2.5. DIAGNOSIS: IMAGING

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QUESTION 1: What imaging modalities are available to help evaluate the extent of an infection and guide bone resection?

RECOMMENDATION: Imaging methods have a potential to demonstrate the extent of soft-tissue/bone involvement in patients with periprosthetic joint infection (PJI). The use of computed tomography, magnetic resonance imaging (MRI) or nuclear medicine techniques may help to delineate the extent of bone and soft tissue involvement and may guide bone resection.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 86%, Disagree: 8%, Abstain: 6% (Super Majority, Strong Consensus)

DEFINING THE STRENGTH OF THE RECOMMENDATIONS

Assigning the strength of the recommendations was provided by concise presentation of the literature quantity and quality while accounting for the trade-off between the clinical experience and their limitations. In order to standardize the approach across the consensus document/specialists from different medical branches, we adopted the methodology of defining the strength of the recommendations and evaluating the evidence from the American Academy of Orthopaedic Surgeons (AAOS) Clinical Practice Guideline and Systematic Review Methodology v2.0 [1].

The selected studies might be flawed in a number of parameters. For example, study design (randomized-control/prospective/retrospective), type of study (diagnostic/case-control/ observational/case reports), primary purpose, population, study inclusion/exclusion criteria, definition of PJI, gold standard for diagnosis of PJI/distinct clinical entities (abscess, presence of soft-tissue edema, periprosthetic fluid collections, bone damage), data collection/analysis/ interpretation etc. Therefore, methods for assigning the quality of the selected studies were appraised in accordance with the GRADE recommendations [2]. In the GRADE approach randomized trials start as high-quality evidence and observational studies as low-quality evidence. Five factors may lead to rating down the quality of evidence: study limitations or risk of bias, inconsistency of results, indirectness of evidence, imprecision and publication bias [3]. In accordance with the AAOS manual [1], high-quality diagnostic studies cannot have any substantial flaw,
moderate-quality studies can have less than two flaws, low-quality diagnostic studies less than three flaws and very low-quality studies have more than three substantial flaws. Observational studies were classified as follows: high-quality studies have less than two flaws, moderate-quality studies have between two and four flaws, low-quality studies from four to six flaws and very low-quality studies have more than six flaws.

RATIONALE

Removal of all infected/necrotic tissues is pivotal in the treatment of PJI. In practice, surgeons are guided mainly by experience of what constitutes infected and/or necrotic tissue that must be excised. Tissue color/structure/consistency can guide the degree of resection, in addition to active bleeding from apparently healthy tissue and bone surfaces. Surgeons may use specific dyes (e.g., methylene blue) as a visual aid to differentiate between necrotic tissue and healthy soft tissue. Currently, there is no consensus on whether imaging modalities could be used preoperatively to better define the location of infected soft tissue and bone or be used to guide the degree and depth of surgical debridement. While imaging methods, such as Indium labeled bone scans, have been used for diagnosis of PJI in very select cases, whether a preoperative imaging modality can provide the spatial resolution and accuracy to determine the exact regions of soft tissue involvement of osteomyelitis that require debridement is still debated [4]. The primary question of this paper is to determine, based on the available evidence, if preoperative imaging, and which type of imaging, could best define the border between the infected and non-infected soft tissue and bone and quantitatively and qualitatively assess the extent of associated soft tissue and osseous damage associated with chronic PJI.

The literature search was conducted utilizing databases such as PubMed, Embase, Cochrane Library, Scopus, ScienceDirect and Google Scholar. The search strategy utilized the following Medical Subjection Headings (MeSH) terms: “hip arthroplasty,” “hip replacement,” “hip prosthesis,” “knee arthroplasty,” “knee replacement,” “knee prosthesis,” “infection,” “periprosthetic infection,” “prosthetic joint infection,” “nuclear imaging,” “leukocyte imaging,” “antigranulocyte imaging,” “18F-fluorodeoxyglucose,” “positron emission tomography,” “ultrasound,” “computed tomography,” “magnetic resonance imaging,” “conventional radiography” and “best match” for each database.

We used the Boolean operators “AND” and “OR” to identify the intersection and union of the terminology sets. References for all the selected articles were cross-checked.

Two of the authors (EN and LQ) performed the literature search. First, articles were screened by title and abstract; 495 potentially interesting studies were identified. Of them, 229 relevant publications including reviews and meta-analyses were then selected for data extraction.

