surgery)	present sluggish speed sign (SSS)	0.9375|0.966	27.81|0.07	**STRONG**	**STRONG**
Moderate Quality	Arya,S., 2000	42	suspected of recurrence (surgical excision)	recurrent STT from primary STS after surgical excision	US VS. histopathology(surgical excision)	poorly reflective, discrete fairly well defined lesion	0.9167|0.944	16.50|0.09	**STRONG**	**STRONG**

Quality	Author	N	Study Notes	Tumor Type	Imaging VS. Reference	Index Cutoff	Sens|Spec	LR+|LR-	Rule In Test	Rule Out Test
Moderate Quality	De,Marchi A., 2003	80	includes 4 aggressive desmoid fibromatosis (benign)	soft tissue tumors or tumor-like (limbs)	US(echocolor power doppler; 99.9% galactose and 0.01% palmitic acid) VS. histology(biopsy or surgical specimen)	type III(rapid & irregular peaks/plateau)/type II(between III & I)/type I(regular peaks)	0.9143|0.2	1.14|0.43	POOR	WEAK

DETAILED DATA FINDINGS

FIGURE 4: PICO 8 HSROC META-ANALYSIS - ULTRASOUND VS HISTOPATHOLOGY FOR DETERMINING MALIGNANCY OF SOFT TISSUE TUMORS



Meta-analysis of diagnostic accuracy

Log likelihood = -24.584418 Number of studies = 5

	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
Bivariate						
E(logitSe)	1.679896	.255415			1.179291	2.1805
E(logitSp)	1.669735	.3844066			.9163121	2.423158
Var(logitSe)	.0833507	.1544508			.002206	3.149248
Var(logitSp)	.5715621	.4821983			.1093824	2.986617
Corr(logits)	1	.			.	.
HSROC						
Lambda	3.750279	.947408			1.893394	5.607165
Theta	.8433076	.8633917			-.8489091	2.535524
beta	.9626584	.9056597	1.06	0.288	-.812402	2.737719
s2alpha	.8730643	.9770927			.0973691	7.828367
s2theta	0	.			.	.
Summary pt.						
Se	.8428907	.0338236			.7648204	.8984847
Sp	.8415405	.0512606			.7142901	.9185763
DOR	28.49221	15.71937			9.662996	84.01183
LR+	5.319282	1.829861			2.710411	10.43929
LR-	.1866925	.0465847			.11448	.3044557
1/LR-	5.356402	1.336563			3.28455	8.73515

Covariance between estimates of E(logitSe) & E(logitSp) .045688

Reference	Quality	Sens | Spec	LR+ | LR-
Chen,T., 2015	High Quality	0.7727|0.8864	6.8|0.256
Belli,P., 2000	Moderate Quality	0.9|0.9167	10.8|0.109
Chen,C.Y., 2009(a)	Moderate Quality	0.9063|0.8767	7.35|0.107
Lagalla,R., 1998	Moderate Quality	0.75|0.5	1.5|0.5
Nagano,S., 2015	Moderate Quality	0.8507|0.8689	6.49|0.172

HISTORY OF PAIN

A. Moderate evidence supports that both radiographs and MRI have weak sensitivity in determining malignancy but moderate to strong specificity in determining benignity of bone tumors in patients reporting pain.

Strength of Recommendation: Moderate 

Description: Evidence from two or more "Moderate" quality studies with consistent findings, or evidence from a single "High" quality study for recommending for or against the intervention.

B. Limited evidence supports that a Tc99 bone scan may assist with obtaining a diagnosis or planning further diagnostic studies or treatment in patients with a bone tumor of unknown etiology and pain in the area of the tumor.

Strength of Recommendation: Limited 

Description: Evidence from one or more "Low" quality studies with consistent findings ***or*** *evidence from a single "Moderate" quality study recommending for or against the intervention or diagnostic test or the evidence is insufficient or conflicting and does not allow a recommendation for or against the intervention.*

C. In the absence of reliable evidence, it is the opinion of this work group that an MRI of a bone or soft-tissue tumor of unknown etiology should be considered, and is the preferred advanced imaging study, in patients with a complaint of pain at the site of the identified tumor.

Strength of Recommendation: Consensus 

Description: There is no supporting evidence. In the absence of reliable evidence, the work group is making a recommendation based on their clinical opinion.

D. In the absence of reliable evidence, it is the opinion of this work group that contrast-enhanced CT scan of the site should be considered in patients with pain at the site of a bone or soft tissue mass when there are patient specific contraindications to MRI, such as a pacemaker or cerebral aneurysm clips.

Strength of Recommendation: Consensus 

Description: There is no supporting evidence. In the absence of reliable evidence, the work group is making a recommendation based on their clinical opinion.

E. In the absence of reliable evidence, it is the opinion of this work group that, in the setting of a bone or soft-tissue tumor of unknown etiology with a complaint of pain at the site of the identified but undiagnosed tumor, CT of the chest/abdomen/pelvis, PET-CT, and Tc99 bone scan may assist with the diagnostic workup but should be utilized at the discretion of the treating oncologic specialists.

Strength of Recommendation: Consensus 

Description: There is no supporting evidence. In the absence of reliable evidence, the work group is making a recommendation based on their clinical opinion.

RATIONALE

In addition to a critical analysis of imaging studies, it is important to interview patients to determine their initial awareness of the condition, changes over time, and symptoms of presentation. Specifically, the presence or absence of pain can help determine the relative likelihood of an indolent or aggressive process. A physical exam is also necessary to determine alternative explanations for pain in the area of a bone or soft tissue lesion. It is not uncommon that unrelated symptoms due to arthritis, bursitis, and tendonitis can occur in the area of a lesion that is not the origin of the pain, but rather an incidental finding in close proximity. Therefore, pain by itself does not reliably indicate an aggressive process and a dedicated history and examination to investigate other potential causes is required. These recommendations apply primarily to the scenario of pain that cannot be attributed to a competing explanation and is likely due to the underlying lesion. The majority of bone malignancies will cause pain, often described as unassociated with activity and present at rest and night. In the setting of a bone lesion of unknown etiology, the presence of pain suggests an active process that requires further investigation to determine the underlying biology.

One moderate quality study (Barai, 2004) found that patients presenting with soft tissue tumors and reporting bone pain at distant sites of metastases reliably correlated to the presence or absence of metastatic sarcoma, which were detected by Tc99 bone scan. Among a population of patients mostly reporting bone pain, two moderate quality studies (Kotb, 2014 and Weger, 2013) found that MRI and radiographs can determine benignity of bone tumors with high accuracy but determined malignancy had a weaker association to the reference standard. Although the advanced imaging modality of choice is an MRI, an exception may be in the case of an obvious bone-forming lesion without a broken periosteal reaction on radiographs that is suggestive of an osteoid osteoma, in which case CT is the preferred imaging modality.

RISKS AND HARMS OF IMPLEMENTING THIS RECOMMENDATION

MRI poses minimal risk to the patient. There is a radiation dose associated with CT of the site and Tc 99m bone scans but it is low enough to pose no demonstrable risk to the patient.

FUTURE RESEARCH

Prospective comparative studies comparing imaging to histological diagnosis within subset populations such as patients with bone pain could be helpful for further investigation.

RESULTS

STUDY QUALITY TABLE 5: HISTORY OF PAIN

Study	Representative Population	Clear Selection Criteria	Detailed Enough to Replicate	Reference Standard Identifies Target Condition	Blinding	Other Bias?	Inclusion	Strength
Barai,S., 2004	●	●	●	○	●	◑	Include	Moderate Quality
Kotb,S.Z., 2014	●	◑	●	●	◑	◑	Include	Moderate Quality
Murphey,M.D., 1998	●	◑	●	○	●	○	Include	Low Quality
Nilsson-Ehle,H., 1982	●	●	●	●	◑	◑	Include	Moderate Quality
Pereira,H.M., 2014	●	◑	●	●	◑	◑	Include	Moderate Quality
Thommesen,P., 1976	●	◑	●	●	○	◑	Include	Low Quality
Weger,C., 2013	●	●	●	●	○	◑	Include	Moderate Quality

SUMMARY OF DATA FINDINGS

SUMMARY TABLE 15: PICO 9 - DIAGNOSING MALIGNANCY OF BONE TUMORS AMONG PATIENTS REPORTING PAIN

DIAGNOSING TUMORS OR MALIGNANCY IN PATIENTS PRESENTING PAIN					Moderate			Low
Outcome	**Tumor Type**	**Pain Present**	**Imaging Method**	**Diagnostic Threshold**	**Kotb,S.Z., 2014**	**Pereira,H.M., 2014***	**Weger,C., 2013****	**Thommesen,P., 1976**
Tumor diagnosis	Bone tumors	86% patients	MRI(1.5 T; w/ or w/o gadolinium)	Multiple cysts Involving 50% or more of lesion		71.43 56.2		
Malignancy	Bone tumors	71% patients	MRI(magnet unspecified; contrast not mentioned; DWI)	Restricted diffusion(high SI)	50.98 **89.8**			
		80% patients	Radiograph	Radiologist interpretation				**94.12** 8.3
		66% patients	Radiograph	Radiologist interpretation			30 **100**	

DATA TABLE 16: PICO 9 - BONE TUMOR DIAGNOSIS

Quality	Author	N	Study Notes	Tumor Type	Imaging VS. Reference	Index Cutoff	Sens|Spec	LR+|LR-	Rule In Test	Rule Out Test
Moderate Quality	Pereira,H.M., 2014	30	confirmed giant cell bone tumor pts; 86% present pain	secondary aneurysmal bone cyst	MRI(1.5 T; w/ or w/o gadolinium) VS. Histopathology	involving 50% or more of lesion	0.7143|0.562	1.63|0.51	POOR	POOR

DATA TABLE 17: PICO 9 - MALIGNANCY

Quality	Author	N	Study Notes	Tumor Type	Imaging VS. Reference	Index Cutoff	Sens|Spec	LR+|LR-	Rule In Test	Rule Out Test
Moderate Quality	Kotb,S.Z., 2014	100	71% pain pts	Bone tumors and tumor-like lesions	MRI(magnet unspecified; contrast not mentioned; DWI) VS. pathology(surgery or needle biopsy)	Restricted diffusion(high SI)	0.5098|0.898	5.00|0.55	**MODERATE**	POOR
Moderate Quality	Weger,C., 2013	85	66% pain pts	osteolytic lesions of os calcis	Radiograph(plain) VS. Histopathology(biopsy)	radiologist interpretation	0.3|1	30.00|0.70	**STRONG**	POOR
Low Quality	Thommesen,P., 1976	34	all pts under 20 years old; 80% with pain	bone tumors	radiograph VS. Histology(biopsy)	radiologist interpretation	0.9412|0.083	1.03|0.71	POOR	POOR
Low Quality	Murphey,M.D., 1998	187		chondrosarcoma vs enchondroma	patient report VS. Pathology (172) or CFU (15 ECs; 5yrs)	Pain present	0.9474|0.206	1.19|0.26	POOR	WEAK

DATA TABLE 18: PICO 9 - STAGE OF TUMOR

Quality	Author	N	Study Notes	Tumor Type	Imaging VS. Reference	Index Cutoff	Sens|Spec	LR+|LR-	Rule In Test	Rule Out Test
Moderate Quality	Barai,S., 2004	122		Soft tissue sarcoma (metastatic stage vs benign/indeterminate)	patient reported VS. BS(Tc99m-MDP; 3hrs post IV)	Bone pain	0.9412|0.866	7.06|0.07	**MODERATE**	**STRONG**
Moderate Quality	Nilsson-Ehle,H., 1982	25	durie salmon staging criteria	multiple myeloma (stage 3 vs stage 1/2)	patient reported VS. histology	presence of bone pain	0.9167|0.769	3.97|0.11	WEAK	**MODERATE**

HISTORY OF GROWTH

A. Moderate strength evidence supports that, in patients suspected of soft tissue tumor recurrence, an MRI of the tumor site can reliably identify neoplastic tissue and differentiate between solid and cystic areas.

Strength of Recommendation: Moderate 

Description: Evidence from two or more "Moderate" quality studies with consistent findings, or evidence from a single "High" quality study for recommending for or against the intervention.

B. In the absence of reliable evidence, it is the opinion of this work group that an MRI should be considered, and is the preferred advanced imaging study, in patients with a clear history of rapid growth of a bone or soft tissue mass.

Strength of Recommendation: Consensus 

Description: There is no supporting evidence. In the absence of reliable evidence, the work group is making a recommendation based on their clinical opinion.

C. In the absence of reliable evidence, it is the opinion of this work group that contrast-enhanced CT scan of the site should be considered in patients with a clear history of rapid growth of a bone or soft tissue mass when there are patient specific contraindications to MRI, such as a pacemaker or cerebral aneurysm clips.

Strength of Recommendation: Consensus 

Description: There is no supporting evidence. In the absence of reliable evidence, the work group is making a recommendation based on their clinical opinion.

D. In the absence of reliable evidence, it is the opinion of this work group that, in the setting of a bone or soft-tissue tumor of unknown etiology with rapid growth, CT of the chest/abdomen/pelvis, PET-CT, and Tc99 bone scan may assist with the diagnostic workup but should be utilized at the discretion of the treating oncologic specialists.

Strength of Recommendation: Consensus 

Description: There is no supporting evidence. In the absence of reliable evidence, the work group is making a recommendation based on their clinical opinion.

RATIONALE

One aspect of a patient history that is important when evaluating a tumor of the bone or soft tissue is the general stability of the mass over time. Palpable masses that have been present and not enlarging for months or years are unlikely to represent a life-threatening malignancy, whereas tumors with rapid growth over a period of weeks may be concerning for an aggressive process. Much of the literature we found did not focus on the initial evaluation of a growing mass, but rather an attempt to distinguish recurrent tumor from a non-neoplastic process (post-operative scar, fluid collections, normal tissue). Although the clinical setting varied from our intended scenario, the question remained relevant, as the imaging was performed in attempt to determine the presence of a tumor in a patient with a concern for recurrent or residual sarcoma.

One moderate quality study (Gingrich, 2017) reported on the ability of MRI to identify residual sarcoma after a prior resection and found 86.7% sensitivity, 57.9% specificity, and overall accuracy of 78.1%. One low quality study (Jiang, 2016) found that a soft tissue mass was a reliable indicator of tumor recurrence when an MRI was

performed adjacent to a total joint arthroplasty, with 100% sensitivity and 96% specificity. One moderate quality study (Lehotska, 2013) used time-to-intensity curves to reflect the dynamic enhancement of soft tissue in contrast MRI and determined a positive predictive value of 95.7% and negative predictive value of 100% in their ability to diagnose recurrent sarcoma. One low quality study (Park, 2016) compared MRI to PET-CT and found that each could reliably detect soft tissue sarcoma recurrence and were statistically equivalent. They recommended MRI as the primary modality to investigate recurrence, with PET-CT as an additional option if the MRI was inconclusive. In bone tumors, one moderate quality study (Pereira, 2014) reported that MRI was helpful and accurate at distinguishing solid and cystic components.

The work group was concerned that a statement recommending MRI in all patients with a history of growth of a mass would result in a large number of unnecessary MRI scans. In our cumulative clinical experience, many patients report slow growth over time (a common history in benign entities such as lipomas) or may report a contradictory history of an enlarging mass which, by objective measures such as bony remodeling on conventional radiographs, is likely to be an inadvertent misrepresentation of tumor growth. Therefore, we recommend that an MRI be considered as an imperative study only when there is a clear history of rapid growth (such as a tumor doubling or tripling in size in a matter of weeks). Clinicians should use other measures, such as the appearance on conventional radiographs, presence of pain, size, and depth of the lesion as additional factors that can help with decision-making.

RISKS AND HARMS OF IMPLEMENTING THIS RECOMMENDATION

MRI poses minimal risk to the patient. There is a radiation dose associated with CT of the site but it is small enough to pose no real risk to the patient.

FUTURE RESEARCH

The use of a clinical history of growth is a common factor used to assess the likelihood of an underlying malignancy when evaluating a bone or soft tissue mass. From our literature review, it is clear that a more diligent assessment of the correlation of a patient-reported history of mass growth and the presence of malignancy is warranted.

RESULTS

STUDY QUALITY TABLE 6: HISTORY OF GROWTH

Study	Representative Population	Clear Selection Criteria	Detailed Enough to Replicate	Reference Standard Identifies Target Condition	Blinding	Other Bias?	Inclusion	Strength
Al-Ibraheem,A., 2013	●	◑	●	○	●	○	Include	Low Quality
Arya,S., 2000	●	◑	●	●	●	◑	Include	Moderate Quality
Charest,M., 2009	●	●	●	●	○	◑	Include	Moderate Quality
Dimitrakopoulou-Strauss,A., 2001	●	◑	●	●	◑	◑	Include	Moderate Quality
Gingrich,A.A., 2017	●	●	●	●	◑	◑	Include	Moderate Quality
Jiang,M.H., 2016	●	◑	●	●	○	◑	Include	Low Quality
Lehotska,V., 2013	●	◑	●	●	◑	◑	Include	Moderate Quality
Okazumi,S., 2009	●	◑	●	●	◑	◑	Include	Moderate Quality
Park,S.Y., 2016	●	◑	●	○	●	○	Include	Low Quality
Pereira,H.M., 2014	●	◑	●	●	◑	◑	Include	Moderate Quality
Schwarzbach,M.H., 2000	●	●	●	●	●	○	Include	Moderate Quality

SUMMARY OF DATA FINDINGS

SUMMARY TABLE 16: PICO 10 - DIAGNOSING RECURRENT TUMORS AMONG PATIENTS WITH GROWTH HISTORY

				Moderate							Low			
Outcome	**Tumor Type**	**Imaging Method**	**Diagnostic Threshold**	**Arya,S., 2000**	**Dimitrakopoulou-Strauss,A., 2001**	**Gingrich,A.A., 2017**	**Lehotska,V., 2013**	**Okazumi,S., 2009**	**Pereira,H.M., 2014***	**Schwarzbach,M.H., 2000**	**Jiang,M.H., 2016**	**Al-Ibraheem,A., 2013*** **	**Charest,M., 2009*** **	**Park,S.Y., 2016*** **
Tumor diagnosis	Secondary aneurysmal bone cyst	MRI(1.5 T; w/ or w/o gadolinium)	Involving 50% or more of lesion						71.43 56.2					
	Recurrent bone tumors	PET(F-FDG)	Clinician interpretation									**90.91 100**		
		PET(F-FDG)/CT(diluted oral sodium meglumine iosithalamate)	Clinician interpretation									**100 100**		
		PET/CT(oral barium sulfate and IV FDG; 60min post IV)	Radiologist interpretation(tracer uptake)										**91.67 100**	
	Recurrent bone/soft tissue tumors	MRI(1.5 T; no contrast mentioned)	Presence of bone destruction								29.41 **98**			
			Presence of soft tissue mass								**100 96**			
		PET/CT(oral barium sulfate and IV FDG; 60min post IV)	Radiologist interpretation(tracer uptake)										**88.89 100**	
	Recurrent soft tissue tumors	CE MRI(3.0 or 1.5 T; contrast unspecified)	Radiologist interpretation(mass showing both high signal intensity on T2 and contrast enhancement)											**90 97.73**
		MRI(magnet unspecified; no contrast mentioned)	Focal or discrete enhancement			57.78 **89.4**								
		PET/CT(18F-FDG; 60min post IV; CT no contrast)	Radiologist interpretation(abnormal focal contrast uptake above background)											**95 95.45**
		PET/CT(oral barium sulfate and IV FDG; 60min post IV)	Radiologist interpretation(tracer uptake)										**88.1 100**	
		US	Poorly reflective, discrete fairly well defined lesion	**91.67 94.4**										
Malignancy	Recurrent soft tissue tumors	CE MRI(magnet unspecified; gadolinium)	Rapid enhancement present				**100 80**							
		PET(18F-FDG; 60min post IV)	SUV >4					57.45 **95.8**						
			SUV >4, FD >1.25, and Ki >0.03					**80.85 87.5**						
	70% recurrent soft tissue tumors	PET(18F-FDG; 60min post IV)	SUV value		**100** 0									
			Radiologist interpretation of parameters(SUV, K1, k3, vascular fraction, fractal dimension)		**100** 23.08									
			Visual evaluation by radiologist		76.74 38.4									
Stage of Tumor	60% recurrent soft tissue tumors	PET(18F-FDG; 55-60min post IV)	SUV value		**84.85** 50									
			Radiologist interpretation of parameters(SUV, K1, k3, vascular fraction, fractal dimension)		**87.88 80**									
	Recurrent malignant soft tissue tumors		FDG uptake and SUV(unspecified cutoff)							75 **100**				

