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SPECT-CT may aid in determining which side of a revision stemmed implant problematic total knee replacement is loose when planning revision surgery

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ABSTRACT

Aim: To evaluate SPECT-CT in the diagnosis of single component aseptic loosening in patients with a problematic cemented stemmed TKR (Total Knee Replacement).
Methods: SPECT-CT was performed where aseptic loosening was suspected but was not clear on plain radiography. Demographics, suspected diagnosis and intention to revise were collected prospectively before and after SPECT-CT.
Results: 30 patients were investigated. 43% (95% CI: 0.5–0.9) had clear evidence of loosening on SPECT-CT. In 23% (95% CI: 0.1–0.4) intention to perform revision surgery following SPECT-CT changed (7/30) (p = 0.0004, standard error = 42.1, z = 3.5).

Intentions to perform revision surgery according to the radiologist's overall summary were:

Normal SPECT-CT – 0% (95% CI: 0.0–0.8) intention to revise (0/2).
Possibly abnormal SPECT-CT – 13% (95% CI: 0.0–0.4) intention to revise (2/15).
Definitely abnormal SPECT-CT – 77% (95% CI: 0.5–0.9) intention to revise (10/13).

We report that SPECT-CT had a test sensitivity of 90.9% (95% CI: 0.6–1.0), a specificity of 100% (95% CI: 0.9–1.0), a positive predictive value of 100% and a negative predictive value of 97.7%.

In 70% (95% CI: 0.3–0.9) of cases where revision surgery was performed for aseptic loosening SPECT-CT provided information that guided pre-operative planning with regards single component or both component revision surgery (7/10).
CONCLUSION: When positive SPECT-CT was useful in determining single component revision. A normal SPECT-CT may have a negative predictive value; however, overall half of our series had a possibly abnormal or equivocal investigation.

1. Introduction

Total Knee Replacement (TKR) is one of the most successful and cost-effective surgical procedures [1]. Estimates show that by 2030 the demand for TKR surgery will grow by 673% and for revision TKR surgery by 601% from the level in 2005 [2]. The increase in revision surgery has been attributed to the increasing number of primary procedures performed,

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increased life expectancy, an increased prevalence of obesity, and extending the threshold for surgery to younger patients [3]. This in combination with increasing use of distal femoral replacement to manage both native and *peri*-prosthetic distal femoral fractures in low demand patients [4] contributes to an increasing population of patients with a stemmed and constrained implant TKR. It is reported that between 10% and 20% of patients are not satisfied with their TKR [5], although little is known around the incidence of a problematic stemmed implant constrained system TKR. Identifying the underlying problem in these patients can be challenging. Differentiating a patient's perception of the non-physiological feeling of a hinge constrained TKR from those with a true underlying problem for which there may be a surgical solution can be difficult. The physiological insult of revising a stemmed prosthesis cannot be underestimated, with a significantly higher *peri*-operative risk profile. There is potential for this to be reduced through revising only a single component in cases where only one side of the TKR system is loose, however this can be difficult to identify pre-operatively.

To make a diagnosis, a systematic approach is required including the quadruple assessment of; history, examination, radiological imaging, and laboratory tests [6]. Radiological assessments include; plain radiographs with long leg alignment views, Computerised-Tomography, and nuclear medicine scans [7]. Plain radiographs can be diagnostic as a primary imaging modality in the detection of prosthetic loosening, but in the context of stemmed implants can be inconclusive. Serial radiographs are useful in identifying subtle loosening, but even small differences in limb position dramatically alter the visualisation of radiolucencies. Observed interval changes must therefore be interpreted with caution, and further imaging may be required. Using plain radiography to diagnose prosthetic loosening can be challenging in patients with a stemmed prosthesis. The pistoning effect of a loose stemmed TKR prosthesis may not be appreciated in a weight bearing radiograph. In addition, it can be difficult to ascertain if one or both sides of a stemmed implant system are loose. SPECT-CT has been proposed as an imaging adjunct in the evaluation of patients with a problematic TKR [8–17]however its role and utility has not been fully established [18]. The natural history of radionuclide uptake following stemmed implant prosthetic implantation remains relatively unknown, together with clinical correlations between radionuclide uptake and typical pain patterns. The lack of a "true gold standard test" of component loosening present challenges to the scientific study of the utility of SPECT-CT in this context.

We present a prospective evaluation of SPECT-CT in patients with suspected aseptic loosening of a problematic revision cemented stemmed implant constrained system TKR. Our aim was to confirm or refute the diagnosis of aseptic loosening, and to identify single component loosening in patients seen in a regional tertiary referral centre.

2. Methods

Patients were seen in a designated multi-disciplinary clinic consisting of four surgeons, physiotherapists, and pain management specialists in a tertiary referral centre during a four-year period (October 2017–October 2021). All data was collected prospectively following Institutional Board Review (October 2017), and a minimum of 24 month follow up is provided in all cases.

Inclusion criteria were:

- Patients with a stemmed implant and a constrained system[1] TKR assessed where a diagnosis of aseptic loosening was suspected, but not definitively confirmed through a standardised assessment protocol, including plain radiography.
- A minimum of three years had passed since prosthetic implantation surgery.
- Infection was not suspected clinically or serologically (defined as normal laboratory reference range of WCC (White Cell Count) and CRP (C-Reactive Protein) at time of evaluation.
- The problem was thought to arise from the knee joint.

2.1. Before SPECT-CT

All pre-scan data was prospectively collected using a bespoke electronic imaging request order form. Details around the surgeons' pre-scan suspicion of aseptic loosening, and intention to perform revision surgery (i.e no/yes) were collected, together with implant details and time since index surgery. All fields were mandatory for the imaging request to be submitted to the radiology department, and all details were viewable by the radiologist. Patients were assessed using a structured and systematic approach [6].