Study Selection

Based on the clinical question, we proposed inclusion and exclusion criteria to be applied when reviewing the search results of each database. An initial review of titles and abstracts was carried out to identify potential studies. The inclusion criterion was human studies. The exclusion criterion was “studies limited to the English language.” This study is based on 49 full texts that have been analyzed to date.

Data Extraction

Once the study selection was completed, the relevant data (number of patients, age, gender, location of PJI, type of PJI, single/multi-center study, study period, type of study, design of study, type of imaging, definition of PJI, gold standard, characteristics of particular imaging methods, limitations of the study) from the included studies were extracted. A spreadsheet was customized to the specific question. After the data extraction and completion of the tables, the senior authors (JG and MK) assessed the quality of the particular studies used in assigning the strength of the recommendations.

Conventional radiography (CR) can show "signs of damage" in the bone surrounding infected arthroplasty as well as in swollen soft-tissues [5,6]. However, these changes are not specific for PJI, and these are seen only in a minority of PJIs. We did not find any diagnostic study supporting the role of CR in showing the bone/soft-tissue extension of PJI. The conclusion should therefore be *no evidence* for using CR as a tool for visualization of tissues affected by PJI. The only exception is when radiography shows clear presence of osteomyelitis, periosteal reaction and so on and may provide some degree of confidence in planning the extent of bone resection needed during resection arthroplasty.

Ultrasonography can demonstrate collections of fluid inside and around an infected joint as well as it can distinguish between solid and fluid lesions. Sdao et al. reported superficial collections, subcutaneous fistulae, as well as deep periprosthetic collections of fluids around total hip arthroplasty [7]. However, these are not specific for infection. Ultrasound guided aspiration (biopsy) of a hip joint improves reliability of aspiration [8]. Here we suggest concluding the strength of *evidence as low (limited)*. A support for that conclusion is predominantly on anecdotal (case reports) and small-series studies of low quality [9–11].

Computed tomography (CT) is excellent for evaluating bony structures, but it can also contribute to assessment of soft tissue pathology [12]. However, this is not specific for infection. CT can detect abscesses around total joint arthroplasty, which is clinically very useful as a psoas abscess can also mimic PJI [13]. On the other hand, CT arthrography can reveal bone erosions, radiolucency, fistulae, extra-articular extensions of PJI or communications between fluid collections [14,15]. In addition, CT can show displacement of the external iliac vessels with venous compression [11]. Taking these findings into account, alongside the clinical value of CT findings (either positive or negative), we conclude the strength of the recommendations for abdominal/hip CT as *moderate* despite the fact that it is based on anecdotal [16,17] to small-series study evidence [15,18,19]. Therefore, CT should be combined with other imaging/laboratory methods in order to visualize the extension of the soft-tissue/bone damage associated with PJI.

Magnetic resonance imaging (MRI) can detect bone marrow changes, cavities and soft-tissue extension of PJI (edema, fluid collections). In addition, the new metal artifact reduction sequences (MARS) enabled a more reliable assessment of periprosthetic tissues [14]. Contrast MRI can contribute to detection of psoas abscesses [20]. In contrast to radiography, MRI might be more specific for hip PJI as it can differentiate between fluid collections (serous, purulent or hematomas) [21]. Further, progress might lie in optimized MRI parameters with and without view angle tilting (VAT) correction at 1.5 T in coronal fast-spin-echo T2-weighted MRI [22]. Intravenous gadolinium contrast MRI demonstrates improved specificity for abscess detection, despite the fact that non contrast-enhanced MRI with diffusion-weighted imaging has recently achieved comparable performance [23]. Despite that, MRI should be still combined with other imaging/laboratory methods in order to demonstrate the true extension of soft-tissue/bone damage associated with PJI. We suggest concluding the strength of the recommendations for MRI in this specific clinical question as *moderate*, similar to CT.