DATA TABLE 19: PICO 10 - BONE TUMOR DIAGNOSIS

Quality	Author	N	Study Notes	Tumor Type	Imaging VS. Reference	Index Cutoff	Sens|Spec	LR+|LR-	Rule In Test	Rule Out Test
Moderate Quality	Pereira,H.M., 2014	30	confirmed giant cell bone tumor pts; 86% present pain	secondary aneurysmal bone cyst	MRI(1.5 T; w/ or w/o gadolinium) VS. Histopathology	involving 50% or more of lesion	0.7143|0.562	1.63|0.51	POOR	POOR
Low Quality	Al-Ibraheem,A., 2013	43	suspected of recurrence (complete remission)	recurrent bone tumor	PET(F-FDG)/CT(diluted oral sodium meglumine iosithalamate) VS. Histopathology and/or CFU(19 pts; 20mo)	clinician interpretation	1|1	100.00|0.00	**STRONG**	**STRONG**
Low Quality	Al-Ibraheem,A., 2013	43	suspected of recurrence (complete remission)	recurrent bone tumor	PET(F-FDG) VS. Histopathology and/or CFU(19 pts; 20mo)	clinician interpretation	0.9091|1	90.91|0.09	**STRONG**	**STRONG**
Low Quality	Charest,M., 2009	25	suspected of recurrence (previously treated); pts received oral and IV contrast simultaneously	recurrent bone tumors	PET/CT(oral barium sulfate and IV FDG; 60min post IV) VS. histopathology and/or CFU(13pts; no time given)	radiologist interpretation (tracer uptake)	0.9167|1	91.67|0.08	**STRONG**	**STRONG**

DATA TABLE 20: PICO 10 - BONE/SOFT TISSUE TUMOR DIAGNOSIS

Quality	Author	N	Study Notes	Tumor Type	Imaging VS. Reference	Index Cutoff	Sens|Spec	LR+|LR-	Rule In Test	Rule Out Test
Low Quality	Charest,M., 2009	86	suspected of recurrence (previously treated); pts received oral and IV contrast simultaneously	recurrent bone and soft tissue tumors	PET/CT(oral barium sulfate and IV FDG; 60min post IV) VS. histopathology and/or CFU(32pts; no time given)	radiologist interpretation (tracer uptake)	0.8889|1	88.89|0.11	**STRONG**	**MODERATE**
Low Quality	Jiang,M.H., 2016	67	suspected of recurrence (tumor resection with joint replacement)	recurrent bone/soft tissue tumors or tumor-like	MRI(1.5 T; no contrast mentioned) VS. pathology(resection or biopsy)	presence of soft tissue mass	1|0.96	25.00|0.00	**STRONG**	**STRONG**
Low Quality	Jiang,M.H., 2016	67	suspected of recurrence (tumor resection with joint replacement)	recurrent bone/soft tissue tumors or tumor-like	MRI(1.5 T; no contrast mentioned) VS. pathology(resection or biopsy)	presence of bone destruction	0.2941|0.98	14.71|0.72	**STRONG**	POOR

DATA TABLE 21: PICO 10 - MALIGNANCY

Quality	Author	N	Study Notes	Tumor Type	Imaging VS. Reference	Index Cutoff	Sens|Spec	LR+|LR-	Rule In Test	Rule Out Test
Moderate Quality	Lehotska,V., 2013	55	suspected of recurrence (post-surgery, radiotherapy, or chemotherapy)	recurrent STT	MRI(magnet unspecified; gadolinium) VS. Histology(biopsy)	Rapid enhancement present	1|0.8	5.00|0.00	**MODERATE**	**STRONG**
Moderate Quality	Okazumi,S., 2009	71	suspected of recurrent STT post-surgery	recurrent soft tissue tumors	PET(18F-FDG; 60min post IV) VS. Histopathology(surgical or biopsy)	SUV >4, FD >1.25, and Ki >0.03	0.8085|0.875	6.47|0.22	**MODERATE**	WEAK
Moderate Quality	Okazumi,S., 2009	71	suspected of recurrent STT post-surgery	recurrent soft tissue tumors	PET(18F-FDG; 60min post IV) VS. Histopathology(surgical or biopsy)	SUV >4	0.5745|0.958	13.79|0.44	**STRONG**	WEAK
Moderate Quality	Dimitrakopoulou-Strauss,A., 2001	56	70% suspected of recurrence (previous surgery/radiotherapy)	soft tissue tumors or tumor-like	PET(18F-FDG; 60min post IV) VS. Histology(surgery)	radiologist interpretation of parameters(SUV, K1, k3, vascular fraction, fractal dimension)	1|0.2308	1.30|0.00	POOR	**STRONG**
Moderate Quality	Dimitrakopoulou-Strauss,A., 2001	56	70% suspected of recurrence (previous surgery/radiotherapy)	soft tissue tumors or tumor-like	PET(18F-FDG; 55-60min post IV) VS. Histology(surgery)	SUV value	1|0	1.00|0.00	POOR	**STRONG**
Moderate Quality	Dimitrakopoulou-Strauss,A., 2001	56	70% suspected of recurrence (previous surgery/radiotherapy)	soft tissue tumors or tumor-like	PET(18F-FDG; 60min post IV) VS. Histology(surgery)	visual evaluation by radiologist	0.7674|0.384	1.25|0.61	POOR	POOR

DATA TABLE 22: PICO 10 - SOFT TISSUE TUMOR DIAGNOSIS

Quality	Author	N	Study Notes	Tumor Type	Imaging VS. Reference	Index Cutoff	Sens|Spec	LR+|LR-	Rule In Test	Rule Out Test
Moderate Quality	Gingrich,A.A., 2017	64	suspected of recurrence (previous chemotherapy or radiation prior to excision)	recurrent STS	MRI(magnet unspecified; no contrast mentioned) VS. pathology(excision)	focal or discrete enhancement	0.5778|0.894	5.49|0.47	**MODERATE**	WEAK
Moderate Quality	Arya,S., 2000	42	suspected of recurrence (surgical excision)	recurrent STT from primary STS after surgical excision	US VS. histopathology(surgical excision)	poorly reflective, discrete fairly well defined lesion	0.9167|0.944	16.50|0.09	**STRONG**	**STRONG**
Low Quality	Park,S.Y., 2016	152	suspected of recurrent STS	recurrent soft tissue sarcoma	PET/CT(18F-FDG; 60min post IV; CT no contrast) VS. histopathology or CFU(4pts; 2yrs)	radiologist interpretation (abnormal focal contrast uptake above background)	0.95|0.9545	20.90|0.05	**STRONG**	**STRONG**
Low Quality	Park,S.Y., 2016	152	suspected of recurrent STS	recurrent soft tissue sarcoma	MRI(3.0 or 1.5 T; contrast unspecified) VS. histopathology or CFU(4pts; 2yrs)	radiologist interpretation (mass showing both high signal intensity on T2 and contrast enhancement)	0.9|0.9773	39.60|0.10	**STRONG**	**STRONG**
Low Quality	Charest,M., 2009	61	suspected of recurrence (previously treated); pts received oral and IV contrast simultaneously	recurrent soft tissue tumors	PET/CT(oral barium sulfate and IV FDG; 60min post IV) VS. histopathology and/or CFU(19pts; no time given)	radiologist interpretation (tracer uptake)	0.881|1	88.10|0.12	**STRONG**	**MODERATE**

DATA TABLE 23: PICO 10 - STAGE OF TUMOR

Quality	Author	N	Study Notes	Tumor Type	Imaging VS. Reference	Index Cutoff	Sens|Spec	LR+|LR-	Rule In Test	Rule Out Test
Moderate Quality	Schwarzbach,M. H., 2000	24	Confirmed recurrent malignant STT	recurrent soft tissue tumors (high grade vs low/intermediate grade)	PET(FDG; 55-60min post IV) VS. Histopathology(biopsy)	FDG uptake and SUV(unspecified cutoff)	0.75|1	75.00|0.25	**STRONG**	WEAK
Moderate Quality	Dimitrakopoulou-Strauss,A., 2001	43	60% suspected of recurrence (previous surgery/radiotherapy)	soft tissue sarcomas (high grade 2/3 vs low grade 1)	PET(18F-FDG; 60min post IV) VS. Histology(surgery)	radiologist interpretation of parameters(SUV, K1, k3, vascular fraction, fractal dimension)	0.8788|0.8	4.39|0.15	WEAK	**MODERATE**
Moderate Quality	Dimitrakopoulou-Strauss,A., 2001	43	60% suspected of recurrence (previous surgery/radiotherapy)	soft tissue sarcomas (high grade 2/3 vs low grade 1)	PET(18F-FDG; 55-60min post IV) VS. Histology(surgery)	SUV value	0.8485|0.5	1.70|0.30	POOR	WEAK

TUMOR SIZE

A. Strong evidence supports the use of MRI imaging for a bone or soft tissue tumor of unknown etiology with a size greater than 5 cm to assist with obtaining a diagnosis and planning further treatment.

Strength of Recommendation: Strong ★★★★

Description: Evidence from two or more "High" quality studies with consistent findings for recommending for or against the intervention.

B. In the absence of reliable evidence, the work group recommends that, in aggressive appearing bone or soft tissue tumors, advanced imaging studies be requested with the guidance of an orthopedic oncologist or musculoskeletal radiologist.

Strength of Recommendation: Consensus ★☆☆☆

Description: There is no supporting evidence. In the absence of reliable evidence, the work group is making a recommendation based on their clinical opinion.

RATIONALE

Size is an important feature noted by clinicians on initial evaluation of a bone or soft tissue tumor. For malignancy, increasing size of the mass is correlated with adverse outcomes such as local recurrence and diminished overall survival, implying a relationship with tumor biology. The importance of size is also reflected in tumor classifications, such as the widely-used American Joint Committee on Cancer (AJCC) staging system which includes the maximal dimension of soft tissue sarcoma (5 and 10 cm) and bone sarcoma (8 cm) as one of the few characteristics used to determine cancer stage. A unifying feature of aggressive neoplasia is growth over time. By this reasoning, larger tumors may be more likely to represent a malignancy and require an assertive imaging investigation. Our review focused on literature that discusses the relationship of size to an underlying malignancy, and the use of advanced imaging modalities to determine the cause and formulate a treatment plan.

There were 5 high and 11 moderate quality studies evaluating the use of MR imaging for a bone or soft tissue tumor of unknown etiology with a mass of a certain size or depth to assist with obtaining a diagnosis or planning further treatment. High strength studies have evaluated the ability of MR imaging to differentiate benign from malignant tumors in a variety of locations in the axial (Matsumoto 2016) and appendicular (Liu 2011) regions and soft tissue masses with a variety of sizes, appearances (cystic or solid [Harish 2006]) and tissue types (fatty [Rougraff 1997], neurogenic [Zhang 2015], etc).

Two high quality studies (Matsumoto 2016 and Zhang 2015) and 6 moderate quality studies (Calleja 2012, Chen 2009c, Chung 2012, Datir 2008, Gruber 2016, and Sen 2010) found MRI to have a moderate to strong relationship to histopathological results in determining malignancy of soft tissue tumors with a size of 5cm or larger. MRI is first option for staging malignant bone tumors and for evaluation of all indeterminate soft tissue tumors. Other imaging modalities (CT of the site, PET/CT, Tc 99m Bone Scan) are used in specific cases and should be implemented by, or with the guidance of, the treating oncology team.

RISKS AND HARMS OF IMPLEMENTING THIS RECOMMENDATION

There are no known minimal risks and harms associated with implementing this recommendation for MR imaging.

There is a radiation dose associated with CT of the site, CT chest/abdomen/pelvis, Tc 99m bone scans, or PET/CT scans but it is small enough to pose no real risk to the patient.

FUTURE RESEARCH

Larger prospective studies investigating the utility of CT of the site, nuclear scintigraphy (bone scans), or PET/CT scans to assist with obtaining a diagnosis or planning further treatment are needed.

RESULTS

STUDY QUALITY TABLE 7: TUMOR SIZE

Study	Representative Population	Clear Selection Criteria	Detailed Enough to Replicate	Reference Standard Identifies Target Condition	Blinding	Other Bias?	Inclusion	Strength
Berquist,T.H., 1990	●	●	●	○	●	◑	Include	Moderate Quality
Brenner,W., 2004	●	◑	●	●	○	◑	Include	Low Quality
Calleja,M., 2012	●	●	●	●	○	◑	Include	Moderate Quality
Chen,C.K., 2009	●	◑	●	●	●	◑	Include	Moderate Quality
Chung,W.J., 2012	●	●	●	●	○	◑	Include	Moderate Quality
Daniel,A.,Jr., 2009	●	●	●	●	◑	◑	Include	Moderate Quality
Datir,A., 2008	●	●	●	●	○	◑	Include	Moderate Quality
De,Marchi A., 2015	●	●	●	○	●	◑	Include	Moderate Quality
Gruber,L., 2016	●	●	●	●	○	◑	Include	Moderate Quality
Harish,S., 2006	●	●	●	●	●	◑	Include	High Quality
Higuchi,T., 2002	●	◑	●	●	○	◑	Include	Low Quality
Hoshi,M., 2014	●	◑	●	●	●	◑	Include	Moderate Quality
Imaeda,T., 1991	●	◑	●	●	◑	◑	Include	Moderate Quality
Kalayanarooj,S., 2008	●	◑	●	●	◑	◑	Include	Moderate Quality
Kobayashi,H., 1994	●	◑	●	●	◑	◑	Include	Moderate Quality
Leal,A.L., 2014	●	◑	●	●	◑	●	Include	Moderate Quality
Liu,L., 2011	●	●	●	●	●	◑	Include	High Quality
Loizides,A., 2012	●	●	●	●	●	◑	Include	High Quality
Matsumoto,Y., 2016	●	●	●	●	●	◑	Include	High Quality
Moulton,J.S., 1995	●	●	●	○	●	○	Include	Low Quality
Rougraff,B.T., 1997	●	●	●	●	●	◑	Include	High Quality
Russo,F., 2012	●	◑	●	●	●	◑	Include	Moderate Quality
Schwartz,H.S., 1990	●	◑	●	●	◑	◑	Include	Moderate Quality
Sen,J., 2010	●	●	●	●	◑	◑	Include	Moderate Quality

Study	Representative Population	Clear Selection Criteria	Detailed Enough to Replicate	Reference Standard Identifies Target Condition	Blinding	Other Bias?	Inclusion	Strength
Yildirim,A., 2016	●	◑	●	○	●	◑	Include	Low Quality
Zhang,Z., 2015	●	●	●	●	●	◑	Include	High Quality
Zhao,F., 2014	●	●	●	●	○	◑	Include	Moderate Quality

SUMMARY OF DATA FINDINGS

SUMMARY TABLE 17: PICO 11 - DIAGNOSING MALIGNANCY AMONG SOFT TISSUE TUMORS OF A CERTAIN SIZE

DIAGNOSING MALIGNANCY OF SOFT TISSUE TUMORS OF A CERTAIN SIZE			High	Moderate	
Imaging Method	Tumor Size	Diagnostic Threshold	Zhang,Z., 2015*	Kobayashi,H., 1994	Schwartz,H.S., 1990
BS(99mTc-DMS; 2 hr post IV)	2cm	Positive uptake		**100** 38.46	
	3cm			**100** 35.56	
	5cm			**100** 39.29	
BS(Ga-67 citrate; 72hr post IV)	2cm	Positive uptake		57.14 73.6	
	3cm			57.14 69.7	
	5cm			57.14 65	
BS(gallium-67 citrate; 24/48hr, and 72hr post IV)	2.54cm	Clinician interpretation			**95.83** **87.1**
CE MRI(1.5T and 3T; gadolinium)	5-11cm	Bright rim sign absent	**96** 73.33		
		Lobular shape present	**84** **86.67**		
		Maximal peritumoral edema extent greater than 18mm	**100** **89**		

SUMMARY TABLE 18: PICO 11 - SIZE AND DEPTH DIAGNOSING BONE AND/OR SOFT TISSUE TUMORS

				High				Moderate													Low
Outcome	**Tumor Type**	**Imaging Method**	**Diagnostic Threshold**	**Harish,S., 2006**	**Liu,L., 2011**	**Matsumoto,Y., 2016****	**Rougraff,B.T., 1997**	**Calleja,M., 2012**	**Chen,C.K., 2009(c)**	**Chung,W.J., 2012**	**Daniel,A.,Jr., 2009**	**Datir,A., 2008**	**Gruber,L., 2016**	**Hoshi,M., 2014**	**Imaeda,T., 1991**	**Leal,A.L., 2014**	**Russo,F., 2012**	**Sen,J., 2010**	**Zhao,F., 2014**	**Higuchi,T., 2002***
Stage of Tumor	Soft tissue tumors	MRI(magnet unspecified; no contrast)	Intramuscular or intermuscular																70.89 31.2	
			Size 5.5cm or more																79.75 56.2	
Tumor diagnosis	Soft tissue tumors	MRI(1 T; no contrast mentioned)	Deep lesion									**84.12** 16.2								
			Size of 5cm or more									79.38 33.7								
Malignancy	Bone tumors	BS(Tl-chloride; 15min and 3hr post IV)	Size >5cm																	64.29 61.1
		CE MRI(magnet unspecified; gadolinium)	> or =5 cm			75 79.49														
	Soft tissue tumors	1H-MRS(1.5 T; gadobutrol paramagnetic)	Size of 5.5cm or more														72.22 66.6			
			Size of 5cm or more														55.56 66.6			
		BS(gallium-67 citrate; 48hr and 72hr post IV)	Size of 5 cm or more												78.95 43.6					
		MRI(1 T; no contrast mentioned)	Deep lesion									**84.38** 16.2								
			Size of 5cm or more									**89.58** 35.5								
		CE MRI(1.5 T; Gd-DPTA)	Size of 5 cm or more															**82.61** 71.8		
		MRI(1.5 T; w/ or w/o gadolinium)	Depth of 8 cm or more						59.68 73.2											
			Size of 5 cm or more						59.68 78.5											
		CE MRI(1.5T or 3T; contrast unspecified)	Deep location							73.53 42.6										
			Size of 50 mm or more							69.61 57.3										
		CE MRI(1.5T; gadolinium)	Size of 6 cm or more								**95.83** 57.6									
			Size of 8 cm or more								75 76.92									
		MRI(3T; w/ or w/o gadopentetate dimeglumine)	Deep(interspace of deep fascia or intramuscular)		68.97 42.1															
		MRI(magnet unspecified; contrast not mentioned; T1, T2, & STIR)	Intramuscular or intermuscular				**88.89** 35.7													
		MRI(magnet unspecified; w/ or w/o gadolinium)	Deep location	**92.31** 0																
		MRI(magnet unspecified; w/ or w/o unspecified contrast)	Size of 5cm or more					68.06 42.1												
		MRI(T1w, T2w, or contrast unspecified) and US(for 10% of pts)	IRAS(Index of age*size*RALD^3)>62.9										77.05 **80.1**							
			RALD(ratio of lateral to axial diameter)>0.5										**83.61** 53.6							
			Size >50mm										68.85 51.6							
			Size >70mm										65.57 66.2							
		PET/CT(18F-FDG PET 1 and 2hr post IV; CT oral pielograf)	Size of 4 cm or more													**94.44** 50				
		PET/CT(18F-FDG PET 60min post IV; CT no contrast mentioned) and tumor size	Size 5cm or more AND SUV of 2 or more											55.32 47.3						