2.1.1. Clinical evaluation

The aetiology of a problematic TKR can be broadly divided into extrinsic (problem independent of the knee arthroplasty) and intrinsic (problem directly arising from the knee arthroplasty). Our priority was to confirm that the patients' reported problem was related to their TKR, and not referred from elsewhere. Most frequently reported symptoms were pain, instability, stiffness or swelling, with pain being the most reported symptom. It was established if the patient's reported problems were different or the same when compared with their pre-operative status. Symptoms unchanged following surgery were likely to be related to an extrinsic problem. Our next priority was to determine if the reported symptoms began in the early post-operative period or developed after a period of being problem free. Early post-operative problems are often caused by

[1] We defined a constrained system as being anything more constrained than a cruciate retaining or posterior stabilised implant system.

infection, instability, soft tissue imbalance, and component malalignment. Whereas problems of a delayed onset are more likely to be caused by prosthetic loosening, insidious ligamentous instability, haematogenous infection, or a stress fractures (especially in stemmed implants). Pain related to activity rather than rest in our view raises our suspicion of aseptic loosening, but this can also be caused by instability or impingement.

2.1.2. Clinical examination

Gait was assessed to evaluate for instability and component malrotation. The presence of overt soft tissue swelling and/or an effusion add weight to the cause of the patient's problem being intrinsic to their TKR. Although clinical examination can be extremely useful, we find it difficult to elucidate clinical signs specific to supporting a diagnosis of aseptic loosening. Therefore, our aim of clinical examination was to exclude pathologies other than aseptic loosening.

2.1.3. Imaging

Standard plain film radiographs were obtained in all patients in our series including weight bearing anterior-posterior, lateral, skyline, and long leg alignment views. These were scrutinised for alignment, component sizing and position, component loosening, osteolysis, and polyethylene wear. Radiological signs of component loosening include a progressive increase in a radiolucent line, change in component position, fracture, or traction around the tip of a stemmed component. SPECT-CT was not performed as a routine screening tool in all patients assessed, but sparingly in patients where aseptic loosening was suspected but not definitively confirmed through a combination of clinical evaluation, clinical examination, and plain radiographs.

2.1.4. Laboratory investigations

All patients underwent a standard series of serological investigations including CRP and WCC. Our inclusion criteria stipulated that a normal laboratory reference range for the WCC and CRP must be present at time of requesting a SPECT-CT scan. In keeping with our inclusion criteria (i.e. infection not suspected clinically nor serologically) joint aspiration and synovial fluid analysis was not performed prior to SPECT-CT in any cases.

2.2. SPECT-CT

SPECT-CT was performed after intravenous injection of ^{99m}Tc HMDP (Osteocis, Curium Pharma, London UK). All patients received doses in the range 550–600 MBq. A GE Optima hybrid SPECT-CT system was used, with dual gamma camera detectors fitted with Low Energy High Resolution collimators and low-dose integrated CT system. Perfusion and blood pool images were acquired at the time of injection. Delayed bone phase imaging was performed for all patients at 2 h after injection. Dual anterior and posterior whole-body scanning was performed at 200 s/pixel, followed by SPECT-CT acquisition covering the knee prosthesis. The SPECT scans were acquired in a 128x128 matrix over 60 steps at 6^{o} intervals, 25 s per step; then CT of the same volume. Low dose CT was used with tube current at 30 mA and voltage at 120 kV. Helical scanning at slice thickness 2.5 mm, spacing 2.5 mm, pitch 1.25, reconstructed into a 512x512 image matrix using a proprietary Bone reconstruction kernel. The SPECT image data was reconstructed on a GE Xeleris workstation using an OSEM iterative process. Attenuation correction was applied using the CT data as an attenuation map. SPECT and CT image sets were then fused for viewing. Adapted skeletal metal artifact reduction SPECT-CT acquisition and post processing were not performed. The embarked CT images from the combined SPECT-CT were occasionally used as a co-diagnostic tool, but not routinely.

Our nuclear medicine musculoskeletal radiologists reported imaging as per their routine practice (i.e. a detailed analysis of radionuclide uptake interpreted in the context of their training and experience, followed by a clinical conclusion to aid the surgeon's decision making). The criteria for perfusion and blood pool phase images were based on our radiologist's visual assessment. Given the low dose CT imaging element utilised and assessment of bone stock and integrity was possible, together with effusions. We did not attempt to quantify limb alignment profiles. The different components of SPECT-CT were all incorporated into the radiologist's evaluation and used to inform on overall impression. A greater weighting was given to the SPECT-CT findings over the pure CT element.

Our radiologists classified their diagnostic suspicion of aseptic prosthetic loosening for each component (no evidence/possible evidence/clear evidence), as well an overall impression of the scan (normal/possibly abnormal/ definitely abnormal.) We provide example imaging of cases we considered as negative, equivocal, and positive for prosthetic loosening (Figure 1). We were aware that this study design would likely produce non-dichotomous indeterminate outcomes that would be challenging to interpret, however the reality is that reporting of nuclear medicine imaging in this context is not supported by quantitively validated tools but is based on the radiologist's overall impression.

2.3. After SPECT-CT

Details of the surgeon's diagnostic suspicion for aseptic loosening following SPECT-CT, together with their intention to perform revision surgery were prospectively collected in our clinic using a bespoke electronic data collection form. All cases were discussed in a Multi-Disciplinary Team meeting. Where revision surgery was performed, intraoperative details were linked to the patients' study database record, including the presence or absence of component loosening, together with the procedure performed. We provide a minimum of 24 months follow up data in all cases we present.

2.4. Data storage and analysis

All data was managed in our institutions REDCap database to allow surveillance and monitoring. This is a secure web application for building and managing secure online databases. Our system servers were based on the mainframe server of the Royal Devon University Hospitals NHS trust.

2.5. Data analysis

We considered three scenarios in the analysis of our series:

- Scenario A – Possible SPECT-CT scintigraphic evidence of prosthetic loosening and clear SPECT-CT scintigraphic evidence of prosthetic loosening combined (i.e. equivocal SPECT-CT results considered as TEST POSITIVE).
- Scenario B – Possible SPECT-CT scintigraphic evidence of prosthetic loosening and no SPECT-CT scintigraphic evidence of prosthetic loosening combined (i.e. equivocal results considered as TEST NEGATIVE).

