

## The Use of Bone Scan Combined with SPECT for the Evaluation of Infection in Total Knee Replacements

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### Abstract

**Introduction:** The use of radionuclide scans in the evaluation of the cause of painful total knee arthroplasty (TKA) is controversial. Three-phase <sup>99m</sup>Tc bone scans, indium-labelled white blood cell bone scans, and sulphur-colloid marrow scans are widely used imaging modalities. According to clinical practice guidelines, no preferred diagnostic tests are available to rule out a suspected periprosthetic joint infection.

**Objectives:** The aim of this study was to evaluate the usefulness of <sup>99m</sup>Tc HDP combined with Single Photon Emission Computerised Tomography (SPECT) in ruling out infection in painful TKA.

**Methods:** 210 patients that had previously received a TKA attended a painful knee arthroplasty clinic at a single centre between May 2007 and September 2013. The patients were investigated to determine the cause of pain. 141 patients received a <sup>99m</sup>Tc HDP bone scan with SPECT. After exclusion of patients with an equivocal finding, 120 patients were included in this study, of whom 57 were males and 63 were females. The median (range) age of the patients was 68 (40 - 88) years.

**Results:** The bone scan was positive in 23 (19.2%) patients, negative in 97 (80.8%) patients. The sensitivity of bone scan was 72.7% and the specificity of bone scan was 86.2%. The positive predictive value of bone scan was 34.8% (CI = 18.8 - 55.1%), the negative predictive value was 96.9% (CI = 91.3 - 98.9%), and the accuracy was 85%.

**Conclusions:** <sup>99m</sup>Tc HDP with SPECT scan was highly accurate and had a very high negative predictive value. The use of bone scan with SPECT should be considered when investigating patients with painful TKA to rule out infection.

**Level of Evidence:** Diagnostic level 4 study.

**Keywords:** Bone Scan; Technetium HDP; SPECT; Infection; Knee Replacement

### Introduction

Total knee arthroplasty (TKA) is a successful procedure that provides pain relief and improved function for the majority of patients with symptomatic osteoarthritis (OA) of the knee [1]. However, some patients develop symptoms of pain, stiffness and impaired mobility [2]. The cause of knee pain after TKA can be due to various reasons, most commonly including infection, aseptic loosening and instability [3,4]. Correct diagnosis of the reason for pain and implant failure is vital to ensure that the most appropriate treatment is given [5,6].

Radionuclide scans are a useful tool for evaluating the cause of a painful TKA. Three-phase Technetium (Tc) bone scintigraphy is often used in evaluating for suspected component loosening in TKA. When used alone, only modest sensitivities (50 - 85%) have been reported, whilst specificities of between 70% and 90% have been observed [7-9]. When used in combination with different radionuclide scans (e.g. Indium-111 labelled white blood cell, hexamethylpropylene amine oxime (HMPAO) labelled leucocytes), both the sensitivity and specificity can be increased for the detection of periprosthetic infection and osteomyelitis [10,11].

Single photon emission computed tomography (SPECT) is often used in combination with planar bone scintigraphy. The main advantage of SPECT is the ability to view the reconstructed image in multiple planes and to spatially define the anatomic location of various areas of increased or decreased radiopharmaceutical uptake [12]. SPECT has been reported to be more useful than planar scintigraphy in the evaluation of knee pain in an elderly population [13]. SPECT findings have shown to correlate well with clinical findings in a knee OA

population [14]. SPECT is highly specific in diagnosing structural lesions in the knee, but its sensitivity is low [15]. It has been suggested that SPECT should be used as a complementary investigation to planar scintigraphy, rather than being used alone [16].

The use of SPECT in combination with planar scintigraphy has received little attention in the literature, especially in diagnosing periprosthetic infection in painful TKAs. The American Association of Orthopaedic Surgeons reported only a weak recommendation for the use of nuclear medicine in the diagnosis of periprosthetic infections in the knee due to the paucity of a coherent body of research relating to individual imaging modalities [17-23].

**Aim of the Study**

The aim of this study was to determine the diagnostic value of three-phase technetium-hydroxymethylene diphosphonate (HDP) bone scintigraphy combined with SPECT in patients with suspected periprosthetic infection following a TKA.