DATA TABLE 24: PICO 11 - MALIGNANCY

Quality	Author	N	Study Notes	Tumor Type	Imaging VS. Reference	Index Cutoff	Sens|Spec	LR+|LR-	Rule In Test	Rule Out Test
High Quality	Rougraff,B.T., 1997	46		Lipomatous masses	MRI(magnet unspecified; contrast not mentioned; T1, T2, & STIR) VS. pathology(resection and biopsy)	Intramuscular or intermuscular	0.8889|0.357	1.38|0.31	POOR	WEAK
High Quality	Zhang,Z., 2015	40	large tumors (5-11cm)	Malignant soft tissue tumors vs Schwannoma	MRI(1.5T and 3T; gadolinium) VS. Histology	Bright rim sign absent	0.96|0.7333	3.60|0.06	WEAK	**STRONG**
High Quality	Zhang,Z., 2015	40	large tumors (5-11cm)	Malignant soft tissue tumors vs Schwannoma	MRI(1.5T and 3T; gadolinium) VS. Histology	Lobular shape present	0.84|0.8667	6.30|0.19	**MODERATE**	**MODERATE**
High Quality	Zhang,Z., 2015	40	AUTHOR REPORTED RESULTS; large tumors (5-11cm)	Malignant soft tissue tumors vs Schwannoma	MRI(1.5T and 3T; gadolinium) VS. Histology	Maximal peritumoral edema extent greater than 18mm	1|0.89	9.09|0.00	**MODERATE**	**STRONG**
High Quality	Harish,S., 2006	40	gadolinium contrast used in only 13 pts	soft tissue tumors	MRI(magnet unspecified; w/ or w/o gadolinium) VS. Histopathology	deep location	0.9231|0	0.92|7.69	POOR	POOR
High Quality	Loizides,A., 2012	51		soft tissue tumors	US(Sono Vue) VS. histology(US-guided biopsy)	3.3 cm or more, and diffuse enhanced mass	0.875|0.8148	4.73|0.15	WEAK	**MODERATE**
High Quality	Loizides,A., 2012	51		soft tissue tumors	US(Sono Vue) VS. histology(US-guided biopsy)	3.3 cm or more, and diffuse or peripherally enhanced mass	0.9583|0.777	4.31|0.05	WEAK	**STRONG**

Quality	Author	N	Study Notes	Tumor Type	Imaging VS. Reference	Index Cutoff	Sens|Spec	LR+|LR-	Rule In Test	Rule Out Test
High Quality	Loizides,A., 2012	51		soft tissue tumors	US(Sono Vue) VS. histology(US-guided biopsy)	3.3 cm or more, and peripheral enhanced mass	0.0833|0.963	2.25|0.95	WEAK	POOR
High Quality	Loizides,A., 2012	51		soft tissue tumors	US(Sono Vue) VS. histology(US-guided biopsy)	5 cm or more, and diffuse or peripherally enhanced mass	0.8333|1	83.33|0.17	**STRONG**	**MODERATE**
High Quality	Loizides,A., 2012	51		soft tissue tumors	US(Sono Vue) VS. histology(US-guided biopsy)	5 cm or more, and diffusely enhanced mass	0.6667|0.888	6.00|0.38	**MODERATE**	WEAK
High Quality	Loizides,A., 2012	51		soft tissue tumors	US(Sono Vue) VS. histology(US-guided biopsy)	5 cm or more, and peripheral enhanced mass	0.125|1	12.50|0.88	**STRONG**	POOR
High Quality	Loizides,A., 2012	51		soft tissue tumors	US(Sono Vue) VS. histology(US-guided biopsy)	6.6 cm or more, and diffusely enhanced mass	0.5417|0.925	7.31|0.50	**MODERATE**	POOR
High Quality	Loizides,A., 2012	51		soft tissue tumors	US(Sono Vue) VS. histology(US-guided biopsy)	6.6 cm or more, and peripheral enhanced mass	0.0833|1	8.33|0.92	**MODERATE**	POOR
High Quality	Loizides,A., 2012	51		soft tissue tumors	US(Sono Vue) VS. histology(US-guided biopsy)	deep and diffusely enhanced mass	0.875|0.8889	7.88|0.14	**MODERATE**	**MODERATE**

Quality	Author	N	Study Notes	Tumor Type	Imaging VS. Reference	Index Cutoff	Sens|Spec	LR+|LR-	Rule In Test	Rule Out Test
High Quality	Loizides,A., 2012	51		soft tissue tumors	US(Sono Vue) VS. histology(US-guided biopsy)	deep and diffusely or peripherally enhanced mass	0.9583|0.814	5.18|0.05	**MODERATE**	**STRONG**
High Quality	Loizides,A., 2012	51		soft tissue tumors	US(Sono Vue) VS. histology(US-guided biopsy)	deep and peripheral enhanced mass	0.0833|0.925	1.13|0.99	POOR	POOR
High Quality	Loizides,A., 2012	51		soft tissue tumors	US(Sono Vue) VS. histology(US-guided biopsy)	deep, 3.3 cm or more, and diffusely enhanced mass	0.8333|0.888	7.50|0.19	**MODERATE**	**MODERATE**
High Quality	Loizides,A., 2012	51		soft tissue tumors	US(Sono Vue) VS. histology(US-guided biopsy)	deep, 3.3 cm or more, and peripheral or diffusely enhanced mass	0.9167|0.851	6.19|0.10	**MODERATE**	**STRONG**
High Quality	Loizides,A., 2012	51		soft tissue tumors	US(Sono Vue) VS. histology(US-guided biopsy)	deep, 5 cm or more, and diffusely enhanced mass	0.6667|0.925	9.00|0.36	**MODERATE**	WEAK
High Quality	Loizides,A., 2012	51		soft tissue tumors	US(Sono Vue) VS. histology(US-guided biopsy)	deep, 5 cm or more, and peripheral or diffusely enhanced mass	0.6667|0.925	9.00|0.36	**MODERATE**	WEAK
High Quality	Liu,L., 2011	48	31 patients received IV contrast	soft tissue tumors (lower limbs)	MRI(3T; w/ or w/o gadopentetate dimeglumine) VS. histopathology(biopsy or excision)	Deep(interspace of deep fascia or intramuscular)	0.6897|0.421	1.19|0.74	POOR	POOR

Quality	Author	N	Study Notes	Tumor Type	Imaging VS. Reference	Index Cutoff	Sens|Spec	LR+|LR-	Rule In Test	Rule Out Test
High Quality	Matsumoto,Y., 2016	59		spinal dumbbell tumors	MRI(magnet unspecified; gadolinium) VS. histopathology(surgery or biopsy)	> or =5 cm	0.75|0.7949	3.66|0.32	WEAK	WEAK
Moderate Quality	Berquist,T.H., 1990	95		soft tissue tumors	MRI(0.15T or 1.5T; no contrast mentioned) VS. Histopathology(surgery) or clinical follow-up(n=9)	>5cm	0.8667|0.5	1.73|0.27	POOR	WEAK
Moderate Quality	Chen,C.K., 2009(c)	118	4 metastases included; 2 pts without IV contrast	soft tissue tumors	MRI(1.5 T; w/ or w/o gadolinium) VS. Histology	depth of 8 cm or more	0.5968|0.732	2.23|0.55	WEAK	POOR
Moderate Quality	Chen,C.K., 2009(c)	118	4 metastases included; 2 pts without IV contrast	soft tissue tumors	MRI(1.5 T; w/ or w/o gadolinium) VS. Histology	size of 5 cm or more	0.5968|0.785	2.79|0.51	WEAK	POOR
Moderate Quality	Daniel,A.,Jr., 2009	50		soft tissue tumors	MRI(1.5T; gadolinium) VS. Histopathology	size of 6 cm or more	0.9583|0.576	2.27|0.07	WEAK	**STRONG**
Moderate Quality	Daniel,A.,Jr., 2009	50		soft tissue tumors	MRI(1.5T; gadolinium) VS. Histopathology	size of 8 cm or more	0.75|0.7692	3.25|0.33	WEAK	WEAK
Moderate Quality	Datir,A., 2008	485		soft tissue tumors	MRI(1 T; no contrast mentioned) VS. histology	deep lesion	0.8438|0.162	1.01|0.96	POOR	POOR
Moderate Quality	Datir,A., 2008	485		soft tissue tumors	MRI(1 T; no contrast mentioned) VS. histology	size of 5cm or more	0.8958|0.355	1.39|0.29	POOR	WEAK
Moderate Quality	De,Marchi A., 2015	216	clinical FU only for all benign	soft tissue tumors	US(SonoVue sulphur hexaflouride) VS. histology(biopsy or surgery) or clinical FU(22 pts; benign only; no time given)	deep location	0.6923|0.348	1.06|0.88	POOR	POOR

Quality	Author	N	Study Notes	Tumor Type	Imaging VS. Reference	Index Cutoff	Sens|Spec	LR+|LR-	Rule In Test	Rule Out Test
Moderate Quality	De,Marchi A., 2015	215	clinical FU only for all benign	soft tissue tumors	US(SonoVue sulphur hexaflouride) VS. histology(biopsy or surgery) or clinical FU(22 pts; benign only; no time given)	size of 6 cm or more	0.6|0.5882	1.46|0.68	POOR	POOR
Moderate Quality	Gruber,L., 2016	212		soft tissue tumors	MRI(T1w, T2w, or contrast unspecified) and US(for 10% of pts) VS. Histopathology(US guided needle core biopsy or resection)	IRAS(Index of age*size*RALD^3)>62.9	0.7705|0.801	3.88|0.29	WEAK	WEAK
Moderate Quality	Gruber,L., 2016	212		soft tissue tumors	MRI(T1w, T2w, or contrast unspecified) and US(for 10% of pts) VS. Histopathology(US guided needle core biopsy or resection)	RALD(ratio of lateral to axial diameter)>0.5	0.8361|0.536	1.80|0.31	POOR	WEAK
Moderate Quality	Gruber,L., 2016	212		soft tissue tumors	MRI(T1w, T2w, or contrast unspecified) and US(for 10% of pts) VS. Histopathology(US guided needle core biopsy or resection)	Size >50mm	0.6885|0.516	1.42|0.60	POOR	POOR
Moderate Quality	Gruber,L., 2016	212		soft tissue tumors	MRI(T1w, T2w, or contrast unspecified) and US(for 10% of pts) VS. Histopathology(US guided needle core biopsy or resection)	Size >70mm	0.6557|0.662	1.94|0.52	POOR	POOR

Quality	Author	N	Study Notes	Tumor Type	Imaging VS. Reference	Index Cutoff	Sens|Spec	LR+|LR-	Rule In Test	Rule Out Test
Moderate Quality	Hoshi,M., 2014	113		soft tissue tumors	PET/CT(18F-FDG PET 60min post IV; CT no contrast mentioned) and tumor size VS. Histopathology(surgical or biopsy)	Size 5cm or more AND SUV of 2 or more	0.5532|0.473	1.05|0.94	POOR	POOR
Moderate Quality	Leal,A.L., 2014	44		soft tissue tumors	PET/CT(18F-FDG PET 1 and 2hr post IV; CT oral pielograf) VS. Histopathology(US-guided core needle or excision biopsy)	size of 4 cm or more	0.9444|0.5	1.89|0.11	POOR	**MODERATE**
Moderate Quality	Russo,F., 2012	36	Excluding 1 metastases and 6 undetermined	soft tissue tumors	1H-MRS(1.5 T; gadobutrol paramagnetic) VS. pathology(surgical resection or biopsy)	size of 5.5cm or more	0.7222|0.666	2.17|0.42	WEAK	WEAK
Moderate Quality	Russo,F., 2012	36	Excluding 1 metastases and 6 undetermined	soft tissue tumors	1H-MRS(1.5 T; gadobutrol paramagnetic) VS. pathology(surgical resection or biopsy)	size of 5cm or more	0.5556|0.666	1.67|0.67	POOR	POOR
Moderate Quality	Schwartz,H.S., 1990	55	STT diameters 1in or more	soft tissue tumors	BS(gallium-67 citrate; 24/48hr, and 72hr post IV) VS. histology	clinician interpretation	0.9583|0.871	7.43|0.05	**MODERATE**	**STRONG**
Moderate Quality	Sen,J., 2010	55		soft tissue tumors	MRI(1.5 T; Gd-DPTA) VS. Histopathology(surgical resection)	size of 5 cm or more	0.8261|0.718	2.94|0.24	WEAK	WEAK
Moderate Quality	Chung,W.J., 2012	266		soft tissue tumors (extremities)	MRI(1.5T or 3T; contrast unspecified) VS. Histopathology(biopsy or surgical resection)	deep location	0.7353|0.426	1.28|0.62	POOR	POOR

Quality	Author	N	Study Notes	Tumor Type	Imaging VS. Reference	Index Cutoff	Sens|Spec	LR+|LR-	Rule In Test	Rule Out Test
Moderate Quality	Chung,W.J., 2012	266		soft tissue tumors (extremities)	MRI(1.5T or 3T; contrast unspecified) VS. Histopathology(biopsy or surgical resection)	size of 50 mm or more	0.6961|0.573	1.63|0.53	POOR	POOR
Moderate Quality	Imaeda,T., 1991	74	avg of 2 readers	soft tissue tumors (extremities)	BS(gallium-67 citrate; 48hr and 72hr post IV) VS. histology(surgical resection)	size of 5 cm or more	0.7895|0.436	1.40|0.48	POOR	WEAK
Moderate Quality	Calleja,M., 2012	129		soft tissue tumors (superficial)	MRI(magnet unspecified; w/ or w/o unspecified contrast) VS. histology(image-guided needle/primary excision biopsy	size of 5cm or more	0.6806|0.421	1.18|0.76	POOR	POOR
Moderate Quality	Kobayashi,H., 1994	47	masses of 3cm or more in diameter	soft tissue tumors or tumor-like	BS(Ga-67 citrate; 72hr post IV) VS. histology(surgical specimen or needle biopsy)	positive uptake	0.5714|0.697	1.89|0.62	POOR	POOR
Moderate Quality	Kobayashi,H., 1994	34	masses of 5cm or more in diameter	soft tissue tumors or tumor-like	BS(Ga-67 citrate; 72hr post IV) VS. histology(surgical specimen or needle biopsy)	positive uptake	0.5714|0.65	1.63|0.66	POOR	POOR
Moderate Quality	Kobayashi,H., 1994	64	masses of 3cm or more in diameter	soft tissue tumors or tumor-like	BS(99mTc-DMS; 2 hr post IV) VS. histology(surgical specimen or needle biopsy)	positive uptake	1|0.3556	1.55|0.00	POOR	**STRONG**
Moderate Quality	Kobayashi,H., 1994	52	masses of 2cm or more in diameter	soft tissue tumors or tumor-like	BS(Ga-67 citrate; 72hr post IV) VS. histology(surgical specimen or needle biopsy)	positive uptake	0.5714|0.736	2.17|0.58	WEAK	POOR

Quality	Author	N	Study Notes	Tumor Type	Imaging VS. Reference	Index Cutoff	Sens|Spec	LR+|LR-	Rule In Test	Rule Out Test
Moderate Quality	Kobayashi,H., 1994	46	masses of 5cm or more in diameter	soft tissue tumors or tumor-like	BS(99mTc-DMS; 2 hr post IV) VS. histology(surgical specimen or needle biopsy)	positive uptake	1|0.3929	1.65|0.00	POOR	**STRONG**
Moderate Quality	Kobayashi,H., 1994	71	masses of 2cm or more in diameter	soft tissue tumors or tumor-like	BS(99mTc-DMS; 2 hr post IV) VS. histology(surgical specimen or needle biopsy)	positive uptake	1|0.3846	1.63|0.00	POOR	**STRONG**
Low Quality	Higuchi,T., 2002	32		bone tumors (OS or chordoma vs Giant cell tumor)	bone scan (TI-chloride; 15min and 3hr post IV) VS. Histopathology	size >5cm	0.6429|0.611	1.65|0.58	POOR	POOR
Low Quality	Kalayanarooj,S., 2008	85	LOW QUAL DOWNGRADE FOR REF	soft tissue tumors	MRI(1.5 T; gadolinium) VS. histopathology(biopsy, 82/85 pts) or benign MRI characteristics (3/85 pts)	deep lesion	0.6571|0.22	0.84|1.56	POOR	POOR
Low Quality	Kalayanarooj,S., 2008	85	LOW QUAL DOWNGRADE FOR REF	soft tissue tumors	MRI(1.5 T; gadolinium) VS. histopathology(biopsy, 82/85 pts) or benign MRI characteristics (3/85 pts)	size greater than 5cm	0.8|0.26	1.08|0.77	POOR	POOR
Low Quality	Moulton,J.S., 1995	225		soft tissue tumors	MRI(1.5T, no contrast) VS. Histopathology or CFU(41pts; 2yrs)	Intramuscular, mixed, or joint depth	0.7391|0.553	1.65|0.47	POOR	WEAK
Low Quality	Moulton,J.S., 1995	225		soft tissue tumors	MRI(1.5T, no contrast) VS. Histopathology or CFU(41pts; 2yrs)	size >10cm	0.4783|0.877	3.89|0.60	WEAK	POOR

Quality	Author	N	Study Notes	Tumor Type	Imaging VS. Reference	Index Cutoff	Sens|Spec	LR+|LR-	Rule In Test	Rule Out Test
Low Quality	Moulton,J.S., 1995	225		soft tissue tumors	MRI(1.5T, no contrast) VS. Histopathology or CFU(41pts; 2yrs)	size 5cm or more	0.6522|0.558	1.48|0.62	POOR	POOR
Low Quality	Yildirim,A., 2016	35	4 metastases pts	soft tissue tumors	MRI(1.5T; no contrast) VS. histology(32/35 pts) or clinical FU(3/35 pts)	size greater than 5cm	0.9474|0.375	1.52|0.14	POOR	**MODERATE**

DATA TABLE 25: PICO 11 - SOFT TISSUE TUMOR DIAGNOSIS

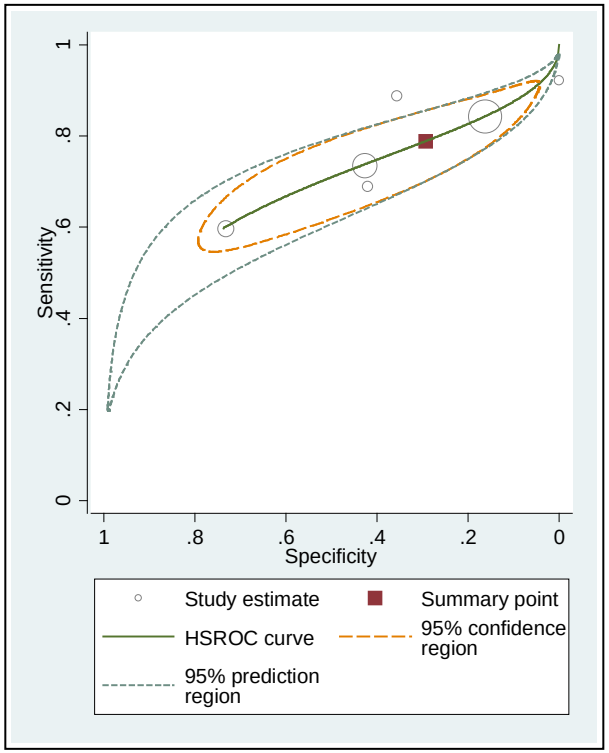
Quality	Author	N	Study Notes	Tumor Type	Imaging VS. Reference	Index Cutoff	Sens|Spec	LR+|LR-	Rule In Test	Rule Out Test
Moderate Quality	Datir,A., 2008	571		soft tissue tumors	MRI(1 T; no contrast mentioned) VS. histology	deep lesion	0.8412|0.162	1.01|0.98	POOR	POOR
Moderate Quality	Datir,A., 2008	571		soft tissue tumors	MRI(1 T; no contrast mentioned) VS. histology	size of 5cm or more	0.7938|0.337	1.20|0.61	POOR	POOR