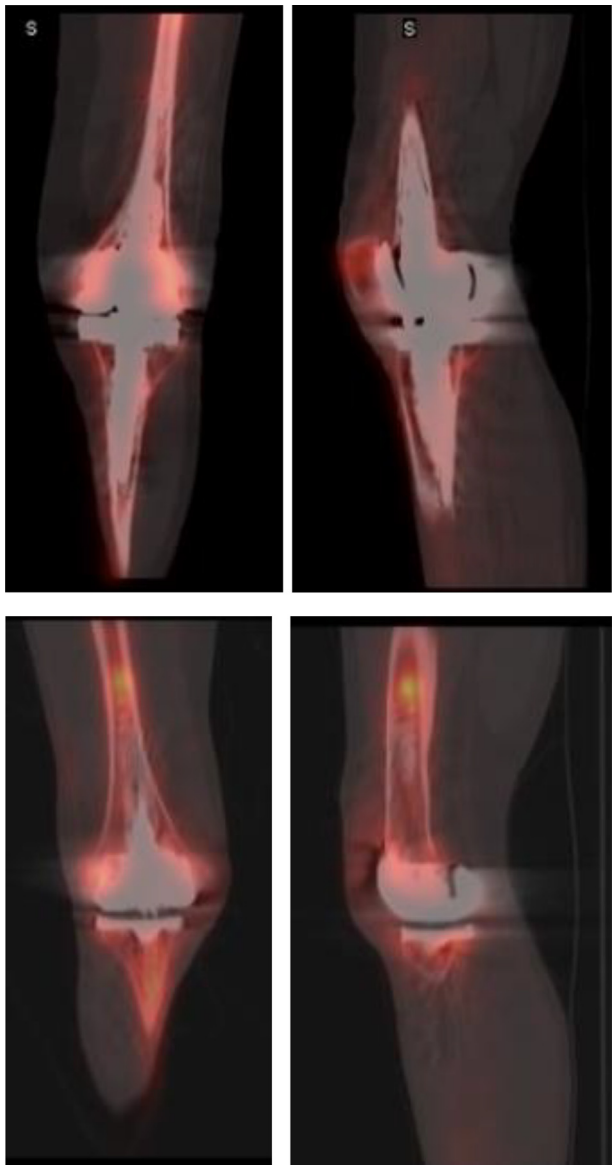

Figure 1. Example SPECT-CT images of cases considered by our radiologists are being negative, equivocal, and positive for prosthetic loosening.

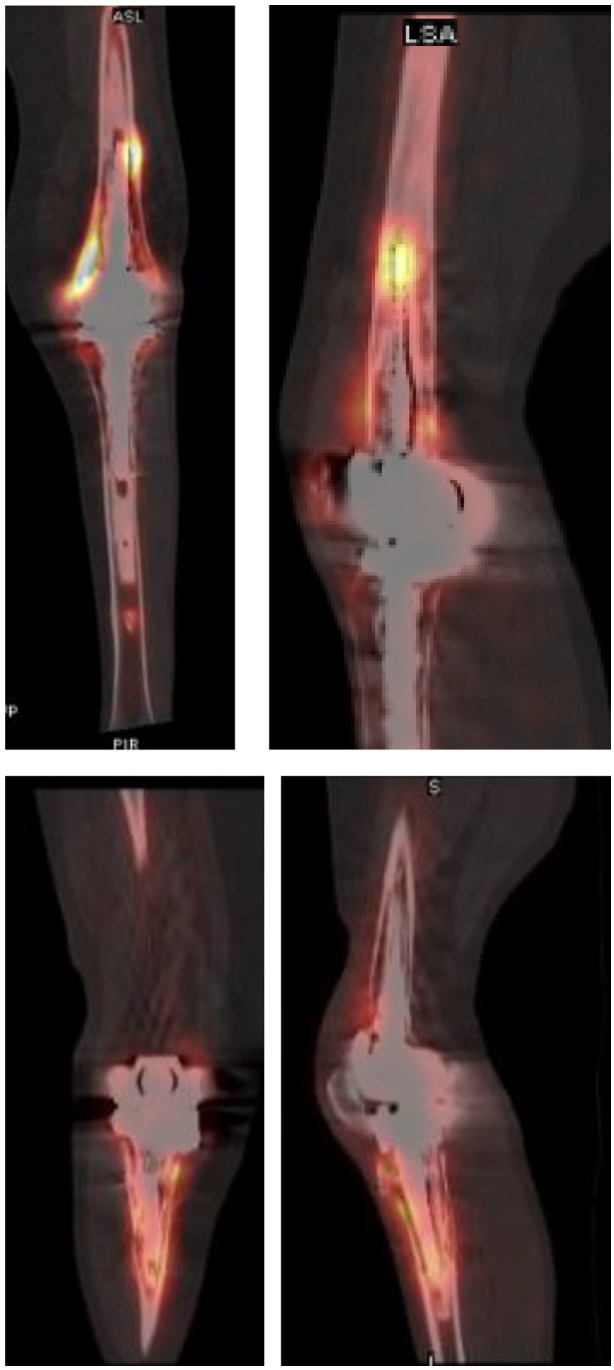

Fig. 1 (*continued*)

- Scenario C – Cases with clear SPECT-CT scintigraphic findings confirming or excluding prosthetic loosening (i.e. equivocal results excluded).

Diagnostic test calculations were carried out for each scenario, and Clopper-Pearson confidence intervals determined using the online calculator EPITOOLS (epitools.ausvet.com.au). The following assumptions were made:

1. Measures were based on individual components and not per patient. Femoral and tibial components were considered independently, with each patient contributing two data points (i.e. radiologists' impression of femoral component loosening and radiologists' impression of tibial component loosening).

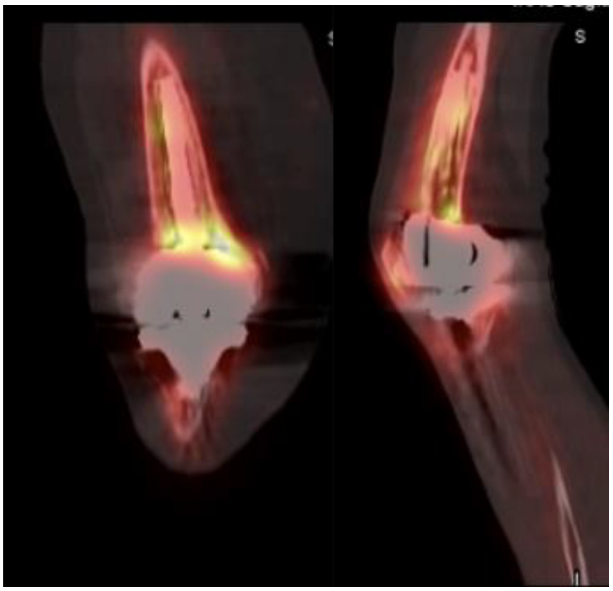

Fig. 1 (*continued*)

2. Patients who were planned for revision surgery but did not receive it were excluded.
3. Intraoperatively confirmed component loosening at revision surgery was used as the gold standard positive test for comparison.
4. If revision surgery was not performed at 24 months follow up absence of component loosening was assumed.