**Methods**

Two hundred and ten (210) patients that had previously received a TKA attended a painful knee arthroplasty clinic at a single centre between May 2007 and September 2013. Patients were investigated to determine the cause of pain. One hundred and forty one (141) patients received Tc bone scintigraphy combined with SPECT. Of these, 120 patients had a clearly positive or negative finding for infection. The remaining 21 patients had an equivocal finding for infection and were excluded from the statistical analysis. These patients required additional investigations to determine the likelihood of infection. Of the 120 patients included in the study, 57 were male and 63 were female. The median (range) age of the patients was 68 (40 - 88) years. This study was approved by the local trust Research and Development department as an audit.

Of the 120 patients that received bone scintigraphy, 118 patients had blood tests for erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and white cell count (WCC). 100 patients underwent aspiration of the knee under sterile conditions. The aspirated synovial fluid was checked for synovial WCC, gram stain, culture and sensitivity reports. The detailed pathway of the patients who attended the painful TKA clinic is shown in figure 1.

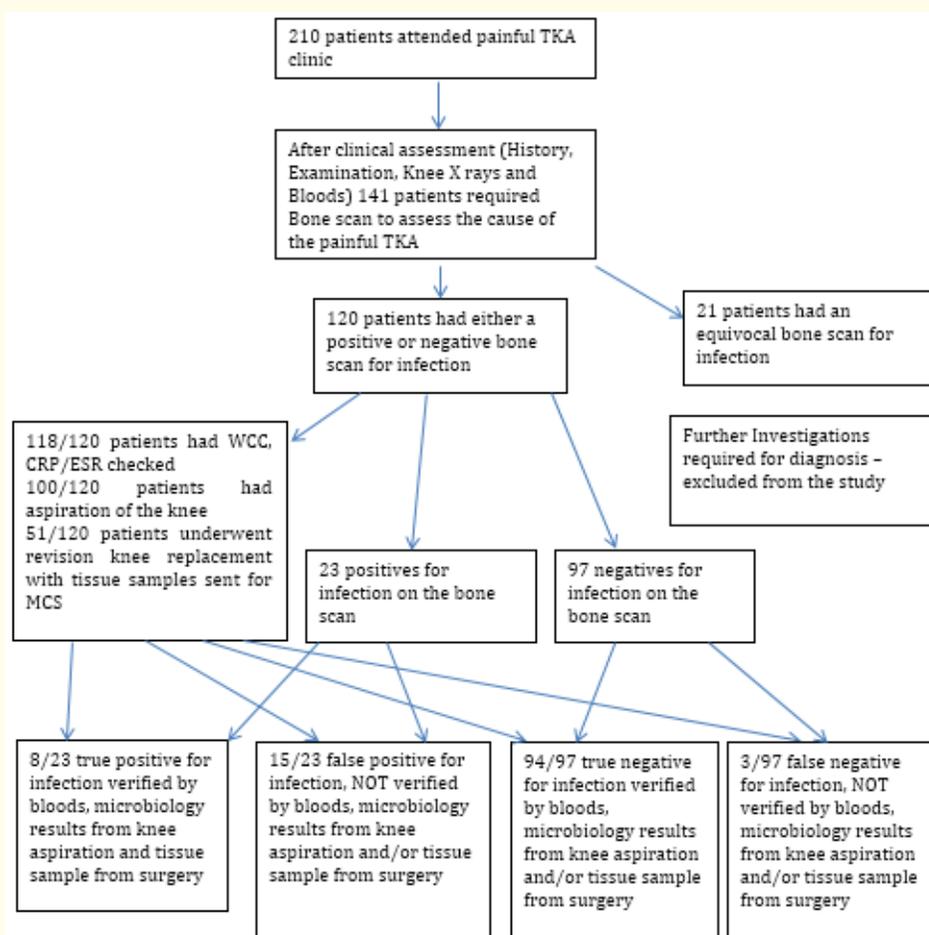
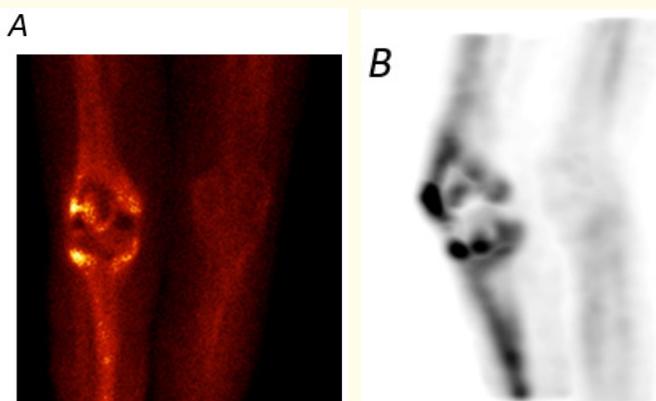