DATA TABLE 26: PICO 11 - STAGE OF TUMOR

Quality	Author	N	Study Notes	Tumor Type	Imaging VS. Reference	Index Cutoff	Sens|Spec	LR+|LR-	Rule In Test	Rule Out Test
Moderate Quality	Zhao,F., 2014	95	FNCLCC criteria for high and low grade	soft tissue sarcomas (high grade 2/3 vs low grade 1)	MRI(magnet unspecified; no contrast) VS. Histology(surgical resection)	Intramuscular or intermuscular	0.7089|0.312	1.03|0.93	POOR	POOR
Moderate Quality	Zhao,F., 2014	95	FNCLCC criteria for high and low grade	soft tissue sarcomas (high grade 2/3 vs low grade 1)	MRI(magnet unspecified; no contrast) VS. Histology(surgical resection)	Size 5.5cm or more	0.7975|0.562	1.82|0.36	POOR	WEAK
Low Quality	Brenner,W., 2004	31		chondrosarcomas (high grade vs low grade)	histopathology(surgical excision) VS. histopathology(surgical excision)	size of 9 cm or more	0.5625|0.466	1.06|0.94	POOR	POOR

DETAILED DATA FINDINGS

FIGURE 5: PICO 11 HSROC META-ANALYSIS - DEEP TUMOR LOCATION ON MRI VS HISTOPATHOLOGY FOR DETERMINING MALIGNANCY OF SOFT TISSUE TUMORS



Meta-analysis of diagnostic accuracy

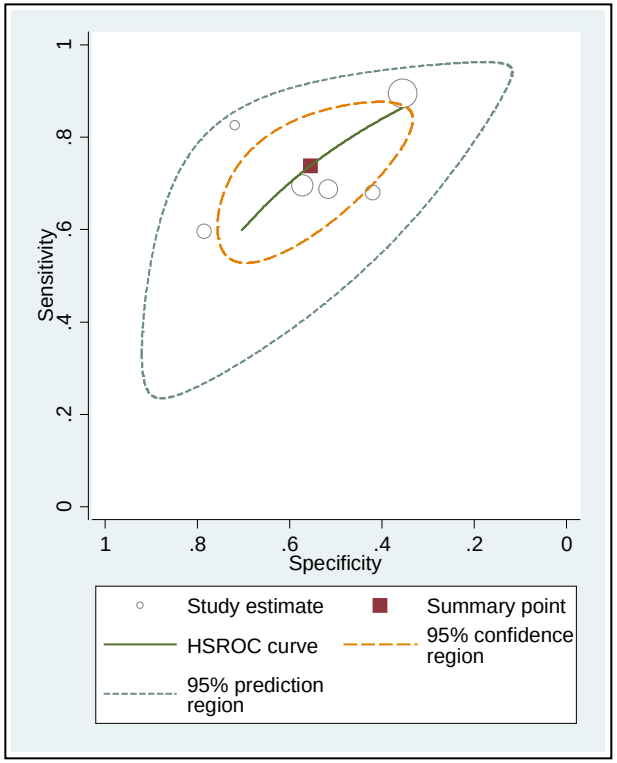
Log likelihood = -36.434438 Number of studies = 6

	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
Bivariate						
E(logitSe)	1.320405	.3047495			.7231074	1.917703
E(logitSp)	-.882363	.5969722			-2.052407	.287681
Var(logitSe)	.4420206	.3693443			.0859397	2.273479
Var(logitSp)	1.897645	1.434431			.4313118	8.349082
Corr(logits)	-1	.			.	.
HSROC						
Lambda	1.287651	.3395511			.6221435	1.953159
Theta	1.256817	.4242792			.4252448	2.088389
beta	.7285063	.2552706	2.85	0.004	.2281852	1.228827
s2alpha	0	.			.	.
s2theta	.9158593	.691233			.2086389	4.020334
Summary pt.						
Se	.7892491	.0506905			.6732909	.8718821
Sp	.2926883	.1235863			.1138094	.5714283
DOR	1.549671	.5311291			.7915919	3.033734
LR+	1.115844	.132916			.8835084	1.409276
LR-	.7200521	.1624963			.4626693	1.120617
1/LR-	1.388788	.313412			.8923658	2.161371

Covariance between estimates of E(logitSe) & E(logitSp) -.1658898

Reference	Quality	Sens | Spec	LR+ | LR-
Harish,S., 2006	High Quality	0.9231|0	0.92|7.69
Liu,L., 2011	High Quality	0.6897|0.4211	1.19|0.74
Rougraff,B.T., 1997	High Quality	0.8889|0.3571	1.38|0.31
Chen,C.K., 2009(c)	Moderate Quality	0.5968|0.7321	2.23|0.55
Chung,W.J., 2012	Moderate Quality	0.7353|0.4268	1.28|0.62
Datir,A., 2008	Moderate Quality	0.8438|0.1624	1.01|0.96

FIGURE 6: PICO 11 HSROC META-ANALYSIS - TUMOR SIZE >5CM ON MRI VS HISTOPATHOLOGY FOR DETERMINING MALIGNANCY OF SOFT TISSUE TUMORS



Meta-analysis of diagnostic accuracy

Log likelihood = -43.698059 Number of studies = 6

	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
Bivariate						
E(logitSe)	1.03861	.2485889			.5513845	1.525835
E(logitSp)	.2205968	.2452671			-.2601179	.7013115
Var(logitSe)	.2931365	.195906			.0791049	1.086266
Var(logitSp)	.2982178	.2212816			.0696515	1.27684
Corr(logits)	-.8095826	.2787487			-.9912084	.429855
HSROC						
Lambda	1.262733	.2790126			.7158782	1.809587
Theta	.4117153	.2490806			-.0764737	.8999044
beta	.0085928	.3719701	0.02	0.982	-.7204552	.7376409
s2alpha	.1126	.171515			.0056881	2.228996
s2theta	.2675163	.1698745			.0770605	.9286853
Summary pt.						
Se	.7385817	.0479972			.6344567	.8213961
Sp	.5549266	.0605768			.4353347	.6684785
DOR	3.522626	.7186147			2.361683	5.254258
LR+	1.659461	.174784			1.349937	2.039954
LR-	.4710863	.0653062			.359004	.6181611
1/LR-	2.122753	.2942751			1.617701	2.785485

Covariance between estimates of E(logitSe) & E(logitSp) -.0401683

Reference	Quality	Sens | Spec	LR+ | LR-
Calleja,M., 2012	Moderate Quality	0.6806|0.4211	1.18|0.76
Chen,C.K., 2009(c)	Moderate Quality	0.5968|0.7857	2.79|0.51
Chung,W.J., 2012	Moderate Quality	0.6961|0.5732	1.63|0.53
Datir,A., 2008	Moderate Quality	0.8958|0.3553	1.39|0.29
Gruber,L., 2016	Moderate Quality	0.6885|0.5166	1.42|0.60
Sen,J., 2010	Moderate Quality	0.8261|0.7188	2.94|0.24

CORTICAL IRREGULARITY/PERIOSTEAL REACTION

Moderate evidence supports the use of an MRI scan (or CT if MRI is not available) for evaluation of cortical irregularity or periosteal reaction in patients with a potentially malignant bone tumor.

Strength of Recommendation: Moderate 

Description: Evidence from two or more "Moderate" quality studies with consistent findings, or evidence from a single "High" quality study for recommending for or against the intervention.

RATIONALE

As aggressive tumors grow inside or adjacent to bone, eventually the bone cortex will be encountered and breached. Cortical destruction suggests an underlying malignancy or active process, and can be suspected on plain radiographs by identifying a clear cortical perforation, erosion of the cortex, or the host response to tumor invasion manifested as a periosteal reaction. When a cortical irregularity or periosteal reaction is noted, often further assessment is required to determine if the radiographic findings are due to a malignancy, benign tumor, or non-neoplastic condition such as a stress fracture.

Two moderate quality studies (Einstien 2015 and Slavotinek 1991) found that plain radiographs, MRI and CT have demonstrated an excellent diagnostic performance in identifying the presence or absence of a periosteal reaction or cortical erosion in patients with malignant bone/soft tissue tumors as compared with the gold standard of histologic diagnosis. A CT scan may or may not provide additional clinical information, depending on the scenario.

There is one high quality investigation (Schima 1994) demonstrating 100% sensitivity and 69% specificity when using MRI to determine whether joint invasion is present.

RISKS AND HARMS OF IMPLEMENTING THIS RECOMMENDATION

Although demonstrating excellent diagnostic performance, there are risks associated with increased radiation exposure (CT) and identification of incidental findings (CT, MRI) in patients who do not require advanced imaging.

FUTURE RESEARCH

Advanced cross-sectional imaging in the evaluation of malignant bone and soft tissue tumors has space for further investigation in the areas of optimizing appropriate utilization and developing protocols to maximize the diagnostic performance of these modalities. Prospective comparative studies evaluating imaging results as compared to histological confirmation within subset populations (e.g. patients presenting cortical irregularity or periosteal reaction on radiograph) could be used to strengthen the recommendations.

RESULTS

STUDY QUALITY TABLE 8: CORTICAL IRREGULARITY/PERIOSTEAL REACTION

Study	Representative Population	Clear Selection Criteria	Detailed Enough to Replicate	Reference Standard Identifies Target Condition	Blinding	Other Bias?	Inclusion	Strength
Bloem,J.L., 1991	●	◑	●	●	●	◑	Include	Moderate Quality
Calleja,M., 2012	●	●	●	●	○	◑	Include	Moderate Quality
Chen,C.K., 2009	●	◑	●	●	●	◑	Include	Moderate Quality
Choi,B.B., 2013	●	◑	●	●	○	◑	Include	Low Quality
Daniel,A.,Jr., 2009	●	●	●	●	◑	◑	Include	Moderate Quality
Dosda,R., 1999	●	●	●	◑	●	●	Include	High Quality
Douis,H., 2014	●	◑	●	●	●	◑	Include	Moderate Quality
Einstien,A., 2015	●	◑	●	●	◑	◑	Include	Moderate Quality
Furuta,T., 2017	●	◑	●	●	◑	◑	Include	Moderate Quality
Haussler,M.D., 1999	●	◑	●	●	◑	◑	Include	Moderate Quality
Henninger,B., 2013	●	●	●	●	●	◑	Include	High Quality
Jiang,M.H., 2016	●	◑	●	●	○	◑	Include	Low Quality
Keller,S., 2017	●	◑	●	●	●	◑	Include	Moderate Quality
Lahat,G., 2009	●	◑	●	●	●	◑	Include	Moderate Quality
Liu,L., 2011	●	●	●	●	●	◑	Include	High Quality
Matsumoto,Y., 2016	●	●	●	●	●	◑	Include	High Quality
McCarville,M.B., 2015	●	◑	●	●	●	◑	Include	Moderate Quality
Mori,T., 2005	●	●	●	●	○	◑	Include	Moderate Quality
Moulton,J.S., 1995	●	●	●	○	●	○	Include	Low Quality

Study	Representative Population	Clear Selection Criteria	Detailed Enough to Replicate	Reference Standard Identifies Target Condition	Blinding	Other Bias?	Inclusion	Strength
Murphey,M.D., 1998	●	◑	●	○	●	○	Include	Low Quality
Oudenhoven,L.F., 2006	●	●	●	●	●	◑	Include	High Quality
Schima,W., 1994	●	●	●	●	●	●	Include	High Quality
Sen,J., 2010	●	●	●	●	◑	◑	Include	Moderate Quality
Slavotinek,J.P., 1991	●	●	●	●	◑	◑	Include	Moderate Quality
Wasa,J., 2010	●	◑	●	●	○	◑	Include	Low Quality
Yildirim,A., 2016	●	◑	●	○	●	◑	Include	Low Quality
Yoo,H.J., 2009	●	●	●	●	●	◑	Include	High Quality
Zhao,F., 2014	●	●	●	●	○	◑	Include	Moderate Quality

SUMMARY OF DATA FINDINGS

SUMMARY TABLE 19: PICO 12 - DIAGNOSING CORTICAL IRREGULARITY OR PERIOSTEAL REACTION VS HISTOPATHOLOGICAL DETERMINATION

DIAGNOSTIC AGREEMENT ON TUMOR CHARACTERISTICS		High		Moderate	
Imaging Method	Diagnostic Threshold	Schima,W., 1994	Dosda,R., 1999***	Einstien,A., 2015	Slavotinek,J.P., 1991
Radiograph(plain)	Cortical breach				61.54 **100**
	Periosteal reaction				**100** **100**
Radiograph(plain; 2 views)	Cortical erosion present			**100** **100**	
	Periosteal reaction			**100** **100**	
MRI(0.5T; no contrast mentioned)	Periosteal reaction		**84.85** 57.1		
	Very dense/dense osteoid matrix		**87.8** 61.54		
CE MRI(0.5T or 1.5T; gadopentetate dimeglumine)	Joint invasion present	**100** 69.44			
MRI(1.5T, no contrast mentioned)	Cortical erosion present			**94.74** **100**	
	Periosteal reaction			**92.86** **100**	
MRI(1T; no contrast mentioned)	Cortical breach				**92.31** **100**
	Periosteal reaction				**88.89** **100**
CT(no contrast mentioned)	Cortical erosion present			**100** **100**	
	Periosteal reaction			**100** **100**	
CT(w or w/o contrast)	Cortical breach				**84.62** **100**
	Periosteal reaction				**88.89** **100**

DATA TABLE 27: PICO 12 - BONE TUMOR DIAGNOSIS

Quality	Author	N	Study Notes	Tumor Type	Imaging VS. Reference	Index Cutoff	Sens|Spec	LR+|LR-	Rule In Test	Rule Out Test
Moderate Quality	Haussler,M.D., 1999	46		malignant bone tumor (osteosarcoma/ ewing sarcoma vs bone lymphoma)	MRI(1.0-1.5T; gadopentetate dimeglumine) VS. Histopathology(biopsy)	abnormal cortex	0.9355|0.4	1.56|0.16	POOR	**MODERATE**
Moderate Quality	Haussler,M.D., 1999	46		malignant bone tumor (osteosarcoma/ ewing sarcoma vs bone lymphoma)	Radiograph(plain) VS. Histopathology(biopsy)	abnormal cortex	0.9032|0.466	1.69|0.21	POOR	WEAK
Moderate Quality	Haussler,M.D., 1999	46		malignant bone tumor (osteosarcoma/ ewing sarcoma vs bone lymphoma)	Radiograph(plain) VS. Histopathology(biopsy)	complete cortical penetration	0.6129|0.866	4.60|0.45	WEAK	WEAK
Moderate Quality	Haussler,M.D., 1999	46		malignant bone tumor (osteosarcoma/ ewing sarcoma vs bone lymphoma)	MRI(1.0-1.5T; gadopentetate dimeglumine) VS. Histopathology(biopsy)	complete cortical penetration	0.7742|0.866	5.81|0.26	**MODERATE**	WEAK
Moderate Quality	Haussler,M.D., 1999	46		malignant bone tumor (osteosarcoma/ ewing sarcoma vs bone lymphoma)	MRI(1.0-1.5T; gadopentetate dimeglumine) VS. Histopathology(biopsy)	complete destruction	0.1613|1	16.13|0.84	**STRONG**	POOR
Moderate Quality	Haussler,M.D., 1999	46		malignant bone tumor (osteosarcoma/ ewing sarcoma vs bone lymphoma)	Radiograph(plain) VS. Histopathology(biopsy)	complete destruction	0.2258|1	22.58|0.77	**STRONG**	POOR

Quality	Author	N	Study Notes	Tumor Type	Imaging VS. Reference	Index Cutoff	Sens|Spec	LR+|LR-	Rule In Test	Rule Out Test
Moderate Quality	Haussler,M.D., 1999	46		malignant bone tumor (osteosarcoma/ ewing sarcoma vs bone lymphoma)	Radiograph(plain) VS. Histopathology(biopsy)	cortical penetration	0.7778|0.3	1.11|0.74	POOR	POOR
Moderate Quality	Haussler,M.D., 1999	46		malignant bone tumor (osteosarcoma/ ewing sarcoma vs bone lymphoma)	MRI(1.0-1.5T; gadopentetate dimeglumine) VS. Histopathology(biopsy)	cortical penetration	0.9355|0.4	1.56|0.16	POOR	**MODERATE**
Moderate Quality	Haussler,M.D., 1999	46		malignant bone tumor (osteosarcoma/ ewing sarcoma vs bone lymphoma)	Radiograph(plain) VS. Histopathology(biopsy)	focal destruction	0.4516|0.933	6.77|0.59	**MODERATE**	POOR
Moderate Quality	Haussler,M.D., 1999	46		malignant bone tumor (osteosarcoma/ ewing sarcoma vs bone lymphoma)	MRI(1.0-1.5T; gadopentetate dimeglumine) VS. Histopathology(biopsy)	focal destruction	0.6129|0.866	4.60|0.45	WEAK	WEAK
Moderate Quality	Haussler,M.D., 1999	46		malignant bone tumor (osteosarcoma/ ewing sarcoma vs bone lymphoma)	MRI(1.0-1.5T; gadopentetate dimeglumine) VS. Histopathology(biopsy)	Periosteal reaction	0.871|0.9333	13.07|0.14	**STRONG**	**MODERATE**

DATA TABLE 28: PICO 12 - BONE/SOFT TISSUE TUMOR DIAGNOSIS

Quality	Author	N	Study Notes	Tumor Type	Imaging VS. Reference	Index Cutoff	Sens|Spec	LR+|LR-	Rule In Test	Rule Out Test
Low Quality	Jiang,M.H., 2016	67	suspected of recurrence (tumor resection with joint replacement)	recurrent bone/soft tissue tumors or tumor-like	MRI(1.5 T; no contrast mentioned) VS. pathology(resection or biopsy)	presence of bone destruction	0.2941|0.98	14.71|0.72	**STRONG**	POOR