The nuclear medicine techniques are regularly used in some clinical settings to diagnose particular infections of the musculoskeletal system [24]. They are based on various principles (radio-labelled cells, peptides, antibodies or (18) fluorodeoxyglucose (FDG) to detect patterns highly associated with infected tissues. Recent systematic reviews and meta-analyses show great diagnostic potential in terms of the likelihood ratio for positive/negative results and diagnostic odds ratio for radio-labelled white blood cells [4]. Anti-granulocyte scintigraphy and combined radio-labelled leukocyte and bone marrow scintigraphy appear to be highly-specific imaging modalities in confirming knee PJI. FDG-PET (positron emission tomography) may not be the preferred imaging modality because it is more expensive and not more effective in confirming periprosthetic knee infection [4]. However, much of the evidence is dated and recent innovations in nuclear medicine technology that have improved image quality and sensitivity of investigations (particularly SPECT/CT – single photon emission computed tomography) are not fully represented in this review.

To date, there is a little knowledge of the capability of these methods to visualize the extent of infection across periprosthetic tissues. Radio-labelled leukocyte or antigranulocyte SPECT/CT imaging has been used to differentiate aseptic loosening from infection [4,25].

Filippi and Schillaci [26] described the usefulness of hybrid SPECT/CT in technetium (99mTC)-hexamethylpropleneamineoxime (^{99m}TC-HMPAO)-labelled leukocyte scintigraphy for bone and joint infections. In the sample of 28 consecutive patients (13 of them with suspected orthopaedic implant infection), SPECT/CT differentiated soft-tissue involvement from bone involvement both in patients with osteomyelitis and in patients with orthopaedic implants.

Graute et al. [27] described an added value of the ^{99m}Tc-antigranulocyte SPECT/CT in comparison with SPECT only or planar imaging for detection of low-grade prosthetic joint infections. Joint infections were diagnosed clinically in nine of 31 patients (1 hip and 8 knee prostheses). Hybrid SPECT/CT led to a further increase in sensitivity and specificity to 0.89 and 0.73 (in comparison with 0.89 and 0.45 for SPECT only, and 0.66 and 0.60 for planar imaging, respectively). In the cases presented in this study, SPECT/CT images additionally demonstrated the extent of infection in the bone or bone marrow, revealed infection in patients with a characteristic pattern indicating the presence of synovitis on planar paging, or excluded infection due to physiological uptake in arteria poplitea, etc. Optimal accuracy was obtained through image fusion, which permitted anatomical allocation of foci of pathological tracer accumulation as well as providing information on the extent of infection. By this way this imaging method seems suitable for elimination of both false-positive and false-negative findings.

Trevail et al. [28] similarly described the added value of SPECT/CT for the diagnosis of hip PJI (235 consecutive patients). Imaging comprised Tc-^{99m} bone scintigraphy, Indium-III (In-III) labeled white cell scintigraphy, and bone marrow scintigraphy if required. Similar to previous studies, SPECT/CT allowed more accurate localization of abnormal uptake on bone and white cell scintigraphy. Recently, preliminary results of a study by Liberatore et al. [29] showed potential of white blood cell scan as a guide to open biopsy in the management of hip and knee prosthesis infection.

Tam et al. [30] reviewed the use of SPECT-CT to follow post total hip arthroplasty complications, including aseptic loosening and PJI. The CT component of SPECT/CT may help interpretation of SPECT images. CT may reveal areas of lucency with associated periosteal reaction, which correspond to the increased uptake on scintigraphy. CT can also demonstrate soft-tissues changes, such as joint distension, fluid-filled bursae or collections in muscles.

Also, Palestre et al. [31] suggest the potential impact of SPECT/CT on information about the presence and extent of infection. In patients with positive results, for example, the examination could provide information about the extent of infection as well as other abnormalities involving the native bone and the prosthesis (joint aspiration and culture could be performed at the same time). In patients with negative results, the CT component could provide information about other causes of prosthetic failure.

In comparison with leukocyte or antigranulocyte imaging, FDG-PET may not be the preferred imaging modality because it is not more effective in confirming periprosthetic infection [25,31]. Periprosthetic activity of FDG can be seen not only during infection but also in synovitis and aseptic loosening [32,33] thus, the specificity of FDG-PET/CT was very low. FDG-labelled leucocyte PET/CT with its high specificity may be a method more useful than labelled leucocyte scintigraphy in periprosthetic infection imaging [34,35]. However, there are some drawbacks to FDG-labelled leukocyte PET/CT including the relatively long time needed for labelling leucocytes, longer time between injection and imaging (three hours), and the necessity of higher injected FDG doses (double the doses used as compared to standard oncological imaging) [35].