Figure 1: The pathway of the patients that attended the painful TKA clinic

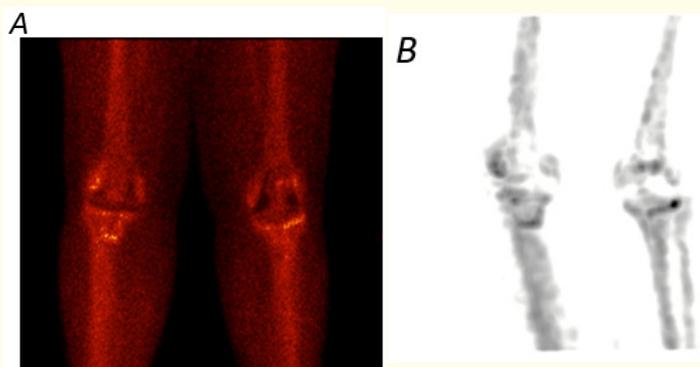
**Bone scan technique**

Patients that had any surgical intervention carried out in the last year were not accepted to have radionuclide imaging uptake, as per local guidelines for adult patients with clinically suspected infection or loosening of a knee prosthesis. Patients were administered with 750 MBq of <sup>99m</sup>Techetium-HDP (<sup>99m</sup>Tc oxidronate, Mallinckrodt Pharmaceuticals Ltd) intravenously whilst lying in supine position, and their knees were flexed at an angle of 20° using a standard support for all images between the imaging heads of a dual detector gamma camera system (Brightview System, Philips Medical Ltd). <sup>99m</sup>Techetium-HDP was used to detect areas of abnormal bone activity such as infected bone around a knee replacement. Images of the knees at injection in the anterior and posterior (A&P) position were obtained a) dynamically in a 128 x 128 matrix with no zoom (pixel size 4.7 mm) of 15 frames at 20 seconds each, simultaneously b) with the acquisition of 2 minute static images (256 x 256 matrix, no zoom, pixel size 2.3 mm), immediately at injection (vascular phase) and at 3 minutes post injection (blood pool phase). Delayed images of the knees were obtained at a nominal 3 hours (minimum 2 ½ hours, maximum 4 hours) again in the supine position consisting of 5 minute A&P planar (256 x 256 matrix, no zoom, 2.3 mm pixel size) images and a 360° SPECT acquisition of 120 frames of 15 seconds each in a 128 x 128 imaging matrix (4.7 mm pixel size). SPECT images were reconstructed using the Philips Medical resolution recovery algorithm (“Astonish”™, 3 iterations, 15 subsets, no filter).

All images were reviewed by a Consultant Medical Physicist and a Consultant Radiologist, both specialists in nuclear medicine with over 25 years’ experience. The Consultant Radiologist also reviewed all other available historical imaging at the time of reporting and a consensus report was issued. Infection was taken to be excluded by the absence of abnormally raised uptake on the images at injection. On delayed images, raised uptake associated with the patella was a very common finding and was ignored unless specific reference to patellar symptoms was made on the clinical request form. Abnormal uptake was classified as (a) mild or marked, (b) discrete or diffuse and (c) multi-focal or solitary. Clinically, studies were reported as either (i) normal, demonstrating no abnormal uptake, (ii) infection (Figure 2), diagnosed by abnormal early uptake and corresponding delayed markedly raised uptake (discrete or diffuse), (iii) loosening (Figure 3), diagnosed by the presence of multi-focal (> 1 site) discrete areas of raised uptake (mild or marked) on the delayed scan adjacent to prosthetic features associated with loosening and/or specific mechanical stress or iv) equivocal (Figure 4), for any scan appearance not falling into one of the previous categories.