DATA TABLE 29: PICO 12 - MALIGNANCY

Quality	Author	N	Study Notes	Tumor Type	Imaging VS. Reference	Index Cutoff	Sens|Spec	LR+|LR-	Rule In Test	Rule Out Test
High Quality	Henninger,B., 2013	28	avg of 2 readers	bone lesion (ewing sarcoma vs osteomyelitis)	MRI(1.5T; gadoterate meglumine or gadobutrol) VS. Histopathology(biopsy ; open or guided)	Cortical involvment	1|0.4	1.67|0.00	POOR	**STRONG**
High Quality	Oudenhoven,L.F., 2006	200		bone tumors (hand)	radiograph VS. histology	presence of cortical destruction or permeation	0.5556|0.861	4.01|0.52	WEAK	POOR
High Quality	Oudenhoven,L.F., 2006	200		bone tumors (hand)	radiograph VS. histology	presence of periosteal reaction	0.2222|0.855	1.54|0.91	POOR	POOR
High Quality	Liu,L., 2011	48	31 patients received IV contrast	soft tissue tumors (lower limbs)	MRI(3T; w/ or w/o gadopentetate dimeglumine) VS. histopathology(biopsy or excision)	Destruction of deep fascia	0.931|1	93.10|0.07	**STRONG**	**STRONG**
High Quality	Matsumoto,Y., 2016	59		spinal dumbbell tumors	CT(no contrast mentioned) VS. histopathology(surgery or biopsy)	presence of bone destruction	0.6|0.9744	23.40|0.41	**STRONG**	WEAK
High Quality	Matsumoto,Y., 2016	59		spinal dumbbell tumors	CT(no contrast mentioned) VS. histopathology(surgery or biopsy)	presence of bone scalloping	0.65|0.2564	0.87|1.37	POOR	POOR
High Quality	Matsumoto,Y., 2016	59		spinal dumbbell tumors	MRI(magnet unspecified; gadolinium) VS. histopathology(surgery or biopsy)	presence of cyst	0.35|0.7949	1.71|0.82	POOR	POOR

Quality	Author	N	Study Notes	Tumor Type	Imaging VS. Reference	Index Cutoff	Sens|Spec	LR+|LR-	Rule In Test	Rule Out Test
Moderate Quality	McCarville,M.B., 2015	54		Ewing Sarcoma vs Osteomyelitis	MRI(magnet and contrast unspecified) VS. Histopathology(biopsy)	Cortical involvment	1|0.2	1.25|0.00	POOR	**STRONG**
Moderate Quality	McCarville,M.B., 2015	60		Ewing Sarcoma vs Osteomyelitis	Radiograph VS. Histopathology(biopsy)	Joint involvement	0.1667|1	16.67|0.83	STRONG	POOR
Moderate Quality	McCarville,M.B., 2015	60		Ewing Sarcoma vs Osteomyelitis	Radiograph VS. Histopathology(biopsy)	Periosteal reaction	0.8333|0.4	1.39|0.42	POOR	WEAK
Moderate Quality	McCarville,M.B., 2015	48		Ewing Sarcoma vs Osteomyelitis	MRI(magnet and contrast unspecified) VS. Histopathology(biopsy)	Permeative cortical involvement	0.8214|0.5	1.64|0.36	POOR	WEAK
Moderate Quality	Bloem,J.L., 1991	68		adamantinoma vs fibrous dysplasia (tibia)	plain radiographs VS. Histopathology(biopsy or surgical resection)	absence of anterior bowing	0.9545|0.239	1.26|0.19	POOR	**MODERATE**
Moderate Quality	Bloem,J.L., 1991	68		adamantinoma vs fibrous dysplasia (tibia)	plain radiographs VS. Histopathology(biopsy or surgical resection)	absence of ground glass appearance	0.8636|0.717	3.06|0.19	WEAK	**MODERATE**
Moderate Quality	Bloem,J.L., 1991	68		adamantinoma vs fibrous dysplasia (tibia)	plain radiographs VS. Histopathology(biopsy or surgical resection)	irregular cortical destruction	0.0455|1	4.55|0.96	WEAK	POOR
Moderate Quality	Bloem,J.L., 1991	68		adamantinoma vs fibrous dysplasia (tibia)	plain radiographs VS. Histopathology(biopsy or surgical resection)	moth-eaten destruction presence	0.0909|1	9.09|0.91	**MODERATE**	POOR
Moderate Quality	Bloem,J.L., 1991	68		adamantinoma vs fibrous dysplasia (tibia)	plain radiographs VS. Histopathology(biopsy or surgical resection)	osteolysis presence	0.8636|0.717	3.06|0.19	WEAK	**MODERATE**

Quality	Author	N	Study Notes	Tumor Type	Imaging VS. Reference	Index Cutoff	Sens|Spec	LR+|LR-	Rule In Test	Rule Out Test
Moderate Quality	Bloem,J.L., 1991	25		adamantinoma vs fibrous dysplasia (tibia)	plain radiographs VS. Histopathology(biopsy or surgical resection)	presence of multilayered periosteal reaction	0.4545|0.928	6.36|0.59	**MODERATE**	POOR
Moderate Quality	Keller,S., 2017	39	atypical requires absence of massive calcification, periosteal reaction, or Codman triangles	atypical osteosarcoma vs. giant cell tumor	CT(w/ or w/o unspecified contrast) VS. histopathology	absence of cortical destruction	0.6316|0.65	1.81|0.57	POOR	POOR
Moderate Quality	Keller,S., 2017	43	atypical requires absence of massive calcification, periosteal reaction, or Codman triangles	atypical osteosarcoma vs. giant cell tumor	plain radiograph VS. histopathology	absence of cortical destruction	0.85|0.3913	1.40|0.38	POOR	WEAK
Moderate Quality	Keller,S., 2017	43	atypical requires absence of massive calcification, periosteal reaction, or Codman triangles	atypical osteosarcoma vs. giant cell tumor	plain radiograph VS. histopathology	absence of osteolysis	0.7|0.9565	16.10|0.31	**STRONG**	WEAK
Moderate Quality	Keller,S., 2017	39	atypical requires absence of massive calcification, periosteal reaction, or Codman triangles	atypical osteosarcoma vs. giant cell tumor	CT(w/ or w/o unspecified contrast) VS. histopathology	absence of osteolysis	0.3684|0.95	7.37|0.67	**MODERATE**	POOR

Quality	Author	N	Study Notes	Tumor Type	Imaging VS. Reference	Index Cutoff	Sens|Spec	LR+|LR-	Rule In Test	Rule Out Test
Moderate Quality	Mori,T., 2005	68		bone/soft tissue lesions	CT(multidetector; nonionic iodine contrast, arterial phase 40-50s and venous phase 90-100s post IV) VS. Histology(surgery or biopsy)	cortical/marrow involvement	1|1	100.00|0.00	**STRONG**	**STRONG**
Moderate Quality	Mori,T., 2005	68		bone/soft tissue lesions	MRI(1T or 1.5T; gadolinium) and plain radiograph VS. Histology(surgery or biopsy)	cortical/marrow involvement	0.4706|0.470	0.89|1.13	POOR	POOR
Moderate Quality	Chen,C.K., 2009(c)	118	4 metastases included; 2 pts without IV contrast	soft tissue tumors	MRI(1.5 T; w/ or w/o gadolinium) VS. Histology	bone involvement	0.3548|0.75	1.42|0.86	POOR	POOR
Moderate Quality	Chen,C.K., 2009(c)	118	4 metastases included; 2 pts without IV contrast	soft tissue tumors	MRI(1.5 T; w/ or w/o gadolinium) VS. Histology	presence of necrosis	0.4516|0.910	5.06|0.60	**MODERATE**	POOR
Moderate Quality	Daniel,A.,Jr., 2009	50		soft tissue tumors	MRI(1.5T; gadolinium) VS. Histopathology	presence of bone changes	0.8333|0.846	5.42|0.20	**MODERATE**	**MODERATE**
Moderate Quality	Daniel,A.,Jr., 2009	50		soft tissue tumors	MRI(1.5T; gadolinium) VS. Histopathology	presence of intratumoral calcification	0.7083|0.884	6.14|0.33	**MODERATE**	WEAK
Moderate Quality	Sen,J., 2010	55		soft tissue tumors	MRI(1.5 T; Gd-DPTA) VS. Histopathology(surgical resection)	bone involvement	0.087|1	8.70|0.91	**MODERATE**	POOR
Moderate Quality	Calleja,M., 2012	135		soft tissue tumors (superficial)	MRI(magnet unspecified; w/ or w/o unspecified contrast) VS. histology(image-guided needle/primary excision biopsy	presence of tumor necrosis	0.2973|0.934	4.53|0.75	WEAK	POOR

Quality	Author	N	Study Notes	Tumor Type	Imaging VS. Reference	Index Cutoff	Sens|Spec	LR+|LR-	Rule In Test	Rule Out Test
Low Quality	Murphey,M.D., 1998	68		chondrosarcoma vs enchondroma	MRI(magnet unspecified, w/wo IV gadolinium based contrast) VS. Pathology (172) or CFU (15 ECs; 5yrs)	cortical destruction	0.7273|0.971	25.46|0.28	**STRONG**	WEAK
Low Quality	Murphey,M.D., 1998	88		chondrosarcoma vs enchondroma	CT(no contrast mentioned) VS. Pathology (172) or CFU (15 ECs; 5yrs)	cortical destruction	0.8776|0.923	11.41|0.13	**STRONG**	**MODERATE**
Low Quality	Murphey,M.D., 1998	187		chondrosarcoma vs enchondroma	radiograph VS. Pathology (172) or CFU (15 ECs; 5yrs)	cortical destruction	0.5684|0.945	10.46|0.46	**STRONG**	WEAK
Low Quality	Murphey,M.D., 1998	68		chondrosarcoma vs enchondroma	MRI(magnet unspecified, w/wo IV gadolinium based contrast) VS. Pathology (172) or CFU (15 ECs; 5yrs)	cortical thickening	0.2727|0.914	3.18|0.80	WEAK	POOR
Low Quality	Murphey,M.D., 1998	88		chondrosarcoma vs enchondroma	CT(no contrast mentioned) VS. Pathology (172) or CFU (15 ECs; 5yrs)	cortical thickening	0.4694|0.897	4.58|0.59	WEAK	POOR
Low Quality	Murphey,M.D., 1998	187		chondrosarcoma vs enchondroma	radiograph VS. Pathology (172) or CFU (15 ECs; 5yrs)	cortical thickening	0.4737|0.826	2.72|0.64	WEAK	POOR
Low Quality	Murphey,M.D., 1998	68		chondrosarcoma vs enchondroma	MRI(magnet unspecified, w/wo IV gadolinium based contrast) VS. Pathology (172) or CFU (15 ECs; 5yrs)	Periosteal reaction	0.1515|0.971	5.30|0.87	**MODERATE**	POOR
Low Quality	Murphey,M.D., 1998	187		chondrosarcoma vs enchondroma	radiograph VS. Pathology (172) or CFU (15 ECs; 5yrs)	Periosteal reaction	0.5053|0.967	15.50|0.51	**STRONG**	POOR

Quality	Author	N	Study Notes	Tumor Type	Imaging VS. Reference	Index Cutoff	Sens|Spec	LR+|LR-	Rule In Test	Rule Out Test
Low Quality	Murphey,M.D., 1998	88		chondrosarcoma vs enchondroma	CT(no contrast mentioned) VS. Pathology (172) or CFU (15 ECs; 5yrs)	Periosteal reaction	0.4694|0.794	2.29|0.67	WEAK	POOR
Low Quality	Choi,B.B., 2013	34		low grade chondrosarcoma vs enchondroma	MRI(1.5T; IV gadopentetate dimeglumine) VS. histopathology	cortical destruction	0.3333|1	33.33|0.67	**STRONG**	POOR
Low Quality	Choi,B.B., 2013	34		low grade chondrosarcoma vs enchondroma	MRI(1.5T; IV gadopentetate dimeglumine) VS. histopathology	Periosteal reaction	0.1111|1	11.11|0.89	**STRONG**	POOR
Low Quality	Wasa,J., 2010	61	gadolinium only in 37 pts	malignant peripheral nerve sheath tumor vs benign neurofibroma	MRI(0.5-1.5 T; gadolinium; T1 & T2) VS. pathology	presence of perilesional edema	0.2927|1	29.27|0.71	**STRONG**	POOR
Low Quality	Wasa,J., 2010	61	gadolinium only in 37 pts	malignant peripheral nerve sheath tumor vs benign neurofibroma	MRI(0.5-1.5 T; gadolinium; T1 & T2) VS. pathology	presence of cystic change	0.3902|0.9	3.90|0.68	WEAK	POOR
Low Quality	Moulton,J.S., 1995	225		soft tissue tumors	MRI(1.5T, no contrast) VS. Histopathology or CFU(41pts; 2yrs)	Bone abnormality	0.1739|0.927	2.40|0.89	WEAK	POOR
Low Quality	Yildirim,A., 2016	35	4 metastases pts	soft tissue tumors	MRI(1.5T; no contrast) VS. histology(32/35 pts) or clinical FU(3/35 pts)	bone involvement	0.3684|1	36.84|0.63	**STRONG**	POOR

DATA TABLE 30: PICO 12 - TUMOR CHARACTERISTICS

Quality	Author	N	Study Notes	Tumor Type	Imaging VS. Reference	Index Cutoff	Sens|Spec	LR+|LR-	Rule In Test	Rule Out Test
High Quality	Schima,W., 1994	46	matching joint involvment numbers among confirmed OS pts	Joint invasion	MRI(0.5T or 1.5T; gadopentetate dimeglumine) VS. pathology(surgical resection)	Joint invasion present	1|0.6944	3.27|0.00	WEAK	**STRONG**
High Quality	Dosda,R., 1999	54	matching imaging results among histo confirmed central osseous osteosarcomas (no histo results presented)	osteoid matrix density	MRI(0.5T; no contrast mentioned) VS. radiograph(plain)	very dense/dense osteoid matrix	0.878|0.6154	2.28|0.20	WEAK	**MODERATE**
High Quality	Dosda,R., 1999	54	matching imaging results among histo confirmed central osseous osteosarcomas (no histo results presented)	periosteal reaction	MRI(0.5T; no contrast mentioned) VS. radiograph(plain)	Periosteal reaction	0.8485|0.571	1.98|0.27	POOR	WEAK
Moderate Quality	Slavotinek,J.P., 1991	27	matching number of characteristics among various b/st tumors	Periosteal reaction	CT(w or w/o contrast) VS. Histopathology(surgery)	Periosteal reaction	0.8889|1	88.89|0.11	**STRONG**	**MODERATE**
Moderate Quality	Slavotinek,J.P., 1991	27	matching number of characteristics among various b/st tumors	Periosteal reaction	plain radiograph VS. Histopathology(surgery)	Periosteal reaction	1|1	100.00|0.00	**STRONG**	**STRONG**
Moderate Quality	Slavotinek,J.P., 1991	27	matching number of characteristics among various b/st tumors	Periosteal reaction	MRI(1T; no contrast mentioned) VS. Histopathology(surgery)	Periosteal reaction	0.8889|1	88.89|0.11	**STRONG**	**MODERATE**

Quality	Author	N	Study Notes	Tumor Type	Imaging VS. Reference	Index Cutoff	Sens|Spec	LR+|LR-	Rule In Test	Rule Out Test
Moderate Quality	Slavotinek,J.P., 1991	27	matching number of characteristics among various b/st tumors	cortical breach	CT(w or w/o contrast) VS. Histopathology(surgery)	cortical breach	0.8462|1	84.62|0.15	**STRONG**	**MODERATE**
Moderate Quality	Slavotinek,J.P., 1991	27	matching number of characteristics among various b/st tumors	cortical breach	MRI(1T; no contrast mentioned) VS. Histopathology(surgery)	cortical breach	0.9231|1	92.31|0.08	**STRONG**	**STRONG**
Moderate Quality	Slavotinek,J.P., 1991	27	matching number of characteristics among various b/st tumors	cortical breach	plain radiograph VS. Histopathology(surgery)	cortical breach	0.6154|1	61.54|0.39	**STRONG**	WEAK
Moderate Quality	Einstien,A., 2015	50	matching number of characteristics among bone tumors (OS, GCT, CS, chondroblastoma, malignant fibrous histiocytoma)	cortical erosion	MRI(1.5T, no contrast mentioned) VS. Histopathology(surgery)	cortical erosion present	0.9474|1	94.74|0.05	**STRONG**	**STRONG**
Moderate Quality	Einstien,A., 2015	50	matching number of characteristics among bone tumors (OS, GCT, CS, chondroblastoma, malignant fibrous histiocytoma)	cortical erosion	Radiograph(plain; 2 views) VS. Histopathology(surgery)	cortical erosion present	1|1	100.00|0.00	**STRONG**	**STRONG**

Quality	Author	N	Study Notes	Tumor Type	Imaging VS. Reference	Index Cutoff	Sens|Spec	LR+|LR-	Rule In Test	Rule Out Test
Moderate Quality	Einstien,A., 2015	50	matching number of characteristics among bone tumors (OS, GCT, CS, chondroblastoma, malignant fibrous histiocytoma)	cortical erosion	CT(no contrast mentioned) VS. Histopathology(surgery)	cortical erosion present	1|1	100.00|0.00	**STRONG**	**STRONG**
Moderate Quality	Einstien,A., 2015	50	matching number of characteristics among bone tumors (OS, GCT, CS, chondroblastoma, malignant fibrous histiocytoma)	periosteal reaction	CT(no contrast mentioned) VS. Histopathology(surgery)	Periosteal reaction	1|1	100.00|0.00	**STRONG**	**STRONG**
Moderate Quality	Einstien,A., 2015	50	matching number of characteristics among bone tumors (OS, GCT, CS, chondroblastoma, malignant fibrous histiocytoma)	periosteal reaction	Radiograph(plain; 2 views) VS. Histopathology(surgery)	Periosteal reaction	1|1	100.00|0.00	**STRONG**	**STRONG**
Moderate Quality	Einstien,A., 2015	50	matching number of characteristics among bone tumors (OS, GCT, CS, chondroblastoma, malignant fibrous histiocytoma)	periosteal reaction	MRI(1.5T, no contrast mentioned) VS. Histopathology(surgery)	Periosteal reaction	0.9286|1	92.86|0.07	**STRONG**	**STRONG**

DATA TABLE 31: PICO 12 - SOFT TISSUE TUMOR DIAGNOSIS

Quality	Author	N	Study Notes	Tumor Type	Imaging VS. Reference	Index Cutoff	Sens|Spec	LR+|LR-	Rule In Test	Rule Out Test
Moderate Quality	Lahat,G., 2009	78		Well differentiated (WD/ALT) vs Dedifferentiated Liposarcoma	CT(omnipaque; 60s post IV) VS. Histopathology(surgical biopsy)	No calcifications	0.8485|0.288	1.19|0.52	POOR	POOR
Moderate Quality	Lahat,G., 2009	78		Well differentiated (WD/ALT) vs Dedifferentiated Liposarcoma	CT(omnipaque; 60s post IV) VS. Histopathology(surgical biopsy)	No cystic/necrotic area	0.4848|0.866	3.64|0.59	WEAK	POOR
Moderate Quality	Furuta,T., 2017	105		hemangioma vs other STT	US(grayscale only) VS. pathology(biopsy or surgery)	intratumoral calcification	0.1875|1	18.75|0.81	**STRONG**	POOR

DATA TABLE 32: PICO 12 - STAGE OF TUMOR

Quality	Author	N	Study Notes	Tumor Type	Imaging VS. Reference	Index Cutoff	Sens|Spec	LR+|LR-	Rule In Test	Rule Out Test
High Quality	Yoo,H.J., 2009	42		chondrosarcoma (high grade vs low grade)	MRI(1.5 T or 1.0 T; gadolinium) VS. pathology(curettage, intralesion or wide excision, or biopsy)	presence of cortical bone destruction with associated soft tissue mass	0.7143|0.964	20.00|0.30	**STRONG**	WEAK
Moderate Quality	Douis,H., 2014	179		high grade chondral lesions (2/3 and dedifferentiated CS) vs low grade chondral lesions (1 and atypical cartilaginous tumors)	MRI(magnet unspecified; no contrast) VS. Histopathology(biopsy, curretage, or resection)	Active periostitis	0.4861|0.990	52.01|0.52	**STRONG**	POOR
Moderate Quality	Douis,H., 2014	179		high grade chondral lesions (2/3 and dedifferentiated CS) vs low grade chondral lesions (1 and atypical cartilaginous tumors)	MRI(magnet unspecified; no contrast) VS. Histopathology(biopsy, curretage, or resection)	Bone Expansion	0.5417|0.915	6.44|0.50	**MODERATE**	POOR

Quality	Author	N	Study Notes	Tumor Type	Imaging VS. Reference	Index Cutoff	Sens|Spec	LR+|LR-	Rule In Test	Rule Out Test
Moderate Quality	Douis,H., 2014	179		high grade chondral lesions (2/3 and dedifferentiated CS) vs low grade chondral lesions (1 and atypical cartilaginous tumors)	MRI(magnet unspecified; no contrast) VS. Histopathology(biopsy, curretage, or resection)	Cortical destruction	0.5556|0.962	14.86|0.46	**STRONG**	WEAK
Moderate Quality	Douis,H., 2014	179		high grade chondral lesions (2/3 and dedifferentiated CS) vs low grade chondral lesions (1 and atypical cartilaginous tumors)	MRI(magnet unspecified; no contrast) VS. Histopathology(biopsy, curretage, or resection)	Cortical thickening	0.2222|1	22.22|0.78	**STRONG**	POOR
Moderate Quality	Zhao,F., 2014	94	FNCLCC criteria for high and low grade	soft tissue sarcomas (high grade 2/3 vs low grade 1)	MRI(magnet unspecified; no contrast) VS. Histology(surgical resection)	Periosteal reaction	0.1646|1	16.46|0.84	**STRONG**	POOR

TUMOR INTERFACE

Moderate evidence suggests that characterizing the tumor interface (borders and zone of transition) on MRI and CT may assist with obtaining a diagnosis or planning further diagnostic studies or treatment for bone or soft tissue tumor of unknown etiology.