Despite lower specificity of FDG described in earlier studies [32,33], a recent retrospective study [36] showed added value of FDG PET/CT in comparison to conventional tests in diagnosing hip PJI (cultures of joint fluid/periprosthetic tissues or clinical follow-up more than six months served as gold standard). Fukui et al. [37] used FDG-PET in order to make more appropriate decision-making in terms of retention of well-fixed uncemented femoral component in two-stage total hip surgery that included delayed reimplantation of an acetabular component in five patients. FDG-PET was employed to assess whether the infection had invaded the bone around femoral component. By a mean follow-up point of 4.2 years after the second-stage operation, none of the 5 patients experienced recurrence of PJI.

Taken together, we suggest concluding the strength of the recommendations for the nuclear medicine techniques in this specific clinical question as *moderate*.

Future Progress

There is an emerging field of new imaging techniques (e.g., molecular imaging methods) that could visualize the extent of infection in musculoskeletal tissues with promising accuracy. However, clinical value of these methods should be demonstrated in well-conducted diagnostic studies.

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QUESTION 2: What are the radiological signs indicative of infection in patients with an arthroplasty component in place?

RECOMMENDATION: The radiographic signs associated with periprosthetic joint infection (PJI) at the site of hip and knee are early loosening, component migration, radiolucent lines and/or bone erosions around the prosthetic components, particularly if seen at less than five years postoperatively. However, it is important to note that plain radiographs are generally normal in the setting of PJI.

LEVEL OF EVIDENCE: Strong

DELEGATE VOTE: Agree: 98%, Disagree: 1%, Abstain: 1% (Unanimous, Strongest Consensus)

RATIONALE

Conventional radiography is a simple, safe, relatively inexpensive and clinically valuable method used for routine evaluation of total joint arthroplasty (TJA). However, it is not considered informative enough to contribute to the diagnostic workup in the case of PJI [1]. On the other hand, osteolytic lesions, heterotopic ossifications, loosening and effusion of periprosthetic soft tissues, all being seen on early radiography of TJA, can increase the suspicion of PJI. Other imaging modalities are not thought to have a direct role in the diagnosis of PJI. Artifacts due to the presence of metal are a well-known problem in cross-sectional imaging, especially in magnetic resonance imaging (MRI) [2].

Currently, the attention of the orthopaedic community is focused on data obtained from analysis of joint fluid/periprosthetic tissues/retrieved implants [3,4]. The reason is that removed implants, aspirated joint fluid as well as sampled periprosthetic tissues were in direct contact with invading bacteria at the time of sampling/reoperation. Therefore, data gleaned from these methods are both highly sensitive and specific in relation to PJI, making this diagnosis almost certain or excluding the diagnosis [5]. As a result, imaging methods, with the only exception of specific nuclear medicine studies [6,7], do not contribute significantly to the PJI diagnostic workup due to its high costs, especially at the early stages of infection. However, it does not mean that radiography is of no clinical value.

1. Application of conventional radiography in daily routine.

There is no doubt that conventional radiography is the most common imaging method used in clinical practice for the diagnosis of TJA complications. According to a recent survey, conventional radiography was the most common imaging exam used in patients undergoing investigation for PJI (87.6% of orthopaedic surgeons surveyed) followed by single photon emission computed tomography-computed tomography (SPECT-CT) scans (41.7% of surgeons) [8].

2. Radiographic features associated with PJI.

Importantly, plain radiographs can be normal in appearance in the early stages of infection. The primary radiological signs suspicious of PJI are early loosening, periprosthetic radiolucency and bone erosions (osteolysis*)* [9]. These features may be present on serial radiographs of patients with either infection or aseptic loosening of the prosthesis [10–12]. Radiographic signs of rapid prosthetic migration (at least 2 mm within 6 to 12 months), rapidly progressive periprosthetic osteolysis and/or irregular periprosthetic osteolysis are highly suspicious of PJI [13,14]. Similarly, bony erosions and new bone formation on plain radiographs occurring within three to six months postoperatively may also suggest PJI [15]. On plain radiographs and computed tomography (CT), diffuse or multifocal osteolysis surrounding the prosthesis (> 2 mm or progressive) raises concern for infection, however this is not always present and can be seen in the setting of aseptic loosening and particle disease too [16].