**Figure 2:** Planar bone scan (A) and planar bone scan with SPECT (B) images for a representative patient with an infected knee.



**Figure 3:** Planar bone scan (A) and planar bone scan with SPECT (B) images for a representative patient showing signs of prosthetic loosening.

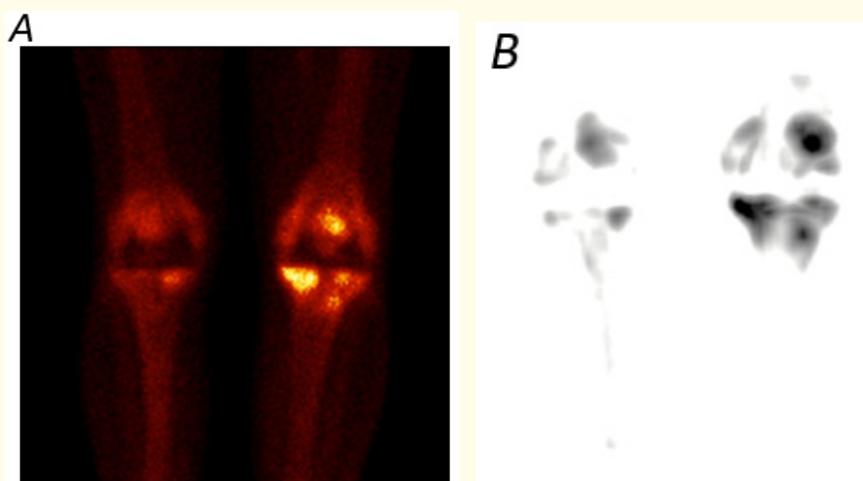


Figure 4: Planar bone scan (A) and planar bone scan with SPECT (B) images for a representative patient that was equivocal.

**Data analysis**

In order to determine the sensitivity and specificity for Technetium bone scan with SPECT for the identification of infection in TKA, all the available microbiological and histological data, as well as intraoperative culture findings for those patients that received revision knee arthroplasty, were reviewed by a Consultant Orthopaedic Surgeon to make a judgement about whether the TKA was infected. The data included in this analysis was: knee aspiration results, ESR, CRP, WCC and intra operative culture and sensitivity findings. The positive predictive values (PPV), negative predictive values (NPV) and accuracy were also calculated.

**Results**

Fifty-one (51) patients underwent a revision knee procedure, of which 42 received a single stage revision and 9 received a two-stage revision. Sixty - nine (69) patients did not receive further surgery. CRP data was available for 118 patients and was within the normal range in 95 (80.5%) patients. ESR was available for 117 patients and was within the normal range in 83 (70.9%) patients. Knee aspiration data was available for 100 patients and was negative for infection in 98 (98%) patients.

Bone scintigraphy with SPECT was positive for infection in 23 (19.2%) patients and negative in 97 (80.8%) patients. Bone scintigraphy with SPECT showed a true positive (TP) in 8 patients (6.7%), a false positive (FP) in 15 patients (12.5%), a false negative (FN) in 3 patients (2.5%) and a true negative (TN) in 94 patients (78.3%). The FP scans were scrutinised by looking at the blood results, culture and sensitivity results from the synovial fluid aspirate and tissue specimens at the time of revision surgery. The breakdown of the patient details, blood results and the isolated organisms seen at revision surgery are given in table 1.