All other reported confidence intervals are that of Clopper-Pearson exact and were calculated using the online calculator EPITOOLS (epitools.ausvet.com.au). The association between Intention to perform revision surgery and SPECT-CT findings was tested using the Jonckheere-Terpstra test.

2.6. Ethical approval

Local Institutional Board Review of our study protocol in October 2017 deemed that our study constituted an observation of practice, and that ethical approval was not mandated.

3. Results

3.1. Demographics

30 patients were investigated with a SPECT-CT during a four-year period (Table 1). Patient age at time of investigation was: median = 70 years (IQR = 60–79), and range = 54–88 years. 63% were female (n = 19) and 37% were male (n = 11). Implant ages at time of investigation had a bimodal distribution and were: median = 5 years (IQR = 4–10), range = 3–14 years (Figure 2). All patients had a cemented stemmed prostheses with a patella resurfacing. Seven patients had a varus-valgus Total Stabilised constrained implant system, and 23 had a Hinge constrained implant system. Although not part of our selection criteria, all cases were revision TKR's, with none having been performed primarily to treat a fracture or ligamentous insufficiency. All patients had a laboratory normal range WCC and CRP at time of referral for SPECT-CT. Implant details, pre-scan intention to perform revision surgery, SPECT-CT report summary, post scan proposed final diagnosis, post-scan intention to perform revision surgery, and if revision was performed at 24 months follow up are presented in Table 1.

3.2. Diagnosis

The radiologists SPECT-CT report summary conclusions were: 7% (95% CI: 0.0–0.2) normal investigation (n = 2), 50% (95% CI: 0.3–0.7) possibly abnormal investigation (n = 15), and 43% (95% CI: 0.3–0.6) definitely abnormal investigation (n = 13). Our surgeons suspected aseptic loosening in all cases, with 43% (95% CI: 0.5–0.9) having clear evidence of this reported on SPECT-CT by our radiologists (10/13) (Table 1). In 37% (95% CI: 0.2–0.6) of patients the surgeons primary suspected diagnosis

Table 1
Implant details, intention to perform revision surgery, SPECT-CT report summary, post scan proposed final diagnosis, and intention to perform revision.

PRE-SCAN DETAILS				SPECT-CT DETAILS		POST-SCAN DETAILS						
ID	Implant details	Age of implant (years)	Intention to perform revision surgery	Report Summary	Report Details	Proposed diagnosis	Intention to perform revision surgery	Outcome	Change in diagnosis	Change in intention to perform revision surgery	Revision surgery performed	Intraoperative details
REVISION SURGERY PERFORMED												
1	Stryker Modular Rotating Hinge	3	YES	Definitely abnormal	Possible evidence of femoral component loosening.Clear evidence of tibial component loosening.	Aseptic loosening of tibial component.	YES	List for revision	NO	NO	YES	Femoral component well fixed and not revised. Tibial component loose and revised. 5/5 intraoperative tissue samples negative for infection.
2	Stryker Triathlon TS	3	YES	Definitely abnormal	Possible evidence of femoral component loosening.Clear evidence of tibial component loosening.	Aseptic loosening of tibial component.	YES	List for revision	NO	NO	YES	Femoral component well fixed and not revised. Tibial component loose and revised. 5/5 intraoperative tissue samples negative for infection.
3	Stanmore LINK Hinge	3	YES	Definitely abnormal	Clear evidence of femoral component loosening.Possible evidence of tibial component loosening.	Aseptic loosening of femoral component.	YES	List for revision	NO	NO	YES	Femoral component loose and revised. Tibial component loose and revised. 5/5 intraoperative tissue samples negative for infection.
4	Stanmore LINK Hinge	4	NO	Possibly abnormal	Possible evidence of femoral component loosening.Clear evidence of tibial component loosening.	Aseptic loosening of tibial component.	YES	List for revision	NO	YES	YES	Femoral component well fixed and not revised. Tibial component loose and revised. 5/5 intraoperative tissue samples negative for infection.
5	Stanmore LINK Hinge	4	NO	Definitely abnormal	Possible evidence of femoral component loosening.Possible evidence of tibial component loosening, but clear evidence of stress fracture around tibial stem.	Fracture around tibial component.	YES	List for fixation of fracture.	YES	YES	YES	Femoral component well fixed and not revised.Plating performed around tibial stem periprosthetic fracture.No components revised. 5/5 intraoperative tissue samples negative for infection.

(*continued on next page*)

Table 1 (*continued*)