Inconsistently, there may be other features present, such as scalloping, ectopic ossification, periosteal reaction and sclerosis. A small, very dense bone fragment isolated from the other trabeculae, corresponding to a sequestrum (fragment harboring a pathogen) is highly suggestive of active infection, but this is a rare event (< 8%). The presence of gas around the prosthesis could suggest an infection by an anaerobic organism [17].

Periosteal new bone formation or adjacent soft tissue collection is highly suggestive of infection but are infrequently present. A wide band of radiolucency at the metal-bone interface (or cement-bone interface) with bone destruction could also suggest that infection is present. CT scans rarely may help diagnosis of PJI despite that the presence of a periosteal reaction or soft tissue accumulation near the area of osteolysis, seen on CT scan, is highly suggestive of infection [18].

In a retrospective study [19] of 102 total hip arthroplasties (THAs), 65 stems and 50 cups were loose at the time of surgery, as reported from a set of radiographic findings. The gold standard used to define PJI was culture (which has its own limitations). They found only five stable non-infected stems and three of these had associated radiolucency. Radiolucency of at least 2 mm was seen in 12 of 27 infected loose cups and 4 of 15 infected stable cups. None of the 9 non-infected stable cups had a radiolucent zone reaching 2 mm. Sclerosis was seen in 24 of 65 loose stems, 18 of which were infected (while 6 of 26 uninfected loose stems showed sclerosis also).

In another study [20], radiographs of 20 confirmed infected hip prostheses were examined for the presence or absence of radiolucency, type of lucency (focal or non-focal), rapidity of radiographic change, periostitis, subsidence and cement fracture. No evidence of periprosthetic lucency was seen in 11 of 20 THAs, and focal osteolysis was seen in only 4 patients in the cohort. Most infected THAs showed no abnormal findings at all (10 prostheses together had normal radiography). The authors concluded that the radiologist should be aware that septic prostheses can appear completely normal.

A retrospective case-control study on 100 total hip replacements assessed the incidence of particular features in the groups of infected THAs, aseptic prosthetic hip failures and successful THAs [21]. The group of failures secondary to infection included 12 of 100 hips. Extensive myositis ossificans was seen in 3 of 12 hips. Resorption of 3 mm in the femoral neck length was noted in 1 hip. Cortical thickening opposite the tip of the stem was seen in one case. Periosteal bone formation was noted in four hips. It involved the proximal part of the femur and usually was circumferential.

In a retrospective case-control study on 41 patients [22], the authors examined which radiographic signs predicted failure of two-stage revision arthroplasty, if present after the first-stage surgery. These radiologic signs were: retained metal implants, new metal implants, retained cement, retained cement restrictor, new fracture, the local antimicrobial delivery system (for example gentamicin loaded beads) and use of a drain. None of these radiographic variables examined was associated with subsequent failure.

A study [23] of 52 patients (32 knees and 20 hips) revised for supposed aseptic loosening and found that there was an association between severity of periprosthetic osteolysis and positive sonication cultures from the retrieved implants (in 30 patients at least 1 sonicated component was positive).

3. Accuracy of conventional radiography for PJI detection.

In a study by Cyteval et al. [24], conventional radiography achieved the following diagnostic characteristics for bone abnormalities (lucency, periostitis): sensitivity 75%, specificity 28%, positive and negative predictive values 19% and 83%, respectively, accuracy 37%. CT images for the same types of findings were similar (75%, 30%, 20%, 84%, 49%, respectively). However, soft tissue abnormalities (joint distension, fluid-filled bursae, fluid collections in muscles and perimuscular fat) were identified on CT as opposed to plain radiography.

In a study by Stumpe et al. [25], serial radiographs had a sensitivity of 84% for the finding of rapid prosthetic migration (at least 2 mm within 6 to 12 months), and/or rapidly progressive periprosthetic osteolysis, and/or irregular periprosthetic osteolysis, whereas specificity was only 57%. In the same study, the inter-observer agreement was very low, limiting the diagnostic value of this technique.

Conclusion

Findings such as early implant loosening, progressive radiolucent lines, early bone erosions (osteolysis) and periosteal reactions (periostitis) can suggest the presence of PJI, especially in the presence of additional supportive clinical data. However, isolated radiographic findings have limited clinical value due to their low specificity.

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QUESTION 3: What is the role of nuclear medicine imaging modalities (three-phase bone scintigraphy, bone marrow scintigraphy, white blood cell (WBC) scintigraphy [with ^{99m}Tc or 111In], anti-granulocyte monoclonal antibody scintigraphy and fluorodeoxyglucose-positron emission tomography/computed tomography (FDG-PET/CT) scan in diagnosing periprosthetic joint infection (PJI)?