No.	Age	Gender	WCC	ESR	CRP	Isolated Organisms
1	73	M	8.4	60	52	<i>Staphylococcus aureus</i>
2	82	F	10.3	26	31	<i>Staphylococcus epidermidis</i>
3	78	M	4.8	23	7.4	<i>Staphylococcus aureus</i>
4	72	F	5.1	5	< 2	<i>Staphylococcus aureus</i>
5	56	M	7.7	117	98	<i>Staphylococcus epidermidis</i>
6	76	F	9.8	2	2.5	<i>Staphylococcus auricularis</i>
7	66	F	6	2	< 2	<i>Staphylococcus epidermidis</i>
8	70	F	7.1	125	174	<i>Staphylococcus hominis</i>
9	85	M	7.4	31	9.7	<i>Streptococcal Group B</i>
10	75	M	8.7	6	< 2	<i>Staphylococcus warneri</i>

Table 1: Patient demographics, blood tests and organisms isolated.

Bone scintigraphy with SPECT correctly agreed with the clinical assessment for infection in 102 (85%) patients, with 15 FPs and only 3 FNs. Overall, the sensitivity of bone scintigraphy with SPECT was 72.7% and the specificity was 86.2%. The PPV of bone scan was 34.8% (CI = 18.8 - 55.1%), the NPV was 96.9% (CI = 91.3 - 98.9%), and the accuracy was 85% (Table 2).

Clinical assessment	Bone Scan	
	Suggestive of infection	Not suggestive of infection
Infection	8	3
No infection	15	94

**Table 2:** Correlation of bone scan with the clinical assessment for identification of peri-prosthetic infection.

### Discussion

The aim of this study was to determine the predictive value of Tc bone scintigraphy combined with SPECT for the identification of periprosthetic infection following TKA. Bone scintigraphy with SPECT was found to have moderately high sensitivity (72.7%), a high specificity (86.2%), a low PPV (34.8%) and a very high NPV (96.9%), with an accuracy of 85%.

The treatment of painful TKA is difficult and different depending on the aetiopathogenesis. It is very important to establish a diagnosis before proceeding with the definitive treatment. The clinical signs and symptoms of infections are often not quite obvious and are unreliable. Laboratory investigations including full blood count, ESR and CRP may be indicative of infection but are not specific [24]. Joint aspirations can often give FP and FN results [25]. Radiographic imaging has only moderate sensitivity and specificity in the diagnosis of periprosthetic joint infection [26,27] and the presence of hardware limits its use because of artefacts, which is avoided by using nuclear imaging.

The present study evaluated the diagnostic capabilities of planar nuclear imaging using <sup>99m</sup>Tc-HDP combined with SPECT. A moderate sensitivity of 73% and a high specificity of 86% were observed. Both sensitivity and specificity were higher than those reported previously for planar scintigraphy alone using <sup>99m</sup>Tc-MDP, with Wong., *et al.* reporting a sensitivity of only 50% when using <sup>99m</sup>Tc-MDP [7]. The increased sensitivity for <sup>99m</sup>Tc-HDP with SPECT compared to planar scintigraphy alone is unsurprising, as SPECT allows improved localisation of bony pathology in comparison to planar scintigraphy [12]. The type of diphosphonate used could also be a contributory factor for the increased sensitivity.

Whilst some studies have reported no advantage of <sup>99m</sup>Tc-HDP compared to <sup>99m</sup>Tc-MDP [28,29], Carciona reported clearly superior images derived using <sup>99m</sup>Tc-HDP over <sup>99m</sup>Tc-MDP suggesting improved uptake in the region of bone pathology [30].

The PPV and NPV observed for <sup>99m</sup>Tc-HDP bone scintigraphy with SPECT were 35% and 97%, respectively. Previously, Wong., *et al.* reported a much lower PPV for planar scintigraphy alone (9%) and a similar NPV (96%).<sup>7</sup> The high NPV suggests that the bone imaging used in the present study and previously [7] is very useful in ruling out infection. This is largely achieved due to the relatively small proportion of patients that are infected and the high number of true negatives reported in the data. The addition of SPECT to planar scintigraphy increases the PPV, increasing the ability to positively identify infection. The PPV for bone scintigraphy with SPECT is still low. However, additional imaging modalities should be used in cases where infection is still suspected [31-37].