PRE-SCAN DETAILS				SPECT-CT DETAILS		POST-SCAN DETAILS						
ID	Implant details	Age of implant (years)	Intention to perform revision surgery	Report Summary	Report Details	Proposed diagnosis	Intention to perform revision surgery	Outcome	Change in diagnosis	Change in intention to perform revision surgery	Revision surgery performed	Intraoperative details
6	Stryker Triathlon TS	4	YES	Definitely abnormal	No evidence of femoral component loosening.Clear evidence of tibial component loosening.	Aseptic loosening of tibial component.	YES	List for revision	NO	NO	YES	Femoral component well fixed but revised. * Tibial component loose and revised. 5/5 intraoperative tissue samples negative for infection. * due to change of implant system.
7	Stryker Triathlon TS	4	NO	Definitely abnormal	Clear evidence of femoral component loosening. No evidence of tibial component loosening.	Aseptic loosening of femoral component.	YES	List for revision	NO	YES	YES	Femoral component loose and revised. Tibial component well fixed and not revised. 5/5 intraoperative tissue samples negative for infection.
8	Stanmore LINK Hinge	4	YES	Definitely abnormal	Clear evidence of femoral component loosening. No evidence of tibial component loosening.	Aseptic loosening of femoral component.	YES	List for revision	NO	NO	YES	Femoral component loose and revised. Tibial component well fixed and not revised. 5/5 intraoperative tissue samples negative for infection.
9	Stanmore LINK Hinge	4	NO	Definitely abnormal	Clear evidence of femoral component loosening. No evidence of tibial component loosening.	Aseptic loosening of femoral component.	YES	List for revision	NO	YES	YES	Femoral component loose and revised. Tibial component well fixed and not revised. 5/5 intraoperative tissue samples negative for infection.
10	Johnson and Johnson SROM hindge	6	NO	Definitely abnormal	Clear evidence of femoral component loosening.Clear evidence of tibial component loosening.	Aseptic loosening of both components.	YES	List for revision	NO	YES	YES	Femoral component loose and revised. Tibial component loose and revised. 5/5 intraoperative tissue samples negative for infection.
11	Stanmore LINK Hinge	12	YES	Possibly abnormal	Clear evidence of femoral component loosening. Possible evidence of tibial component loosening.	Aseptic loosening of femoral component.	YES	List for revision	NO	NO	YES	Femoral component loose and revised. Tibial component well fixed and not revised.5/5 intraoperative tissue samples negative for infection.

Table 1 (*continued*)

PRE-SCAN DETAILS				SPECT-CT DETAILS		POST-SCAN DETAILS						
ID	Implant details	Age of implant (years)	Intention to perform revision surgery	Report Summary	Report Details	Proposed diagnosis	Intention to perform revision surgery	Outcome	Change in diagnosis	Change in intention to perform revision surgery	Revision surgery performed	Intraoperative details
REVISION SURGERY NOT PERFORMED												
12	Stryker Triathlon TS	3	NO	Possibly abnormal	No evidence of femoral component loosening. No evidence of tibial component loosening.	Pain of unknown origin	NO	Referral to pain team	YES	NO	NO – not planned	
13	Stryker Modular Rotating Hinge	3	YES	Definitely abnormal	Possible evidence of femoral component loosening.Clear evidence of tibial component loosening.	Aseptic loosening of tibial component.	YES	List for revision	NO	NO	NO – patient not fit for surgery	
14	Stryker Triathlon TS	4	NO	Possibly abnormal	No evidence of femoral component loosening. No evidence of tibial component loosening.	Pain of unknown origin	NO	Discharge	YES	NO	NO – not planned	
15	Stanmore LINK Hinge	4	NO	Possibly abnormal	No evidence of femoral component loosening. No evidence of tibial component loosening.	Pain of unknown origin	NO	Discharge	YES	NO	NO – not planned	
16	Stanmore LINK Hinge	4	NO	Definitely abnormal	Possible evidence of femoral component loosening.Possible evidence of tibial component loosening.	Pain of unknown origin	NO	Discharge	YES	NO	NO – not planned	
17	Stanmore LINK Hinge	5	NO	Possibly abnormal	No evidence of femoral component loosening.No evidence of tibial component loosening.Possible evidence of stress at tip of femoral stem.	Stress Response at tip of femoral stem	NO	Discharge	YES	NO	NO – not planned	
18	Stanmore LINK Hinge	5	NO	Possibly abnormal	Possible evidence of femoral component loosening.Possible evidence of tibial component loosening.	Pain of unknown origin	NO	Discharge	YES	NO	NO – not planned	
19	Stanmore LINK Hinge	5	NO	Possibly abnormal	No evidence of femoral component loosening.Possible evidence of tibial component loosening.	Pain of unknown origin	NO	Discharge	NO	NO	NO – not planned	
20	Stanmore LINK Hinge	6	YES	Definitely abnormal	Possible evidence of femoral component loosening.Clear evidence of tibial component loosening.	Pain of unknown origin	NO	Discharge	YES	YES	NO – patient not fit for surgery	
21	Stanmore LINK Hinge	6	NO	Definitely abnormal	No evidence of femoral component loosening.Clear evidence of tibial component loosening.	Pain of unknown origin	NO	Discharge	NO	NO	NO – patient declined surgery	

(*continued on next page*)

Table 1 (*continued*)

PRE-SCAN DETAILS				SPECT-CT DETAILS		POST-SCAN DETAILS						
ID	Implant details	Age of implant (years)	Intention to perform revision surgery	Report Summary	Report Details	Proposed diagnosis	Intention to perform revision surgery	Outcome	Change in diagnosis	Change in intention to perform revision surgery	Revision surgery performed	Intraoperative details
22	Stanmore LINK Hinge	7	NO	Normal	No evidence of femoral component loosening. No evidence of tibial component loosening.	Pain of unknown origin	NO	Discharge	YES	NO	NO – not planned	
23	Stanmore LINK Hinge	7	NO	Possibly abnormal	Possible evidence of femoral component loosening.Possible evidence of tibial component loosening.	Pain of unknown origin	NO	Discharge	YES	NO	NO – not planned	
24	Stryker Modular Rotating Hinge	10	NO	Possibly abnormal	Possible evidence of femoral component loosening. Possible evidence of tibial component loosening.Possible evidence of stress at tip of femoral stem.	Stress Response at tip of femoral stem	NO	Discharge	YES	NO	NO – not planned	
25	Stanmore LINK Hinge	12	NO	Possibly abnormal	Possible evidence of femoral component loosening.Possible evidence of tibial component loosening.	Pain of unknown origin	NO	Discharge	YES	NO	NO – not planned	
26	Stanmore LINK Hinge	12	NO	Possibly abnormal	Possible evidence of femoral component loosening.Possible evidence of tibial component loosening.	Pain of unknown origin	NO	Discharge	YES	NO	NO – not planned	
27	Stryker Modular Rotating Hinge	12	NO	Possibly abnormal	Possible evidence of femoral component loosening. Possible evidence of tibial component loosening.Clear evidence of stress at tip of tibial stem.	Stress responses tip of tibial stem	NO	Referral to pain team	YES	NO	NO – not planned	
28	Stanmore LINK Hinge	13	NO	Possibly abnormal	Possible evidence of femoral component loosening.Possible evidence of tibial component loosening.	Pain of unknown origin	NO	Referral to pain team	YES	NO	NO – not planned	
29	Stanmore LINK Hinge	14	NO	Normal	No evidence of femoral component loosening. No evidence of tibial component loosening.	Pain of unknown origin	NO	Discharge	YES	NO	NO – not planned	
30	Stryker Modular Rotating Hinge	14	YES	Possibly abnormal	No evidence of femoral component loosening.Possible evidence of tibial component loosening.	Pain of unknown origin	NO	Discharge	YES	YES	NO – not planned	