RECOMMENDATION: Nuclear imaging may be used for the diagnosis of hip and knee PJI in a select group of patients. The test may be ordered in patients in whom PJI is suspected but when other tests are inconclusive, such as patients with dry aspiration of the joint.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 85%, Disagree: 10%, Abstain: 5% (Super Majority, Strong Consensus)

RATIONALE

The utility of nuclear medicine imaging modalities for diagnosis of PJI has been studied extensively and continues to be debated [1,2]. Two recently published systematic reviews and meta-analysis have evaluated this topic, providing guidance about the utility of nuclear imaging modalities for diagnosis of PJI. Verberne et al. evaluated 31 studies published related to the use of nuclear medicine imaging techniques for the diagnosis of PJI in the hip and found highest accuracy for WBC scintigraphy and highest specificity for combined WBC and bone marrow scintigraphy. FDG-PET and bone scintigraphy were not supported as first imaging technique. FDG-PET showed appropriate accuracy, but its higher costs and limited availability were limitations and bone scintigraphy showed lowest specificity [3]. In a follow-up study, Verberne et al. analyzed 23 publications focused on total knee infections [4]. The authors concluded that antigranulocyte scintigraphy and combined WBC scintigraphy and bone marrow scintigraphy presented the highest specificity values (95% and 93% respectively). In this review (for the knee) bone scintigraphy and FDG-PET/CT were not supported as preferred imaging modality. Bone scintigraphy was not preferred because of low specificity, and FDG-PET/CT was not preferred because of costs and its limited effectiveness in confirming infection for diagnosis of hip and knee PJI.

It is important to realize some facts regarding the nuclear medicine imaging modalities. The three phase bone scan carries a low specificity and low diagnostic accuracy in patients with suspected PJI, particularly in patients with uncemented components and during the early years of arthroplasty [1]. However, the study has a high sensitivity, and normal findings (e.g., no increased perfusion or blood-pool, no periprosthetic uptake in the late phase) can be considered as strong evidence against the presence of infection [5–9]. When having a positive three-phase bone scan in patients with suspected PJI, another imaging modality is necessary. White blood cell scintigraphy is the first nuclear imaging modality of choice in these cases because of the high diagnostic accuracy (> 90%). When correctly labelled, performed and interpreted, FDG-PET/CT has also been used to diagnose PJI. FDG is taken up both in reactive inflammation due to metallic implants such as prosthetic joints and in infection. The differentiation between both is often difficult, leading to lower specificity rates for FDG-PET/CT. Reinartz et al. [10] reviewed the literature on the diagnostic performance of FDG-PET and WBC count scintigraphy in periprosthetic joint infections. They reported higher sensitivity but lower specificity for FDG-PET compared to WBC scintigraphy. In addition, the accuracy for FDG-PET was slightly higher in hip cases than in knee cases. Similarly, a recent review article by Gemmel et al. reported a pooled sensitivity and specificity of 84% for PJI using FDG-PET, which was more accurate for hip than for knee prosthesis [11]. The European Association of Nuclear Medicine/The Society of Nuclear Medicine and Molecular Imaging (EANM/SNMMI) guidelines, based on both review of existing literature data and expert opinion, for the use of FDG in inflammation and infection reported an overall sensitivity of 95% and specificity of 98% for knee and hip periprosthetic infections with FDG-PET [12]. Moreover, the range for both sensitivity (28 to 91%) and specificity (34 to 97%) of the individual studies is quite large, which can be partly explained by the different study design and the lack of standardization in the interpretation criteria (visual interpretation using pattern recognition). Large prospective studies comparing the diagnostic performance of WBC scintigraphy and FDG-PET for PJI are required.

The American College of Radiology published their appropriateness criteria for imaging after total knee replacement [13]. After an extensive literature review by a panel of experts, they recommend that the use of three-phase bone scintigraphy and white blood cell scintigraphy (labelled with In-111 and with SPECT/CT if necessary for exact location) may be appropriate in the particular setting of pain after total knee arthroplasty when joint aspiration culture(s) are negative or inconclusive and the clinician still has strong suspicion of PJI.