Strength of Recommendation: Moderate 

Description: Evidence from two or more "Moderate" quality studies with consistent findings, or evidence from a single "High" quality study for recommending for or against the intervention.

RATIONALE

Seven studies were evaluated regarding the use of various imaging modalities for patients undergoing diagnostic work-up for a bone tumor of unknown etiology. There were 4 studies concerning MRI and 3 concerning combined modalities (MRI and CT, MRI and plain films). There were no articles on PET or Tc99 bone scan. The average number of patients per study was 57 (range=28-101).

Literature pertaining to the use of MRI for differentiating benign and malignant tumors was diagnosis-specific. Choi et al (low quality) evaluated the ability of MRI to differentiate between enchondroma and low-grade chondrosarcoma in 34 patients. They concluded that, "MR imaging shows helpful features for differentiating low-grade chondrosarcoma from enchondroma." De Beuckeleer et al (moderate quality) retrospectively reviewed 79 cartilaginous tumors. These included osteochondromas, enchondromas, low-grade chondrosarcomas, and high-grade chondrosarcomas. They concluded that MR features are highly specific but lack sensitivity. Yoo et al (high quality) retrospectively reviewed 42 chondrosarcomas: 28 low-grade and 14 high-grade. They determined that soft tissue mass formation favored high-grade lesions, and intratumoral fat was suggestive of low-grade lesions. Bernard et al (moderate quality) retrospectively compared cartilage cap thickness using CT and MRI to distinguish between osteochondromas and secondary chondrosarcomas; both studies were highly sensitive and specific.

Henninger et al identified 28 patients in whom the diagnoses of osteomyelitis and Ewing sarcoma were both considered. They concluded that STIR MRI sequences most reliably distinguishes between osteomyelitis and Ewing sarcoma. McCarville et al evaluated the use of MRI and CT to distinguish between osteomyelitis and Ewing sarcoma. They were unable to give imaging-based recommendations for diagnosis. Oudenhoven et al (high quality) evaluated the value of MRI in diagnosing bone tumors of the hand. MRI was found to confirm or enhance the diagnostic accuracy of plain radiographs.

In conclusion, cross-sectional imaging of some kind (either CT or MR) is helpful in obtaining a diagnosis or planning further diagnostic studies or treatment for bone or soft tissue tumor of unknown etiology with radiographs that show a poorly defined interface with the tumor (e.g. permeative border or wide zone of transition). MRI can greatly enhance the diagnostic accuracy of plain radiographs in bony lesions of the hand. CT of the chest/abdomen/pelvis remains an essential aspect of tumor staging. This will reveal the primary site of metastatic bone tumors in many cases, as well determine the presence or absence of pulmonary metastatic disease in patients with sarcoma.

RISKS AND HARMS OF IMPLEMENTING THIS RECOMMENDATION

There is a radiation dose associated with CT of the site, CT chest/abdomen/pelvis, Tc 99m bone scans, or PET/CT scans but it is acceptable given the importance of these imaging modalities to the overall care of the patient.

FUTURE RESEARCH

Larger prospective studies are needed investigating the utility of, nuclear scintigraphy (bone scans), or PET/CT scans to assist with patients who are being evaluated for a bone tumor of unknown etiology with radiographs that show a poorly defined interface with the tumor (e.g. permeative border or wide zone of transition), to assist with obtaining a diagnosis and/or planning further diagnostic studies and/or treatment options.

As MRI techniques improve and as molecular-guided contrast agents become available, there will be renewed need to study the accuracy of imaging studies as stand-alone diagnostic tests.

RESULTS

STUDY QUALITY TABLE 9: TUMOR INTERFACE

Study	Representative Population	Clear Selection Criteria	Detailed Enough to Replicate	Reference Standard Identifies Target Condition	Blinding	Other Bias?	Inclusion	Strength
Belli,P., 2000	●	●	●	●	◑	◑	Include	Moderate Quality
Bernard,S.A., 2010	●	◑	●	●	●	◑	Include	Moderate Quality
Berquist,T.H., 1990	●	●	●	○	●	◑	Include	Moderate Quality
Bloem,J.L., 1991	●	◑	●	●	●	◑	Include	Moderate Quality
Calleja,M., 2012	●	●	●	●	○	◑	Include	Moderate Quality
Chen,C.K., 2009	●	◑	●	●	●	◑	Include	Moderate Quality
Chen,T., 2015	●	●	●	●	●	◑	Include	High Quality
Choi,B.B., 2013	●	◑	●	●	○	◑	Include	Low Quality
Crombe,A., 2016	●	●	●	●	●	●	Include	High Quality
Daniel,A.,Jr., 2009	●	●	●	●	◑	◑	Include	Moderate Quality
De Beuckeleer,L.H., 1995	●	◑	●	●	●	◑	Include	Moderate Quality
Furuta,T., 2017	●	◑	●	●	◑	◑	Include	Moderate Quality
Harish,S., 2006	●	●	●	●	●	◑	Include	High Quality
Henninger,B., 2013	●	●	●	●	●	◑	Include	High Quality
Jee,W.H., 2004	●	◑	●	●	●	◑	Include	Moderate Quality
Keller,S., 2017	●	◑	●	●	●	◑	Include	Moderate Quality

Study	Representative Population	Clear Selection Criteria	Detailed Enough to Replicate	Reference Standard Identifies Target Condition	Blinding	Other Bias?	Inclusion	Strength
Kransdorf,M.J., 1989	●	◑	●	○	●	◑	Include	Low Quality
Lagalla,R., 1998	●	●	●	●	◑	◑	Include	Moderate Quality
Lange,T.A., 1987	●	◑	●	●	◑	○	Include	Low Quality
Lahat,G., 2009	●	◑	●	●	●	◑	Include	Moderate Quality
Matsumoto,Y., 2016	●	●	●	●	●	◑	Include	High Quality
McCarville,M.B., 2015	●	◑	●	●	●	◑	Include	Moderate Quality
Moulton,J.S., 1995	●	●	●	○	●	○	Include	Low Quality
Oebisu,N., 2014	●	●	●	●	◑	◑	Include	Moderate Quality
Ohguri,T., 2003	●	◑	●	●	●	◑	Include	Moderate Quality
Oudenhoven,L.F., 2006	●	●	●	●	●	◑	Include	High Quality
Pang,K.K., 2003	●	◑	●	●	●	◑	Include	Moderate Quality
Sen,J., 2010	●	●	●	●	◑	◑	Include	Moderate Quality
Teo,E.L., 2000	●	◑	●	○	●	◑	Include	Low Quality
Wasa,J., 2010	●	◑	●	●	○	◑	Include	Low Quality
Yildirim,A., 2016	●	◑	●	○	●	◑	Include	Low Quality
Yoo,H.J., 2009	●	●	●	●	●	◑	Include	High Quality
Zhang,Z., 2015	●	●	●	●	●	◑	Include	High Quality
Zhao,F., 2014	●	●	●	●	○	◑	Include	Moderate Quality

SUMMARY OF DATA FINDINGS

DATA TABLE 33: PICO 13 - MALIGNANCY

Quality	Author	N	Study Notes	Tumor Type	Imaging VS. Reference	Index Cutoff	Sens|Spec	LR+|LR-	Rule In Test	Rule Out Test
High Quality	Zhang,Z., 2015	40	large tumors (5-11cm)	Malignant soft tissue tumors vs Schwannoma	MRI(1.5T and 3T; gadolinium) VS. Histology	Bright rim sign absent	0.96|0.7333	3.60|0.06	WEAK	**STRONG**
High Quality	Zhang,Z., 2015	40	large tumors (5-11cm)	Malignant soft tissue tumors vs Schwannoma	MRI(1.5T and 3T; gadolinium) VS. Histology	Lobular shape present	0.84|0.8667	6.30|0.19	**MODERATE**	**MODERATE**
High Quality	Henninger,B., 2013	28	avg of 2 readers	bone lesion (ewing sarcoma vs osteomyelitis)	MRI(1.5T; gadoterate meglumine or gadobutrol) VS. Histopathology(biopsy ; open or guided)	Deep margins or sharp transition zone	1|1	100.00|0.00	**STRONG**	**STRONG**
High Quality	Oudenhoven,L.F ., 2006	200		bone tumors (hand)	radiograph VS. histology	ill-defined margins	0.4828|0.853	3.30|0.61	WEAK	POOR
High Quality	Crombe,A., 2016	95		peripheral soft tissue tumors with myxoid stroma	MRI(1.5T; gadolinium) VS. histopathology(surgery)	ill-defined margins, intra-tumoral fat, hemorrhagic component, fibrosis, or tail sign	0.9275|0.923	12.06|0.08	**STRONG**	**STRONG**
High Quality	Crombe,A., 2016	95		peripheral soft tissue tumors with myxoid stroma	MRI(1.5T; gadolinium) VS. histopathology(surgery)	infiltrative or poorly-defined margins	0.3768|1	37.68|0.62	**STRONG**	POOR
High Quality	Chen,T., 2015	66		soft tissue tumors	US(3D automated breast volume scanner) VS. Pathological diagnosis	absence of hyperechoic rim	0.3725|0.2	0.47|3.14	POOR	POOR

Quality	Author	N	Study Notes	Tumor Type	Imaging VS. Reference	Index Cutoff	Sens|Spec	LR+|LR-	Rule In Test	Rule Out Test
High Quality	Harish,S., 2006	40	gadolinium contrast used in only 13 pts	soft tissue tumors	MRI(magnet unspecified; w/ or w/o gadolinium) VS. Histopathology	ill-defined margins	0.0769|0.888	0.69|1.04	POOR	POOR
High Quality	Harish,S., 2006	40	gadolinium contrast used in only 13 pts	soft tissue tumors	MRI(magnet unspecified; w/ or w/o gadolinium) VS. Histopathology	presence of lobulation	0.7692|0.407	1.30|0.57	POOR	POOR
High Quality	Matsumoto,Y., 2016	59		spinal dumbbell tumors	MRI(magnet unspecified; gadolinium) VS. histopathology(surgery or biopsy)	indistinguishable tumor boundary	0.85|0.9487	16.58|0.16	**STRONG**	**MODERATE**
High Quality	Matsumoto,Y., 2016	59		spinal dumbbell tumors	MRI(magnet unspecified; gadolinium) VS. histopathology(surgery or biopsy)	presence of irregular lobulated shape	0.85|0.6667	2.55|0.23	WEAK	WEAK
Moderate Quality	McCarville,M.B., 2015	60		Ewing Sarcoma vs Osteomyelitis	Radiograph VS. Histopathology(biopsy)	Wide zone of transition	0.9333|0.2	1.17|0.33	POOR	WEAK
Moderate Quality	McCarville,M.B., 2015	48		Ewing Sarcoma vs Osteomyelitis	MRI(magnet and contrast unspecified) VS. Histopathology(biopsy)	Permeative cortical involvement	0.8214|0.5	1.64|0.36	POOR	WEAK
Moderate Quality	Bloem,J.L., 1991	68		adamantinoma vs fibrous dysplasia (tibia)	plain radiographs VS. Histopathology(biopsy or surgical resection)	absence of smooth margins	0.5909|0.478	1.13|0.86	POOR	POOR
Moderate Quality	Bloem,J.L., 1991	68		adamantinoma vs fibrous dysplasia (tibia)	plain radiographs VS. Histopathology(biopsy or surgical resection)	lobular margins presence	0.5909|0.478	1.13|0.86	POOR	POOR

Quality	Author	N	Study Notes	Tumor Type	Imaging VS. Reference	Index Cutoff	Sens|Spec	LR+|LR-	Rule In Test	Rule Out Test
Moderate Quality	Keller,S., 2017	43	atypical requires absence of massive calcification, periosteal reaction, or Codman triangles	atypical osteosarcoma vs. giant cell tumor	plain radiograph VS. histopathology	absence of sclerotic margins	0.9|0.3913	1.48|0.26	POOR	WEAK
Moderate Quality	Keller,S., 2017	43	atypical requires absence of massive calcification, periosteal reaction, or Codman triangles	atypical osteosarcoma vs. giant cell tumor	plain radiograph VS. histopathology	absence of septation	0.95|0.5217	1.99|0.10	POOR	**STRONG**
Moderate Quality	Bernard,S.A., 2010	101		bone/soft tissue tumors (secondary chondrosarcomas vs osteochondromas)	CT(no contrast mentioned) VS. pathology	cartilage cap thickness of 2 cm or more	1|0.9552	22.33|0.00	**STRONG**	**STRONG**
Moderate Quality	Bernard,S.A., 2010	101		bone/soft tissue tumors (secondary chondrosarcomas vs osteochondromas)	MRI(magnet unspecified; w/ or w/o gadolinium) VS. pathology	cartilage cap thickness of 2 cm or more	1|0.9851	67.00|0.00	**STRONG**	**STRONG**
Moderate Quality	De Beuckeleer,L.H., 1995	79	varying MRI magnets and contrast used in 57/79	cartilage tumors	MRI(0.2T, 0.5T, 1.0T, or 1.5T; w/ or w/o gadolinium) VS. Histology(biopsy)	lobular morphology	0.5217|0.732	1.95|0.65	POOR	POOR
Moderate Quality	De Beuckeleer,L.H., 1995	79	varying MRI magnets and contrast used in 57/79	cartilage tumors	MRI(0.2T, 0.5T, 1.0T, or 1.5T; w/ or w/o gadolinium) VS. Histology(biopsy)	presence of septal enhancement (ring-and-arc)	0.6957|0.857	4.87|0.36	WEAK	WEAK

Quality	Author	N	Study Notes	Tumor Type	Imaging VS. Reference	Index Cutoff	Sens|Spec	LR+|LR-	Rule In Test	Rule Out Test
Moderate Quality	Lagalla,R., 1998	46		periskeletal soft tissue tumors	US VS. histology(percutaneous biopsy or surgery)	blurred/irregular margins	0.55|0.5385	1.19|0.84	POOR	POOR
Moderate Quality	Lagalla,R., 1998	46		periskeletal soft tissue tumors	US VS. histology(percutaneous biopsy or surgery)	presence of irregular margins and heterogeneous textural pattern	0.75|0.5	1.50|0.50	POOR	POOR
Moderate Quality	Oebisu,N., 2014	180		soft tissue masses	US(gray scale) VS. pathology(surgical resection or biopsy)	ill defined margins	0.3226|0.898	3.17|0.75	WEAK	POOR
Moderate Quality	Oebisu,N., 2014	180		soft tissue masses	US(gray scale) VS. pathology(surgical resection or biopsy)	Lobular shape present	0.2258|0.720	0.81|1.08	POOR	POOR
Moderate Quality	Berquist,T.H., 1990	95		soft tissue tumors	MRI(0.15T or 1.5T; no contrast mentioned) VS. Histopathology(surgery) or clinical follow-up(n=9)	partially/completely irregular margins	0.8444|0.44	1.51|0.35	POOR	WEAK
Moderate Quality	Chen,C.K., 2009(c)	118	4 metastases included; 2 pts without IV contrast	soft tissue tumors	MRI(1.5 T; w/ or w/o gadolinium) VS. Histology	ill-defined margins	0.7742|0.446	1.40|0.51	POOR	POOR
Moderate Quality	Chen,C.K., 2009(c)	118	4 metastases included; 2 pts without IV contrast	soft tissue tumors	MRI(1.5 T; w/ or w/o gadolinium) VS. Histology	presence of fat rim sign	0.0484|0.785	0.23|1.21	POOR	POOR
Moderate Quality	Daniel,A.,Jr., 2009	50		soft tissue tumors	MRI(1.5T; gadolinium) VS. Histopathology	irregular/infiltrative margins	0.9167|0.653	2.65|0.13	WEAK	**MODERATE**
Moderate Quality	Daniel,A.,Jr., 2009	50		soft tissue tumors	MRI(1.5T; gadolinium) VS. Histopathology	irregular/lobulated shape	0.8333|0.769	3.61|0.22	WEAK	WEAK

Quality	Author	N	Study Notes	Tumor Type	Imaging VS. Reference	Index Cutoff	Sens|Spec	LR+|LR-	Rule In Test	Rule Out Test
Moderate Quality	Sen,J., 2010	55		soft tissue tumors	MRI(1.5 T; Gd-DPTA) VS. Histopathology(surgical resection)	ill-defined or partially defined margins	0.7391|0.812	3.94|0.32	WEAK	WEAK
Moderate Quality	Calleja,M., 2012	132		soft tissue tumors (superficial)	MRI(magnet unspecified; w/ or w/o unspecified contrast) VS. histology(image-guided needle/primary excision biopsy	ill-defined margins	0.3889|0.466	0.73|1.31	POOR	POOR
Moderate Quality	Calleja,M., 2012	135		soft tissue tumors (superficial)	MRI(magnet unspecified; w/ or w/o unspecified contrast) VS. histology(image-guided needle/primary excision biopsy	presence of lobulation	0.8919|0.327	1.33|0.33	POOR	WEAK
Moderate Quality	Pang,K.K., 2003	30		soft tissue tumors and tumor-like conditions	MRI(0.5 T; no contrast mentioned; T2w only) VS. pathology	partially or poorly defined border	0.5625|0.857	3.94|0.51	WEAK	POOR
Moderate Quality	Pang,K.K., 2003	30		soft tissue tumors and tumor-like conditions	MRI(0.5 T; no contrast mentioned; T1w only) VS. pathology	partially or poorly defined border	0.5625|0.785	2.63|0.56	WEAK	POOR
Moderate Quality	Belli,P., 2000	56		soft tissue tumors(limbs)	US VS. Histology(biopsy or surgery)	blurred margins	0.45|0.7778	2.03|0.71	WEAK	POOR
Moderate Quality	Ohguri,T., 2003	58	tumor counts	well-differentiated liposarcoma vs lipoma	MRI(1.5T; gadopentetate dimeglumine) VS. histopathology(surgical resection)	partially/completely irregular margins	0.1304|0.857	0.91|1.01	POOR	POOR
Low Quality	Teo,E.L., 2000	44		ST masses vs hemangiomas	MRI(1.5T; w/wo gadolinium) VS. Histology, angiography, or CFU(6pts; no time given)	lobulation absent	0.772727273|	17.00|0.24	**STRONG**	WEAK