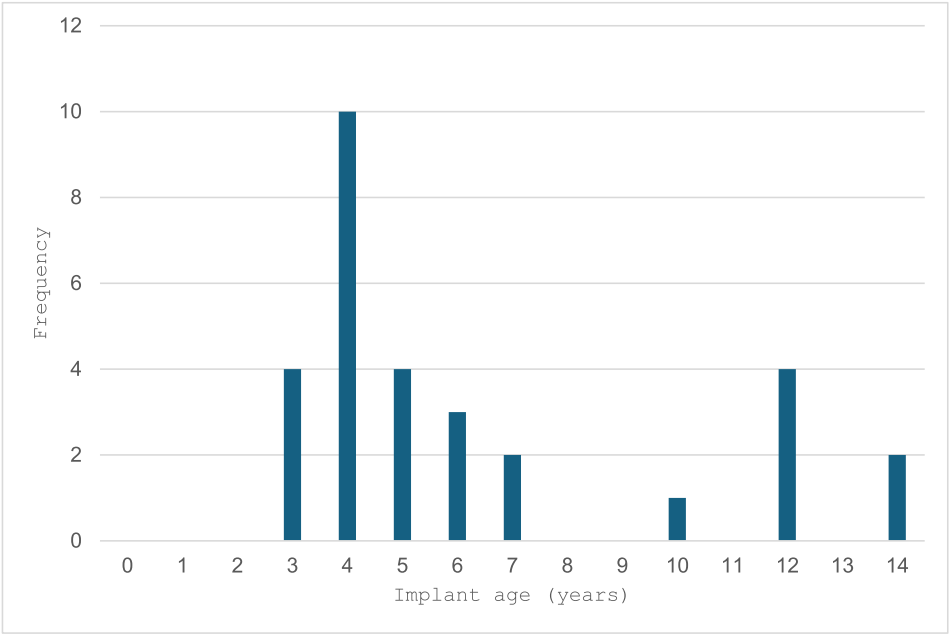

Figure 2. Frequency of implant age at time of investigation with SPECT-CT.

remained that of aseptic loosening following (11/30). In 13% (95% CI: 0.0–0.3) the diagnosis changed from aseptic loosening to an alternative positive diagnosis (4/30), of which one lead to surgical intervention (patient 5). In 50% (95% CI: 0.3–0.7) a diagnosis of pain of unknown origin (i.e. aseptic loosening excluded, and no other diagnosis apparent on SPECT-CT) was made (15/30) (Table 2).

3.3. Intention to perform revision surgery

In 23% (95% CI: 0.1–0.4) the surgeon's intention to perform revision surgery following SPECT-CT changed (7/30) (Table 3): NO → YES (n = 5), and YES → NO (n = 2). The association between intention to perform revision surgery and SPECT-CT findings was evaluated utilising the Jonckheere-Terpstra test, which showed a highly significant linear trend (p = 0.0004, standard error = 42.1, z = 3.5).

Intentions to perform revision surgery according to the radiologist's overall summary were:

Normal SPECT-CT – 0% (95% CI: 0.0–0.8) intention to revise (0/2).
Possibly abnormal SPECT-CT – 13% (95% CI: 0.0–0.4) intention to revise (2/15).
Definitely abnormal SPECT-CT – 77% (95% CI: 0.5–0.9) intention to revise (10/13).

3.4. Revision surgery

At 24 months follow up 77% (95% CI: 0.5–0.9) of patients with "clear evidence" of aseptic loosening reported by our radiologists had undergone revision surgery (10/13) (Table 4). Three patients the surgeon intended to perform revision surgery for did not receive this. Two were deemed not fit for revision surgery, and one declined revision surgery. Intention to perform revision surgery had not changed in any cases at a minimum of 24 months follow up.

3.5. Diagnostic test analysis

We present three scenarios to allow both inclusion and exclusion of equivocal test data (Table 5).

We consider the most pragmatic scenario to be the situation where equivocal uptake as reported by our radiologists in the context of prosthetic loosening is considered "test negative" (scenario B – Table 5).

In this group we report a test sensitivity of 90.9% (95% CI: 0.6–1.0), a specificity of 100% (95% CI: 0.9–1.0), a positive predictive value of 100% and a negative predictive value of 97.7%.

Table 2
Change in surgeons primary diagnosis following SPECT-CT.

Confirmed suspected diagnosis (n = 11)	New diagnosis (n = 19)
Component loosening (n = 11)	Periprosthetic fracture (n = 1) Stress response at stem tip (n = 3) Pain of unknown origin (n = 15)

Table 3
Change in intention to perform revision surgery after SPECT-CT.

	Intention to perform revision surgery AFTER SPECT-CT	
Intention to perform revision surgery BEFORE SPECT-CT	YES	NO
YES	7	2
NO	5	16

Table 4
Comparison of radiologists' suspicion of component loosening and intra-operative findings in cases that underwent revision surgery.