Recently, in a well-designed study, Kwee et al. analyzed the added value of FDGPET /CT to conventional tests performed for the diagnosis of PJI, such as radiography, serum markers and synovial fluid-based tests [14]. They demonstrated that when erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were not elevated and/or serum tests were normal, FDG-PET/CT did not add any diagnostic value. Based on the available data, it is difficult to support the routine use of FDG-PET/CT for the workup of patients suspected of having PJI.

The American Academy of Orthopaedic Surgeons (AAOS) guidelines also state that the nuclear medicine imaging modalities are certainly an option for diagnosis of PJI in a selected group of patients suspected of PJI in whom diagnosis of PJI could not be reached or refuted, such as patient with failed attempts to retrieve synovial fluid. [15].

In summary, there is a role for nuclear imaging modalities in select group of patients with suspected PJI. However, they should not be used as a first diagnostic test. In patients with a low probability of PJI and not within the first years after surgery, three-phase bone scintigraphy can be a good option.

When negative, it excludes an infection. However, a positive result requires additional workup using other nuclear imaging modalities. White blood cell scintigraphy is then first choice because of its high diagnostic accuracy when correctly performed and interpreted. Antigranulocyte monoclonal antibody scintigraphy can be a second choice option for those centers that cannot perform labelling of the leukocytes. At this moment, routine use of FDG-PET/CT in patients with (suspected) PJI is not supported.

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QUESTION 4: What is the diagnostic accuracy of magnetic resonance imaging (MRI) for osteomyelitis in the presence and absence of implants?

RECOMMENDATION: MRI is useful for the diagnosis of osteomyelitis in the absence of metal implants, although there are other diagnostic tools that show greater specificity and sensitivity. The pooled sensitivity and specificity for MRI in diagnosing osteomyelitis without presence of implants are 84% and 60%, respectively. There are no identifiable studies on the diagnostic accuracy of MRI for osteomyelitis around metal implants. Several techniques for reducing metal artifacts exist.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 96%, Disagree: 1%, Abstain: 3% (Unanimous, Strongest Consensus)

RATIONALE

Diagnostic Accuracy of MRI for Osteomyelitis in Absence of Implants

A variety of diagnostic imaging techniques are available for excluding or confirming chronic osteomyelitis, including plain radiography, computed tomography, bone scintigraphy, leukocyte scintigraphy, gallium scintigraphy, combined bone and leukocyte scintigraphy, combined bone and gallium scintigraphy, fluorodeoxyglucose positron emission tomography and MRI [1–6].

Each of these techniques have varying degrees of sensitivity, specificity and diagnostic accuracy. The Termaat's study [7] (Table 1) shows that the sensitivity and specificity of magnetic resonance imaging is sufficiently homogeneous (Q_{sens} = 4.62: four degrees of freedom, Q_{spec} = 0.02: two degrees of freedom) for chronic osteomyelitis in the peripheral skeleton and was not different from that of leukocyte scintigraphy or combined bone and gallium scintigraphy for the studies in this systematic review [7–28].

The literature demonstrates that MRI is useful for the diagnosis of osteomyelitis in the absence of metal implants, although there are other diagnostic tools that show greater specificity and sensitivity.

Diagnostic Accuracy of MRI for Osteomyelitis in Presence of Metallic Implants

There are no identifiable studies on the diagnostic accuracy of MRI for osteomyelitis around metal implants. There are five studies providing some information on this topic.

Table 1. Sensitivity and specificity of various imaging techniques [7]

Type of Study	Pooled Sensitivity (95% CI)	Pooled Specificity (95% CI)
Bone scintigraphy	82% (70% – 89%)	25% (16% – 36%)
Leukocyte scintigraphy	61% (43% – 76%)	77% (63% – 87%)
Combined bone and leukocyte scintigraphy	78% (72% – 83%)	84% (75% – 90%)
Fluorodeoxyglucose positron emission tomography	96 % (88% – 99%)	91% (81% – 95 %)
Magnetic Resonance	84% (69 – 92 %)	60% (38% – 78%)
Radiography	ND	ND
Computed tomography	ND	ND
Combined bone and gallium scintigraphy	ND	ND
Gallium scintigraphy	ND	ND

CI, confidence interval; ND, no data

Jiang et al. [29] analyzed 16 patients who received tumor resection and joint replacement for bone cancer. They were retrospectively analyzed to identify MRI features that were useful for the diagnosis of periprosthetic infection and tumor recurrence using the optimized MRI parameters with and without view angle tilting (VAT) correction at 1.5 T in coronal fast-spin-echo T2-weighted MRI. Irregular soft tissue mass, soft tissue edema, bone destruction and fistula were significant features of periprosthetic infection, with sensitivities of 47.4 to 100% and specificities of 73.1 to 100.0%, which were confirmed based on surgical and pathological findings. Soft tissue masses were a significant feature of tumor recurrence, with 100% sensitivity, 96.0% specificity and 97.0% consistency.