Quality	Author	N	Study Notes	Tumor Type	Imaging VS. Reference	Index Cutoff	Sens|Spec	LR+|LR-	Rule In Test	Rule Out Test
Low Quality	Teo,E.L., 2000	44		ST masses vs hemangiomas	MRI(1.5T; w/wo gadolinium) VS. Histology, angiography, or CFU(6pts; no time given)	septation absent	0.318181818|	31.82|0.68	**STRONG**	POOR
Low Quality	Teo,E.L., 2000	44		ST masses vs hemangiomas	MRI(1.5T; w/wo gadolinium) VS. Histology, angiography, or CFU(6pts; no time given)	Absent lobulation, septation, and cental low SI dots	1|0.90909090	11.00|0.00	**STRONG**	**STRONG**
Low Quality	Lange,T.A., 1987	50		Soft tissue masses	US(no doppler) VS. Histopathology(surgical or biopsy)	Discrete (well defined)	1|0.4167	1.71|0.00	POOR	**STRONG**
Low Quality	Choi,B.B., 2013	34		low grade chondrosarcoma vs enchondroma	MRI(1.5T; IV gadopentetate dimeglumine) VS. histopathology	Ill defined margins	0.1111|1	11.11|0.89	**STRONG**	POOR
Low Quality	Choi,B.B., 2013	34		low grade chondrosarcoma vs enchondroma	MRI(1.5T; IV gadopentetate dimeglumine) VS. histopathology	lobular contour	0.9444|0.187	1.16|0.30	POOR	WEAK
Low Quality	Wasa,J., 2010	61	gadolinium only in 37 pts	malignant peripheral nerve sheath tumor vs benign neurofibroma	MRI(0.5-1.5 T; gadolinium; T1 & T2) VS. pathology	well-defined margins	0.7561|0.15	0.89|1.63	POOR	POOR
Low Quality	Kransdorf,M.J., 1989	112	xray, CT, arteriogram, or CFU in 16 cases	soft tissue tumors	MRI(0.5 or 1.5 T; T1w only; no contrast mentioned) VS. pathology(biopsy) or CFU(16pts; time not given)	ill-defined margins	0.4444|0.529	0.94|1.05	POOR	POOR

Quality	Author	N	Study Notes	Tumor Type	Imaging VS. Reference	Index Cutoff	Sens|Spec	LR+|LR-	Rule In Test	Rule Out Test
Low Quality	Kransdorf,M.J., 1989	112	xray, CT, arteriogram, or CFU in 16 cases	soft tissue tumors	MRI(0.5 or 1.5 T; T2w only; no contrast mentioned) VS. pathology(biopsy) or CFU(16pts; time not given)	ill-defined margins	0.3704|0.564	0.85|1.12	POOR	POOR
Low Quality	Moulton,J.S., 1995	225		soft tissue tumors	MRI(1.5T, no contrast) VS. Histopathology or CFU(41pts; 2yrs)	Poorly defined margins	0.5652|0.743	2.20|0.59	WEAK	POOR
Low Quality	Yildirim,A., 2016	35	4 metastases pts	soft tissue tumors	MRI(1.5T; no contrast) VS. histology(32/35 pts) or clinical FU(3/35 pts)	infiltrating, ill, or partially defined margins	0.7895|0.5	1.58|0.42	POOR	WEAK

DATA TABLE 34: PICO 13 - SOFT TISSUE TUMOR DIAGNOSIS

Quality	Author	N	Study Notes	Tumor Type	Imaging VS. Reference	Index Cutoff	Sens|Spec	LR+|LR-	Rule In Test	Rule Out Test
Moderate Quality	Lahat,G., 2009	78		Well differentiated (WD/ALT) vs Dedifferentiated Liposarcoma	CT(omnipaque; 60s post IV) VS. Histopathology(surgical biopsy)	Regular margins	0.9091|0.244	1.20|0.37	POOR	WEAK
Moderate Quality	Jee,W.H., 2004	52	5 pts no contrast	extra-axial neurofibroma vs neurilemmoma	MRI(1.0 or 1.5 T; w/ or w/o gadopentetate dimeglumine; T2 only) VS. pathology	absence of fascicular appearance(small ringlike structures with peripheral higher signal intensity)	0.75|0.625	2.00|0.40	POOR	WEAK
Moderate Quality	Jee,W.H., 2004	52	5 pts no contrast	extra-axial neurofibroma vs neurilemmoma	MRI(1.0 or 1.5 T; w/ or w/o gadopentetate dimeglumine; T2 only) VS. pathology	absence of thin hyperintense rim	0.9167|0.575	2.16|0.15	WEAK	**MODERATE**
Moderate Quality	Jee,W.H., 2004	52	5 pts no contrast	extra-axial neurofibroma vs neurilemmoma	MRI(1.0 or 1.5 T; w/ or w/o gadopentetate dimeglumine; T2 only) VS. pathology	fusiform shape	0.6667|0.275	0.92|1.21	POOR	POOR
Moderate Quality	Furuta,T., 2017	105		hemangioma vs other STT	US(grayscale only) VS. pathology(biopsy or surgery)	irregular margins	1|0.1573	1.19|0.00	POOR	**STRONG**
Moderate Quality	Furuta,T., 2017	105		hemangioma vs other STT	US(grayscale only) VS. pathology(biopsy or surgery)	presence of bright echogenic margins	1|0.3933	1.65|0.00	POOR	**STRONG**

DATA TABLE 35: PICO 13 - STAGE OF TUMOR

Quality	Author	N	Study Notes	Tumor Type	Imaging VS. Reference	Index Cutoff	Sens|Spec	LR+|LR-	Rule In Test	Rule Out Test
High Quality	Yoo,H.J., 2009	42		chondrosarcoma (high grade vs low grade)	MRI(1.5 T or 1.0 T; gadolinium) VS. pathology(curettage, intralesion or wide excision, or biopsy)	tumor without internal lobular structure	0.7143|0.857	5.00|0.33	**MODERATE**	WEAK
High Quality	Yoo,H.J., 2009	42		chondrosarcoma (high grade vs low grade)	MRI(1.5 T or 1.0 T; gadolinium) VS. pathology(curettage, intralesion or wide excision, or biopsy)	tumor without outer lobular margin	0.2857|0.964	8.00|0.74	**MODERATE**	POOR
Moderate Quality	Zhao,F., 2014	82	given contrast; FNCLCC criteria for high and low grade	soft tissue sarcomas (high grade 2/3 vs low grade 1)	MRI(contrast unspecified; magnet unspecified; T1w only) VS. Histology(surgical resection)	Ill defined margins	0.7353|0.857	5.15|0.31	**MODERATE**	WEAK
Moderate Quality	Zhao,F., 2014	95	FNCLCC criteria for high and low grade	soft tissue sarcomas (high grade 2/3 vs low grade 1)	MRI(magnet unspecified; no contrast, T1w only) VS. Histology(surgical resection)	Ill defined margins	0.7215|0.687	2.31|0.41	WEAK	WEAK
Moderate Quality	Zhao,F., 2014	94	FNCLCC criteria for high and low grade	soft tissue sarcomas (high grade 2/3 vs low grade 1)	MRI(magnet unspecified; no contrast, T2w only) VS. Histology(surgical resection)	Ill defined margins	0.7595|0.733	2.85|0.33	WEAK	WEAK

V. **APPENDIXES**

APPENDIX I. GUIDELINE DEVELOPMENT GROUP ROSTER

1. Benjamin J. Miller, MD
   Musculoskeletal Tumor Society
2. Kenneth R. Gundle, MD
   American Academy of Orthopaedic Surgeons
3. Carlos M. Pereira Betancourt, MD
   American Academy of Orthopaedic Surgeons
4. Ahmet Salduz, MD
   American Academy of Orthopaedic Surgeons
5. Ana Cecilia Belzarena Genovese, MD
   American Academy of Orthopaedic Surgeons
6. Mark D. Murphey, MD
   American College of Radiology
7. Michael Mulligan, MD
   Musculoskeletal Tumor Society
8. Kurt R. Weiss, MD
   Musculoskeletal Tumor Society
9. Lukas M. Nystrom, MD
   Musculoskeletal Tumor Society
10. Matthew R DiCaprio, MD
    Musculoskeletal Tumor Society
11. Eric R. Henderson, MD
    Musculoskeletal Tumor Society
12. Catherine C. Roberts, MD
    American College of Radiology

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   AAOS Senior Manager, Quality and Value Unit
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   AAOS Lead Research Analyst, Quality and Value Unit
3. Anne Woznica, MLIS, AHIP
   AAOS Medical Librarian
4. Mary DeMars
   AAOS Administrative Assistant, Quality and Value Unit

APPENDIX II

MSTS BODIES THAT APPROVED THIS SYSTEMATIC LITERATURE REVIEW

Committee on Evidence-Based Medicine

Vision: The EBM will help the MSTS accomplish its vision as a recognized authority on all aspects of orthopaedic oncology, an influential participant in policy-making for orthopaedic oncology services, and responsive to the needs of orthopaedic oncologists and their patients.

Term: The EBM is an ad hoc committee that will be composed of a chair and four members, each serving a term of three years on a staggered basis. In 2015-2016 the chair and two members will serve a three-year term and two will serve a two year term.

Committee Responsibilities:

1. Use Evidence Based Medicine to develop and periodically update MSTS Position Statements

2. Develop systematic literature reviews on musculoskeletal oncology topics

3. Develop Appropriate Use Criteria on musculoskeletal oncology topics

4. Undertake quality improvement initiatives

5. Write systematic reviews

Executive Committee

Purpose: Along with the other members of the Executive Committee, the Members-at-Large oversee the activities of the Society and ensure the Society is a healthy and viable member organization.

Term of Office: The Members-at-Large serve a two (2) year term to begin and expire at the close of the Society's Annual Meeting. The terms will be staggered.

Qualifications: The Members-at-Large must be an Active or Associate MSTS member-in-good standing. One member must be under the age of 40 at the time of the election, one position does not have an age restriction.

Specific Responsibilities: • Provide leadership, governance and oversight. • Develop, implement, and evaluate the Society's strategic plan. • Approve the Society's annual budget, audit reports, and material business decisions. • Ensure the availability of adequate financial resources • Be informed of, and meet all, legal and fiduciary responsibilities. • Serve on the Society's Nominating Committee • Assist in identifying and recruiting future volunteers. • Ensure Society policies are carried out; modify as needed. • Serve on committees and/or project teams; take on special assignments as requested. • Act as an ambassador for the Society. • Review agendas and supporting materials prior to meetings; participate in meetings.

APPENDIX III
PICO QUESTIONS
PICO 1: ACCURACY OF PLAIN RADIOGRAPHS IN DIAGNOSING BONE OR SOFT TISSUE TUMOR

Section # or Stage of Care	Diagnosis; Note: Also want to correlate effectiveness of radiographs to a reduction in advanced imaging depending on results
Assigned To:	

Question Components	**Constructing Your Question**
P – Patient or Population Describe the most important characteristics of the patient. (e.g., age, disease / condition, gender)	Patients being evaluated for bone or soft tissue tumor of unknown etiology
I – Intervention; Prognostic Factor; Exposure Describe the main intervention. (e.g., drug or other treatment, diagnostic / screening test)	Plain Radiographs
C – Comparison (if appropriate) Describe the main alternative being considered. (e.g., placebo, standard therapy, no treatment, the gold standard)	No imaging, exam only
O – Outcome Describe what you're trying to accomplish measure, improve, affect. (e.g., reduced mortality or morbidity, improved memory, accurate and timely diagnosis)	Accurate diagnosis of bone or soft tissue tumor: *1) Clearly benign or non-neoplastic, 2) Unclear if benign or malignant, 3) Clearly malignant but unlikely a primary sarcoma, 4) Clearly malignant and concerning for a primary sarcoma*
The PICO Clinical Question: In patients who are being evaluated for a bone or soft tissue tumor of unknown etiology, do plain radiographs of the tumor site assist with obtaining a diagnosis or planning further treatment?	

PICO 2: IV CONTRAST IN MRI OR CT SCANS

Section # or Stage of Care	Diagnosis
Assigned To:	

Question Components	**Constructing Your Question**
P – Patient or Population Describe the most important characteristics of the patient. (e.g., age, disease / condition, gender)	patients who are being evaluated for a bone or soft tissue tumor of unknown etiology
I – Intervention; Prognostic Factor; Exposure Describe the main intervention. (e.g., drug or other treatment, diagnostic / screening test)	IV contrast in MRI or CT scans of the primary site
C – Comparison (if appropriate) Describe the main alternative being considered. (e.g., placebo, standard therapy, no treatment, the gold standard)	No IV contrast in MRI or CT scans of the primary site
O – Outcome Describe what you're trying to accomplish measure, improve, affect. (e.g., reduced mortality or morbidity, improved memory, accurate and timely diagnosis)	diagnosis of tumor: all information critical to ideal management of the condition (histology, location, stage, size, bone involvement, etc)
The PICO Clinical Question: In patients who are being evaluated for a bone or soft tissue tumor of unknown etiology, does the use of IV contrast in MRI or CT scans of the primary site assist with obtaining a diagnosis or planning further treatment? Qualitative Definition of Diagnosis: "all information critical to ideal management of the condition (histology, location, stage, size, bone involvement, etc.)"	

PICO 3: MRI MAGNET STRENGTH

Section # or Stage of Care	Diagnosis
Assigned To:	

Question Components	**Constructing Your Question**
P – Patient or Population Describe the most important characteristics of the patient. (e.g., age, disease / condition, gender)	patients who are being evaluated for a bone or soft tissue tumor of unknown etiology
I – Intervention; Prognostic Factor; Exposure Describe the main intervention. (e.g., drug or other treatment, diagnostic / screening test)	MRI magnet strength
C – Comparison (if appropriate) Describe the main alternative being considered. (e.g., placebo, standard therapy, no treatment, the gold standard)	Versus various MRI magnet strengths
O – Outcome Describe what you're trying to accomplish measure, improve, affect. (e.g., reduced mortality or morbidity, improved memory, accurate and timely diagnosis)	Accurate diagnosis (does one range of MRI magnet strength provide a more accurate diagnosis?)
The PICO Clinical Question: In patients who are being evaluated for a bone or soft tissue tumor of unknown etiology, do MRI scans need to have a minimum magnet strength to assist with obtaining a diagnosis or planning further treatment?	

PICO 4: MRI/CT VISUALIZATION

Section # or Stage of Care	Diagnosis
Assigned To:	

Question Components	**Constructing Your Question**
P – Patient or Population Describe the most important characteristics of the patient. (e.g., age, disease / condition, gender)	patients who are being evaluated for a bone or soft tissue tumor of unknown etiology
I – Intervention; Prognostic Factor; Exposure Describe the main intervention. (e.g., drug or other treatment, diagnostic / screening test)	Visualization of entire muscle or bone compartment via MRI and/or CT Scan
C – Comparison (if appropriate) Describe the main alternative being considered. (e.g., placebo, standard therapy, no treatment, the gold standard)	Visualization of the tumor extent only
O – Outcome Describe what you're trying to accomplish measure, improve, affect. (e.g., reduced mortality or morbidity, improved memory, accurate and timely diagnosis)	Accurate diagnosis
The PICO Clinical Question: In patients who are being evaluated for a bone or soft tissue tumor of unknown etiology, does the visualization of the entire muscle or bone compartment in MRI or CT scans of the primary site assist with obtaining a diagnosis or planning further treatment?	

PICO 5: ORAL AND IV CONTRAST IN A STAGING CT CHEST OR CHEST/ABDOMEN/PELVIS SCAN

Section # or Stage of Care	Diagnosis
Assigned To:	

Question Components	**Constructing Your Question**
P – Patient or Population Describe the most important characteristics of the patient. (e.g., age, disease / condition, gender)	patients who are being evaluated for a bone or soft tissue tumor of unknown etiology
I – Intervention; Prognostic Factor; Exposure Describe the main intervention. (e.g., drug or other treatment, diagnostic / screening test)	oral and IV contrast in a staging CT chest or chest/abdomen/pelvis scan
C – Comparison (if appropriate) Describe the main alternative being considered. (e.g., placebo, standard therapy, no treatment, the gold standard)	No use of oral and IV contrast in a staging CT chest or chest/abdomen/pelvis scan
O – Outcome Describe what you're trying to accomplish measure, improve, affect. (e.g., reduced mortality or morbidity, improved memory, accurate and timely diagnosis)	More accurate diagnosis
The PICO Clinical Question: In patients who are being evaluated for a bone or soft tissue tumor of unknown etiology but concerning for metastatic carcinoma, does the use of oral and IV contrast in a staging CT chest or chest/abdomen/pelvis scan assist with obtaining a diagnosis or planning further treatment?	

PICO 6: CHEST RADIOGRAPH PRIOR TO A STAGING CT SCAN

Section # or Stage of Care	Diagnosis
Assigned To:	

Question Components	**Constructing Your Question**
P – Patient or Population Describe the most important characteristics of the patient. (e.g., age, disease / condition, gender)	patients who are being evaluated for a bone or soft tissue tumor of unknown etiology
I – Intervention; Prognostic Factor; Exposure Describe the main intervention. (e.g., drug or other treatment, diagnostic / screening test)	chest radiograph prior to a staging CT scan
C – Comparison (if appropriate) Describe the main alternative being considered. (e.g., placebo, standard therapy, no treatment, the gold standard)	No chest radiograph prior to a staging CT scan
O – Outcome Describe what you're trying to accomplish measure, improve, affect. (e.g., reduced mortality or morbidity, improved memory, accurate and timely diagnosis)	More accurate diagnosis (i.e. more sensitive and specific)
The PICO Clinical Question: In patients who are being evaluated for a bone or soft tissue tumor of unknown etiology, does performing a chest radiograph prior to a staging CT scan assist with obtaining a diagnosis or planning further treatment?	

PICO 7: STAGING CT CHEST/ABDOMEN/PELVIS

Section # or Stage of Care	Diagnosis
Assigned To:	

Question Components	**Constructing Your Question**
P – Patient or Population Describe the most important characteristics of the patient. (e.g., age, disease / condition, gender)	patients who are being evaluated for a bone or soft tissue tumor of unknown etiology
I – Intervention; Prognostic Factor; Exposure Describe the main intervention. (e.g., drug or other treatment, diagnostic / screening test)	staging CT chest/abdomen/pelvis
C – Comparison (if appropriate) Describe the main alternative being considered. (e.g., placebo, standard therapy, no treatment, the gold standard)	staging CT chest alone
O – Outcome Describe what you're trying to accomplish measure, improve, affect. (e.g., reduced mortality or morbidity, improved memory, accurate and timely diagnosis)	More accurate diagnosis
The PICO Clinical Question: In patients who are being evaluated for a bone or soft tissue tumor of unknown etiology but concerning for a primary sarcoma, does obtaining a staging CT chest/abdomen/pelvis rather than a staging CT chest alone assist with obtaining a diagnosis or planning further treatment?	

PICO 8: DIAGNOSTIC ULTRASOUNDS OF THE TUMOR

Section # or Stage of Care	Diagnosis
Assigned To:	

Question Components	**Constructing Your Question**
P – Patient or Population Describe the most important characteristics of the patient. (e.g., age, disease / condition, gender)	patients who are being evaluated for a bone or soft tissue tumor of unknown etiology
I – Intervention; Prognostic Factor; Exposure Describe the main intervention. (e.g., drug or other treatment, diagnostic / screening test)	diagnostic ultrasounds of the tumor
C – Comparison (if appropriate) Describe the main alternative being considered. (e.g., placebo, standard therapy, no treatment, the gold standard)	Advanced imaging (MRI, CT, PET), radiographs (reference standard)
O – Outcome Describe what you're trying to accomplish measure, improve, affect. (e.g., reduced mortality or morbidity, improved memory, accurate and timely diagnosis)	Accurate diagnosis (i.e. sensitivity and specificity is not significantly different from comparator/reference standard)
The PICO Clinical Question: In patients who are being evaluated for a bone or soft tissue tumor of unknown etiology, do diagnostic ultrasounds of the tumor assist with obtaining a diagnosis or planning further treatment?	