ID	Radiologists SPET-CT report	Intra-operative findings	Intra-operatively confirmed SPECT-CT suspicion of aseptic loosening presence	Was SPECT-CT useful in planning single component revision surgery?
1	Possible evidence of femoral component loosening.	Femoral component well fixed and not revised.	EQUIVOCAL	YES
	Clear evidence of tibial component loosening.	Tibial component loose and revised.	YES	
2	Possible evidence of femoral component loosening.	Femoral component well fixed and not revised.	EQUIVOCAL	YES
	Clear evidence of tibial component loosening	Tibial component loose and revised.	YES	
3	Clear evidence of femoral component loosening.	Femoral component loose and revised.	YES	NO
	Possible evidence of tibial component loosening.	Tibial component loose and revised.	EQUIVOCAL	
4	Possible evidence of femoral component loosening.	Femoral component well fixed and not revised.	EQUIVOCAL	YES
	Clear evidence of tibial component loosening.	Tibial component loose and revised.	YES	
6	No evidence of femoral component loosening.	Femoral component well fixed but revised. *	YES	NO(*Would have been useful if not changing implant system)
	Clear evidence of tibial component loosening.	Tibial component loose and revised.	YES	
7	Clear evidence of femoral component loosening.	Femoral component loose and revised.	YES	YES
	No evidence of tibial component loosening.	Tibial component well fixed and not revised.	YES	
8	Clear evidence of femoral component loosening.	Femoral component loose and revised.	YES	YES
	No evidence of tibial component loosening.	Tibial component well fixed and not revised.	YES	
9	Clear evidence of femoral component loosening.	Femoral component loose and revised.	YES	YES
	No evidence of tibial component loosening.	Tibial component well fixed and not revised.	YES	
10	Clear evidence of femoral component loosening.	Femoral component loose and revised.	YES	NO(Both components loose)
	Clear evidence of tibial component loosening.	Tibial component loose and revised.	YES	
11	Clear evidence of femoral component loosening.	Femoral component loose and revised.	YES	YES
	Possible evidence of tibial component loosening.	Tibial component well fixed and not revised.	EQUIVOCAL	

3.6. Clinical value

In 70% (95% CI: 0.3–0.9) of cases where revision surgery was performed for aseptic loosening SPECT-CT provided information that guided pre-operative planning with regards single component or both component revision surgery (7/10). This would have also been the case for an additional patient if the requirement to change TKR system was not present (patient 6). In the only case where radiologists reported clear evidence of component loosening of both the femoral and tibial components (patient 11), both components were found to be grossly loose intraoperatively and were revised.

Table 5
Diagnostic Test Calculation analysis of SPECT-CT in detecting component loosening in patients with suspected prosthetic loosening who were potentially eligible to undergo revision surgery.

Scenario A – Possible SPECT-CT scintigraphic evidence of prosthetic loosening and clear SPECTCT scintigraphic evidence of prosthetic loosening combined (i.e. equivocal SPECT-CT results considered as TEST POSITIVE).

			CONDITION	
			Component looseningPRESENT	Component looseningABSENT
T	**TEST POSITIVE**	Revision performed	11	7
E	*"Clear evidence of component loosening"*	Revision not performed	0	18
S	*"Possible evidence of component loosening"*	**TOTAL**	**11**	**25**
T	**TEST NEGATIVE**	Revision performed	0	4
	"Normal SPECT-CT"	Revision not performed	0	14
		TOTAL	**0**	**18**

SENSITIVITY = 100.0% (95% CI: 0.7–1.0)
SPECIFICITY = 41.9% (95% CI: 0.3 – 0.6)
POSITIVE PREDECTIVE VALUE = 30.6%
NEGATIVE PREDICTIVE VALUE = 100.0%.

Scenario B – Possible SPECT-CT scintigraphic evidence of prosthetic loosening and no SPECT-CT scintigraphic evidence of prosthetic loosening combined (i.e. equivocal results considered as TEST NEGATIVE).

			CONDITION	
			Component looseningPRESENT	Component looseningABSENT
T	**TEST POSITIVE**	Revision performed	10	0
E	*"Clear evidence of component loosening"*	Revision not performed	0	0
S		**TOTAL**	**10**	**0**
T	**TEST NEGATIVE**	Revision performed	1	11
	"Normal SPECT-CT"	Revision not performed	0	32
	"Possible evidence of component loosening"	**TOTAL**	**1**	**43**

SENSITIVITY = 90.9% (95% CI: 0.6–1.0)
SPECIFICITY = 100% (95% CI: 0.9–1.0)
POSITIVE PREDECTIVE VALUE = 100.0%
NEGATIVE PREDICTIVE VALUE = 97.7%.

Scenario C – Cases with clear SPECT-CT scintigraphic findings confirming or excluding prosthetic loosening (i.e. equivocal results excluded).

			CONDITION	
			Component looseningPRESENT	Component looseningABSENT
T	**TEST POSITIVE**	Revision performed	10	0
E	*"Clear evidence of component loosening"*	Revision not performed	0	0
S		**TOTAL**	**10**	**0**
T	**TEST NEGATIVE**	Revision performed	0	4
	"Normal SPECT-CT"	Revision not performed	0	14
		TOTAL	**0**	**18**

SENSITIVITY = 100% (95% CI: 0.7–1.0)
SPECIFICITY = 100% (95% CI: 0.8–1.0)
POSITIVE PREDECTIVE VALUE = 100%
NEGATIVE PREDICTIVE VALUE = = 100%.

4. Discussion

The aim of this study was to prospectively evaluate the role of SPECT-CT in the diagnosis of single component aseptic loosening in patients with suspected loosening of a problematic cemented stemmed constrained implant TKR. We found that in nearly half of our cases (13/30) that SPECT-CT confirmed the surgeons suspected diagnosis of aseptic loosening, and in the other half (15/30) the suspected diagnosis of aseptic loosening was excluded. In all cases where revision surgery was performed, and SPECT-CT was reported as clearly positive or negative for component loosening, SPECT-CT was useful in aiding pre-operative planning of single component versus both component revision and was representative of the intraoperative findings in all.

4.1. How do our results fit into the current literature/evidence base

The use of SPECT-CT in the evaluation of a problematic TKR has been reported [13,16,17,19,8], and we present the first prospective series investigating the use of SPECT-CT in the evaluation of suspected aseptic loosening in stemmed implant constrained system TKR. The natural history of periprosthetic radionuclide tracer uptake has not been clearly defined, nor the existence of what might be considered normal periprosthetic uptake in this patient group. To provide feasibility data in this area a validated form of quantitative or semi quantitative measure of periprosthetic radionuclide tracer uptake would be required, but this does not currently exist. The increased forces at the implant-cement-bone interface of stemmed implant constrained system TKR in comparison with less constrained systems also calls this into question the existence of what could be termed normal periprosthetic radionuclide uptake.