Jungman et al. [30] found that significant reduction of artifacts was achieved by VAT ($p < 0.001$) and VAT and slice encoding for metal artifact correction (SEMAC) ($p = 0.003$) when compared with conventional pulse sequences. On clinical MRIs, artifact diameters were significantly reduced and diagnostic confidence improved ($p < 0.05$). In 2 cases tumor-recurrence was diagnosed, in 10 cases infection was diagnosed and in 13 cases other .pathology was diagnosed

Fritz et al. [31] mention that optimized conventional pulse sequences and metal artifact reduction techniques afford improved depiction of bone, implant-tissue interfaces and periprosthetic soft tissue for the diagnosis of arthroplasty-related complications. They present strategies for MR imaging factors and parameters for: (a) minimization of arthroplasty-related artifacts (imaging at 1.5 T, instead of 3 T, fast spin-echo (SE) sequence, instead of gradient-echo sequences, high receiver (readout) bandwidth, thin sections) and (b) optimization of image quality (use of intermediate echo time, which results in fluid-sensitive images, instead of T1-weighted or heavily T2-weighted imaging, large matrix in the frequency direction (e.g., 512), high number of excitations and inversion-recovery fat suppression, instead of frequency-selective fat suppression). They concluded that MRI is effective for the assessment of the periprosthetic soft tissues in patients who have had a total hip arthroplasty (THA).

Alprandi et al. [32] demonstrated the diagnostic value of MRI when measuring and characterizing periprosthetic fluid collections (classified as serous/purulent/hematic according to signal behavior). For all evaluations, inter-observer agreement was 100%. No significant differences were found between the measurements of the collections ($p > 0.258$). The authors agree that MRI is highly reproducible in detection, localization, quantification and characterization of fluid collections when the presence of implant infection is clinically suspected.

White et al. [33] investigated the use of standard MRI sequences with simple parameter modifications in 14 THAs for the detection and characterization of THA complications and conclude that by using simple modifications to standard MR imaging sequences, diagnostic-quality MR imaging of THA complications can be performed, particularly around the femoral prosthetic stem.

Magnetic Resonance Imaging Considerations

Attempts have been made to obtain a Metal Artifact Reduction Sequence (MARS) to reduce the size and intensity of magnetic susceptibility artifacts resulting from magnetic field distortion. Artifacts are encountered especially while imaging near metallic implants and result from local magnetic field inhomogeneities introduced by the metallic object into the otherwise homogeneous external magnetic field.

A variety of techniques are used for reducing metal artifacts in MRI. Some techniques proposed include single point imaging, prepolarized MRI, VAT, multiacquisition variable-resonance image combination (MAVRIC) and SEMAC. Changes to the scan protocol can address artifacts due to the presence of metal in the image plane (in-plane artifacts) and due to metal in an adjacent plane (through-plane artifacts) [34]. MAVRIC is a specialized sequence to minimize metallic artifact around metallic prostheses [35]. It relies on 3D fast spin echo (FSE) sequences, using multiple different overlapping volumes at different frequency offsets. Another technique used for addressing through-plane metal artifacts is SEMAC, where an additional slice-encoding gradient is added to a standard fast-spin echo sequence [36]. The combination of the MAVRIC and SEMAC technique is known as multiacquisition variable-resonance image combination selective (MAVRIC-SL) sequence[37].

Conclusions

The literature shows that MRI can be useful in the diagnosis of osteomyelitis in the absence of metal implants, although there are other diagnostic tools that show greater specificity and sensitivity. There is a paucity of data regarding the diagnostic value of MRI for osteomyelitis in presence of metallic implants. Several techniques for reducing the artifacts seen on MRI exist and others are in development, but there is no clinical data about the diagnostic accuracy of osteomyelitis for MRI in this setting.

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