PICO 9: ADVANCED IMAGING OF PATIENTS WITH PAIN IN AREA OF TUMOR

Section # or Stage of Care	Diagnosis
Assigned To:	

Question Components	**Constructing Your Question**
P – Patient or Population Describe the most important characteristics of the patient. (e.g., age, disease / condition, gender)	patients who are being evaluated for a bone or soft tissue tumor of unknown etiology with pain in the area of the tumor
I – Intervention; Prognostic Factor; Exposure Describe the main intervention. (e.g., drug or other treatment, diagnostic / screening test)	MRI, CT of the site, CT chest/abdomen/pelvis, bone scans, or PET scans
C – Comparison (if appropriate) Describe the main alternative being considered. (e.g., placebo, standard therapy, no treatment, the gold standard)	Versus each other and radiographs
O – Outcome Describe what you're trying to accomplish measure, improve, affect. (e.g., reduced mortality or morbidity, improved memory, accurate and timely diagnosis)	Accurate diagnosis
The PICO Clinical Question: In patients who are being evaluated for a bone or soft tissue tumor of unknown etiology with pain in the area of the tumor, do MRI, CT of the site, CT chest/abdomen/pelvis, bone scans, or PET scans assist with obtaining a diagnosis or planning further treatment?	

PICO 10: ADVANCED IMAGING FOR PATIENTS WITH A HISTORY OF GROWTH IN AREA OF TUMOR

Section # or Stage of Care	Diagnosis
Assigned To:	

Question Components	**Constructing Your Question**
P – Patient or Population Describe the most important characteristics of the patient. (e.g., age, disease / condition, gender)	patients who are being evaluated for a bone or soft tissue tumor of unknown etiology with a history of growth in the area of the tumor
I – Intervention; Prognostic Factor; Exposure Describe the main intervention. (e.g., drug or other treatment, diagnostic / screening test)	MRI, CT of the site, CT chest/abdomen/pelvis, bone scans, or PET scans
C – Comparison (if appropriate) Describe the main alternative being considered. (e.g., placebo, standard therapy, no treatment, the gold standard)	Various advanced imaging modalities/other imaging modalities
O – Outcome Describe what you're trying to accomplish measure, improve, affect. (e.g., reduced mortality or morbidity, improved memory, accurate and timely diagnosis)	Accurate diagnosis
The PICO Clinical Question: In patients who are being evaluated for a bone or soft tissue tumor of unknown etiology with a history of growth in the area of the tumor, do MRI, CT of the site, CT chest/abdomen/pelvis, bone scans, or PET scans assist with obtaining a diagnosis or planning further treatment?	

PICO 11: ADVANCED IMAGING FOR PATIENTS WITH A MASS

Section # or Stage of Care	Diagnosis
Assigned To:	

Question Components	**Constructing Your Question**
P – Patient or Population Describe the most important characteristics of the patient. (e.g., age, disease / condition, gender)	patients who are being evaluated for a bone or soft tissue tumor of unknown etiology with a mass of a certain size
I – Intervention; Prognostic Factor; Exposure Describe the main intervention. (e.g., drug or other treatment, diagnostic / screening test)	MRI, CT of the site, CT chest/abdomen/pelvis, bone scans, or PET scans
C – Comparison (if appropriate) Describe the main alternative being considered. (e.g., placebo, standard therapy, no treatment, the gold standard)	Various advanced imaging modalities/other imaging modalities and radiographs
O – Outcome Describe what you're trying to accomplish measure, improve, affect. (e.g., reduced mortality or morbidity, improved memory, accurate and timely diagnosis)	Accurate diagnosis
The PICO Clinical Question: In patients who are being evaluated for a bone or soft tissue tumor of unknown etiology with a mass of a certain size, do MRI, CT of the site, CT chest/abdomen/pelvis, bone scans, or PET scans assist with obtaining a diagnosis or planning further treatment?	

PICO 12: ADVANCED IMAGING FOR PATIENTS WITH CORTICAL IRREGULARITY OR A PERIOSTEAL REACTION

Section # or Stage of Care	Diagnosis
Assigned To:	

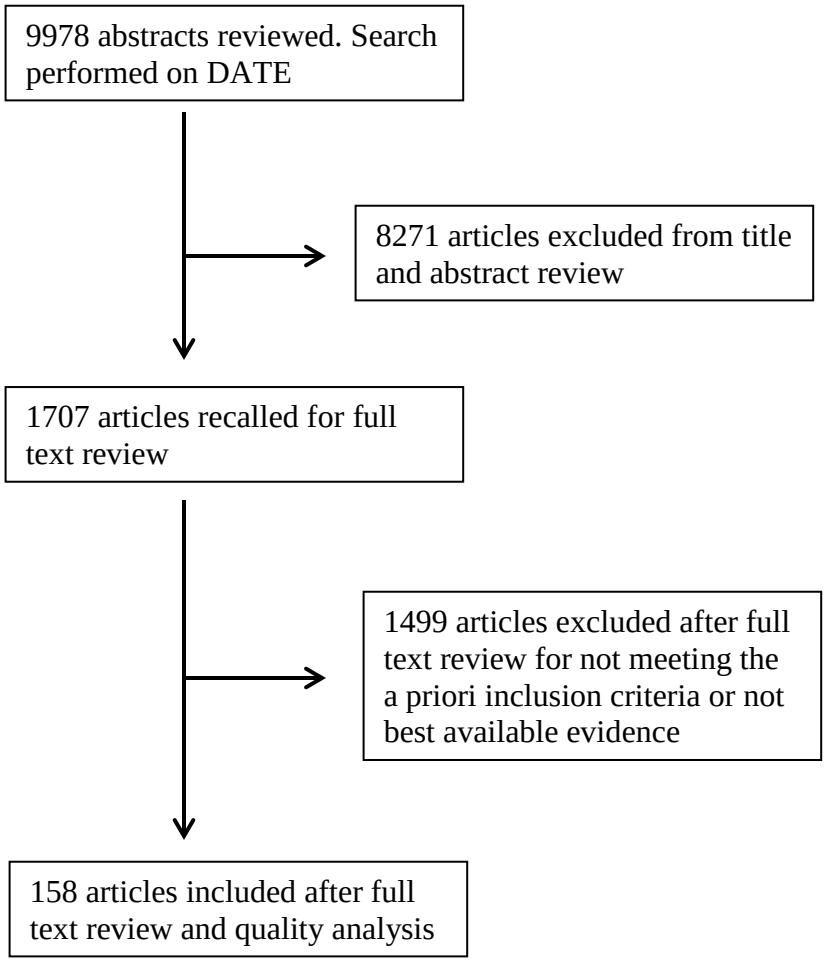
Question Components	**Constructing Your Question**
P – Patient or Population Describe the most important characteristics of the patient. (e.g., age, disease / condition, gender)	patients who are being evaluated for a bone or soft tissue tumor of unknown etiology with plain radiographs that show cortical irregularity or a periosteal reaction
I – Intervention; Prognostic Factor; Exposure Describe the main intervention. (e.g., drug or other treatment, diagnostic / screening test)	MRI, CT of the site, CT chest/abdomen/pelvis, bone scans, or PET scans
C – Comparison (if appropriate) Describe the main alternative being considered. (e.g., placebo, standard therapy, no treatment, the gold standard)	Various advanced imaging modalities/other imaging modalities and radiographs
O – Outcome Describe what you're trying to accomplish measure, improve, affect. (e.g., reduced mortality or morbidity, improved memory, accurate and timely diagnosis)	Accurate diagnosis
The PICO Clinical Question: In patients who are being evaluated for a bone or soft tissue tumor of unknown etiology with plain radiographs that show cortical irregularity or a periosteal reaction, do MRI, CT of the site, CT chest/abdomen/pelvis, bone scans, or PET scans assist with obtaining a diagnosis or planning further treatment?	

PICO 13: ADVANCED IMAGING FOR PATIENTS WITH A POORLY DESIGNED INTERFACE WITH THE TUMOR

Section # or Stage of Care	Diagnosis
Assigned To:	

Question Components	**Constructing Your Question**
P – Patient or Population Describe the most important characteristics of the patient. (e.g., age, disease / condition, gender)	patients who are being evaluated for a bone or soft tissue tumor of unknown etiology with radiographs that show a poorly defined interface with the tumor (e.g. permeative border or wide zone of transition)
I – Intervention; Prognostic Factor; Exposure Describe the main intervention. (e.g., drug or other treatment, diagnostic / screening test)	MRI, CT of the site, CT chest/abdomen/pelvis, bone scans, or PET scans
C – Comparison (if appropriate) Describe the main alternative being considered. (e.g., placebo, standard therapy, no treatment, the gold standard)	Various advanced imaging modalities/other imaging modalities and radiographs
O – Outcome Describe what you're trying to accomplish measure, improve, affect. (e.g., reduced mortality or morbidity, improved memory, accurate and timely diagnosis)	Accurate diagnosis
The PICO Clinical Question: In patients who are being evaluated for a bone or soft tissue tumor of unknown etiology with radiographs that show a poorly defined interface with the tumor (e.g. permeative border or wide zone of transition), do MRI, CT of the site, CT chest/abdomen/pelvis, bone scans, or PET scans assist with obtaining a diagnosis or planning further treatment?	

APPENDIX IV
STUDY ATTRITION FLOWCHART



APPENDIX V
LITERATURE SEARCH STRATEGIES

For PRISMA diagram

Records identified through database searching: 10,239
Additional records identified through other sources (bib searches): 76
Records after duplicates removed: 9,978
Records screened: 9,978

Search Strategy

Date: February 2, 2017
Database: PubMed
Interface: NCBI (http://www.ncbi.nlm.nih.gov/pubmed/)
Search Query:

#1	“Bone Neoplasms”[Mesh] OR "Soft Tissue Neoplasms"[Mesh:NoExp] OR “Muscle Neoplasms”[Mesh]
#2	((“bone”[tiab] OR “skeletal”[tiab] OR “soft tissue”[tiab]) AND (tumor*[tiab] OR tumour*[tiab] OR neoplas*[tiab]))
#3	“diagnostic imaging”[Mesh] OR “radionuclide imaging”[subheading] OR “radiography”[subheading] OR “ultrasonography”[subheading] OR radiograph*[tiab] OR “x-ray”[tiab] OR ultrason*[tiab] OR ultrasound*[tiab] OR “Magnetic Resonance Imaging”[Mesh] OR “magnetic resonance”[tiab] OR “Tomography, X-Ray Computed”[Mesh] OR “computed tomography”[tiab] OR “computer assisted tomography”[tiab] OR “Radionuclide Imaging”[Mesh] OR scintigraph*[tiab] OR “Positron-Emission Tomography”[Mesh] OR “positron emission tomography”[tiab]
#4	diagnosis[subheading] OR diagnos*[tiab] OR refer[tiab] OR refers[tiab] OR referred[tiab] OR referral*[tiab] OR referring[tiab]
#5	(animal[mh] NOT human[mh]) OR cadaver[mh] OR cadaver*[ti] OR comment[pt] OR editorial[pt] OR letter[pt] OR "historical article"[pt] OR addresses[pt] OR news[pt] OR "newspaper article"[pt] OR “case reports”[pt] OR "case report"[ti]
#6	1966:3000[pdat] AND English[la]
#7	#1 OR #2
#8	#3 AND #4
#9	(#7 AND #8 AND #6) NOT #5

Database: Embase
Interface: Elsevier (http://www.embase.com/)
Search Query:

#1	‘locomotor system tumor’/de OR ‘bone tumor’/exp OR ‘cartilage tumor’/exp OR ‘joint tumor’/exp OR ‘soft tissue tumor’/de OR ‘connective tissue tumor’/exp
#2	(('bone' OR 'skeletal' OR 'soft tissue') NEAR/3 (tumor* OR tumour* OR neoplas*)):ab,ti

#3	‘radiodiagnosis’/exp OR ‘CAT scan’:ti,ab OR ‘CT scan’:ti,ab OR ‘computed tomography’:ti,ab OR ‘computer assisted tomography’:ti,ab OR ‘magnetic resonance’:ti,ab OR ultrason*:ti,ab OR ultrasound*:ti,ab OR scintigraph*:ti,ab OR ‘PET scan’:ti,ab OR ‘positron emission tomography’:ti,ab
#4	'diagnosis'/lnk OR diagnos*:ti,ab OR refer*:ti,ab
#5	cadaver/de OR 'in vitro study'/exp OR 'animal experiment'/de OR 'animal model'/de OR ‘nonhuman’/de OR 'abstract report'/de OR book/de OR editorial/de OR note/de OR letter/de OR 'case study'/de OR 'case report'/de OR 'conference abstract'/it OR 'chapter'/it OR 'medical record review'/de
#6	(#1 OR #2) AND (#3 AND #4) NOT #5
#7	#6 AND [english]/lim AND [1966-2017]/py AND ([embase]/lim NOT [medline]/lim)

Database: Cochrane Central Register of Controlled Trials (CENTRAL)
Interface: Wiley Online Library (http://onlinelibrary.wiley.com/cochranelibrary/search)
Search Query:

#1	MeSH descriptor: [Bone Neoplasms] explode all trees and with qualifier(s): [Radiography - RA, Radionuclide imaging - RI, Ultrasonography - US]
#2	MeSH descriptor: [Soft Tissue Neoplasms] this term only and with qualifier(s): [Radiography - RA, Radionuclide imaging - RI, Ultrasonography - US]
#3	MeSH descriptor: [Muscle Neoplasms] explode all trees and with qualifier(s): [Radiography - RA, Radionuclide imaging - RI, Ultrasonography - US]
#4	bone or skeletal or "soft tissue":ti,ab,kw (Word variations have been searched)
#5	tumor or tumour or neoplas*:ti,ab,kw (Word variations have been searched)
#6	MeSH descriptor: [Diagnostic Imaging] explode all trees
#7	"imaging" or "CT scan" or "CAT scan" or "computed tomography" or "computer assisted tomography" or "magnetic resonance" or "MRI scan" or ultrason* or ultrasound* or scintigraph* or "PET scan" or "positron emission tomography":ti,ab,kw (Word variations have been searched)
#8	diagnos* or refer*:ti,ab,kw (Word variations have been searched)
#9	#1 or #2 or #3 or (#4 and #5 and #6 and #7)
#10	#9 and #8 not "conference abstract":pt

APPENDIX VI
PARTICIPATING PEER REVIEW ORGANIZATIONS

Peer review of the guideline is completed by interested external organizations. The MSTS solicits reviewers for each guideline. They consist of experts in the topic area and represent professional societies other than MSTS. Review organizations are nominated by the guideline development group at the introductory meeting. Peer review comments will be available on www.msts.org.

Participation in the MSTS guideline peer review process does not constitute an endorsement nor does it imply that the reviewer supports this document.

STRUCTURED PEER REVIEW FORM

Peer reviewers are asked to read and review the draft of the systematic literature review with a particular focus on their area of expertise. Their responses to the answers below are used to assess the validity, clarity, and accuracy of the interpretation of the evidence.

	Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree
1. The overall objective(s) of the guideline is (are) specifically described.	○	○	○	○	○
2. The health question(s) covered by the guideline is (are) specifically described.	○	○	○	○	○
3. The guideline's target audience is clearly described.	○	○	○	○	○
4. The guideline development group includes individuals from all the relevant professional groups.	○	○	○	○	○
5. There is an explicit link between the recommendations and the supporting evidence.	○	○	○	○	○
6. Given the nature of the topic and the data, all clinically important outcomes are considered.	○	○	○	○	○
7. The patients to whom this guideline is meant to apply are specifically described.	○	○	○	○	○
8. The criteria used to select articles for inclusion are appropriate.	○	○	○	○	○
9. The reasons why some studies were excluded are clearly described.	○	○	○	○	○
10. All important studies that met the article inclusion criteria are included.	○	○	○	○	○
11. The validity of the studies is appropriately appraised.	○	○	○	○	○
12. The methods are described in such a way as to be reproducible.	○	○	○	○	○
13. The statistical methods are appropriate to the material and the objectives of this guideline.	○	○	○	○	○
14. Important parameters (e.g., setting, study population, study design) that could affect study results are systematically addressed.	○	○	○	○	○
15. Health benefits, side effects, and risks are adequately addressed.	○	○	○	○	○
16. The writing style is appropriate for health care professionals.	○	○	○	○	○
17. The grades assigned to each recommendation are appropriate.	○	○	○	○	○

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

Would you recommend these guidelines for use in clinical practice?*

- Strongly Recommend
- Recommend
- Would Not Recommend
- Unsure

Additional Comments:

To view an exampleof the structured peer review form, please select the following link: Structured Peer Review Form

APPENDIX VII
INTERPRETING THE FOREST PLOTS

We use descriptive diagrams known as forest plots to present data from studies comparing the differences in outcomes between two treatment groups when a meta-analysis has been performed (combining results of multiple studies into a single estimate of overall effect). The overall effect is shown at the bottom of the graph as a diamond to illustrate the confidence intervals. The standardized mean difference or odds ratio are measures used to depict differences in outcomes between treatment groups. The horizontal line running through each point represents the 95% confidence interval for that point estimate. The solid vertical line represents “no effect” and is where the standardized mean difference = 0 or odds ratio = 1.

APPENDIX VIII
CONFLICT OF INTEREST

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

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

Benjamin J Miller, MD, Chair: Musculoskeletal Oncology Research Initiative: Board or committee member ($0); Musculoskeletal Tumor Society: Board or committee member ($0); Submitted on: 10/01/2015

Patrick John Getty, MD, Oversight Chair: American Board of Orthopaedic Surgery, Inc.: Board or committee member ($0); Musculoskeletal Transplant Foundation: Other financial or material support ($0); Submitted on: 06/01/2015

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Ana Cecilia Belzarena Genovese, MD (This individual reported nothing to disclose); Submitted on: 01/27/2016

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Eric R Henderson, MD: Abbott: Stock or stock Options Number of Shares: 0; Covidien: Employee ($0); Submitted on: 01/02/2016

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Mark D Murphey, MD (This individual reported nothing to disclose); Submitted on: 05/31/2013

Lukas M Nystrom, MD (This individual reported nothing to disclose); Submitted on: 02/03/2016

Carlos Manuel Pereira Betancourt, MD: DePuy, A Johnson & Johnson Company: Paid presenter or speaker ($0) Number of Presentations: 0; Eli Lilly: Paid presenter or speaker ($0) Number of Presentations: 0 ; Grunental: Paid presenter or speaker ($0) Number of Presentations: 0; Osteotech: Paid presenter or speaker ($0) Number of Presentations: 0; Submitted on: 12/03/2015

Catherine Celeste Roberts, MD: Amirsys, Inc.: Publishing royalties, financial or material support ($0); Submitted on: 01/29/2016

Ahmet Salduz, MD (This individual reported nothing to disclose); Submitted on: 03/14/2016

Kurt Richard Weiss, MD: I am on the scientific advisory board of Eleison pharmaceuticals. I have received exactly $0.00 thus far from this position. Unpaid consultant; Submitted on: 01/28/2016

APPENDIX X
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APPENDIX XIII
LETTERS OF ENDORSEMENT FROM EXTERNAL ORGANIZATIONS