Johnson., *et al.* showed that sequential imaging using <sup>99m</sup>Tc-HDP and Indium-111 white blood cell (WBC) imaging improved results for sensitivity, specificity and accuracy. They reported that the sensitivity of sequential imaging using <sup>99m</sup>Tc-HDP and Indium-111 WBC imaging was 88%, with a specificity of 95% and an accuracy of 93% [10]. In the present study, the accuracy of <sup>99m</sup>Tc-HDP bone scintigraphy with SPECT was 85%, which is similar to that reported by Johnson., *et al.* although the sensitivity and specificity of <sup>99m</sup>Tc-HDP with SPECT were not as high as combining <sup>99m</sup>Tc-HDP with WBC imaging [10]. Whilst the WBC imaging can increase the sensitivity and specificity of the diagnosis of peri-prosthetic joint infection when combined with <sup>99m</sup>Tc-HDP, Johnson., *et al.* reported a low sensitivity when used alone [10]. Combining planar scintigraphy using <sup>99m</sup>Tc-MDP with HMPAO labelled leucocytes, has similarly been shown to increase the sensitivity and specificity in the identification of chronic osteomyelitis compared to using a diphosphonate isotope alone [11], although no studies have reported on this combination of imaging modalities for the identification of periprosthetic joint infection in the knee.

Recently, there has been an increased use of SPECT combined with CT (SPECT/CT), where SPECT images are mapped onto CT images to improve the anatomical localisation of bone pathology [38-40]. Al-Nabhani, *et al.* investigated the diagnostic accuracy of  $^{99m}\text{Tc}$ -HDP with SPECT/CT, finding it to be highly sensitive and specific [41]. Whilst the sensitivity value was not provided, a specificity of 88.1% was reported. Whilst the sensitivity is most likely higher than in the present study, specificity was similar. Mandegaran, *et al.* reported Tc-MDP SPECT/CT has better sensitivity and specificity compared with Tc-MDP Two Phase Bone Scan (TPBS) in diagnosis of aseptic loosening and periprosthetic infection in patients with painful TKA. Results from this study showed Tc-MDP SPECT/CT to have sensitivity and specificity of 100% and 75% respectively in comparison to Tc-MDP TPBS, which had a sensitivity and specificity of 88.9% and 30% respectively [42].

As SPECT/CT will introduce additional radiation compared to SPECT alone [43], then if bone scan is being used to rule out infection, our data suggests that  $^{99m}\text{Tc}$ -HDP bone scan with SPECT would be as successful as  $^{99m}\text{Tc}$ -HDP with SPECT/CT. Bone scan with SPECT alone is also more widely available than SPECT/CT.

This study was the first to investigate  $^{99m}\text{Tc}$ Technetium HDP bone scan with SPECT for the identification of infection in painful TKA, and did so in a relatively large sample of patients at a single centre. However, there are some limitations to this study. The main limitation was that the sensitivity, specificity, PPV, NPV accuracy of  $^{99m}\text{Tc}$ Technetium HDP bone scan with SPECT were determined based on whether other clinical investigations were either suggestive of infection or not suggestive of infection. For the 51 patients that went on to receive either single or two-stage revision surgery, intraoperative cultures provided a definitive indication of whether infection was present, and this was used above all other clinical investigations to categorise patients. For the remaining patients that did not go on to receive revision surgery, intraoperative cultures were not available, so suggestions of infection had to be taken based on the judgement of other factors. Whilst, this could introduce some error in the identification of patients that were suggestive of infection, it was in accordance with clinical practice, where decisions about whether to proceed to surgery are based on the same clinical factors used here. This method allowed a larger sample of patients to be used that included patients with a painful TKA, regardless of whether they went on to receive surgery or not.

### Conclusion

The primary value of nuclear medicine studies in painful TKA to make a differential diagnosis between septic and aseptic causes is a difficult task.  $^{99m}\text{Tc}$ Technetium-HDP bone scan combined with SPECT showed increased sensitivity and specificity over planar bone scintigraphy alone, and similar specificity to planar scintigraphy with SPECT/CT. A high NPV (97%) was observed, suggesting that a negative finding would be highly likely to indicate a lack of infection. A relatively low PPV was found, and additional imaging would be required to confidently identify knees that are positive for infection. Those knees that had an equivocal bone scan result would also require additional investigation to confidently rule infection in or out. The use of bone scan with SPECT should be considered when investigating patients with painful TKA to rule out infection.

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