There are no comparable series to our own. Although Hirschmann et al. . . reported that SPECT-CT changed the diagnosis and treatment in 84 patients with persistent pain after TKR [9],their series consisted of patients with primary TKR's, many uncemented implants, and included cases investigated at only six months following index surgery. A systematic review and meta-analysis of the role of SPECT-CT in the evaluation of a painful TKR has been recently reported [20]. From eight heterogenous level three studies (none of which included stemmed implant constrained system TKR's) the authors conclude that SPECT-CT as a diagnostic test has an overall sensitivity 86% with a specificity of 90% *"in diagnosing the source of pain in painful, noninfected knees after knee arthroplasty*." They conclude that *"SPECT-CT has a high sensitivity and specificity in identifying the source of pain in non-infected knees after knee arthroplasty*." Although not directly comparable we found that where our radiologists reported component loosening as definitively present or absent that SPECT-CT had a sensitivity of 100% and specificity of 100% in the diagnosis of aseptic prosthetic loosening (Table 5 – scenario C). It should however be noted that half of cases in our series had an indeterminate investigation, which may only add to the uncertainty in these challenging patients. We remain uncertain as to the significance increased areas of radionuclide uptake observed in patients with an equivocal investigation. In this series we have only considered the diagnosis of aseptic loosening, however all patients were symptomatic in our series, and other diagnosis are possible. Our diagnostic test calculations have assumed that increased radionuclide uptake that cannot be specifically explained by aseptic loosening represents a false positive investigation, but we are unable to definitively exclude other causative diagnosis. We have no asymptomatic control patients for comparison.

4.2. Study strengths

All data was collected prospectively using our bespoke imaging request order form and follow up database in such a way that this could not be subsequently altered. Our radiologists were provided with higher quality clinical information than might be the case in routine clinical practice. We describe a clear inclusion criterion of cases. By not including cases within three years of index surgery we have minimised the possibility of patients reported symptoms and any increased radionuclide uptake being purely post-surgical. We provide complete follow up to at least 24 months and confirm that reported outcomes are correct to this point.

4.3. Study weaknesses

This study has several limitations and caution should be used when interpreting its generalisability. Although our study represents practice in a large referral centre, due to its small size our data is susceptible to bias and error, and more prone to variability in comparison with larger series. Calculated test accuracy changes according to the prevalence of a particular disease or condition in a certain population, and therefore our findings are only generalisable to our specialist tertiary referral unit pre-selected group of patients and surgeons (i.e. the tip of the iceberg group of patients).

The diagnostic test calculations we present should be interpreted with caution. The issues include:

1. There is no gold standard for diagnosing component loosening against which we can truly compare. We have used our surgeons intraoperatively reported findings to confirm or refute a diagnosis of component loosening, but this is prone to bias and variability. Providing a reliable and reproducible definition for intraoperatively confirmed component loosening is challenging. For example, is a component defined as being loose if it can be removed by hand, with two taps with an osteotome, or following 45 min of chipping away at bone cement?
2. Equally we have no gold standard of the exclusion of component loosening for comparison. We have assumed that in 19 patients that prosthetic loosening was not present on the basis that revision surgery had not been performed during 24 month follow up period, but this may be incorrect.
3. Half of the cases (15/30) had a non-positive/non-negative outcome with respect to the diagnosis of component loosening on SPECT-CT..

We have described that the reporting of SPECT-CT is based on radiologists' overall impression of the combined CT and SPECT-CT imaging, and not a quantitively validated system. There will have been inevitable variation between radiologists in threshold for considering increased radionuclide uptake to be abnormal, or to state that this is of sufficient magnitude to be pathological and reach a diagnostic threshold. This is compounded by the relative rarity of application of SPECT-CT in the investigation of a problematic TKR.

We have not included any cases within three years of index surgery, but the possibility remains any increased radionuclide uptake observed could be purely post-surgical or "physiological" due to loading at the implant-cement-bone interface, especially in the first 5 years following surgery. We have not included cases were a clinical suspicion of infection existed, and report that all cases in our series had a normal laboratory range WCC and CRP. Our view is that this combination of low clinical suspicion and serological factors make infection unlikely, we acknowledge this does not exclude infection absolutely.

4.4. Will results change clinical practice

Reducing the numbers of revision procedures is a key long term health economic target. Understanding the cause of pain in the knee region following TKR surgery is imperative before embarking upon complicated and expensive revision surgery and avoids unnecessary and expensive surgery in cases where pain is generated outside of the knee. The "SPECIFIC" diagnostic tool has been produced to help surgeons focus on key diagnoses [18]. This is particularly important in patients with stemmed implant constrained system TKR's, and revising these implants is a massive surgical insult, with an increased risk of morbidity and mortality. We report that SPECT-CT had a high accuracy in the detection of intraoperatively confirmed aseptic loosening, and that this investigation was useful in aiding the surgeons preoperative planning with regards single component versus both component revision. We would however caution against determining the indication for revision surgery based on the appearances of increased radionuclide uptake on a SPECT-CT, and indeed a report of an abnormal investigation in isolation. Half of the scans in our series were equivocal and could lead the surgeon taking a non-operative observational approach if the scintigraphic findings are not over interpreted.

5. Conclusion

When positive SPECT-CT was useful in determining single component revision in cases where revision surgery was performed. Normal SPECT-CT may have a negative predictive value in selected cases of diagnostic uncertainty; however, overall half of our series had a possibly abnormal or equivocal investigation, which may only add to uncertainty in these challenging patients. Further prospective diagnostic trials of the failing TKR, case-control designed, assessing SPECT-CT imaging criteria array performance, should be undertaken.

CRediT authorship contribution statement

Daniel Hill: Writing – review & editing, Writing – original draft, Resources, Project administration, Methodology, Formal analysis, Data curation. **Patrick Rogers:** Writing – review & editing, Writing – original draft, Investigation. **Jonathan Phillips:** Writing – review & editing, Writing – original draft, Supervision, Investigation, Formal analysis, Conceptualization. **Ben Waterson:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Investigation, Formal analysis. **Andrew D. Toms:** Writing – review & editing, Writing – original draft, Validation, Supervision, Methodology, Investigation, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary material to this article can be found online at https://doi.org/10.1016/j.knee.2024.10.016.

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