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Bloodpool SPECT as part of bone SPECT/CT in painful total knee arthroplasty (TKA): validation and potential biomarker of prosthesis biomechanics

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Abstract

Purpose To compare bloodpool SPECT with planar imaging in bone SPECT/CT of painful total knee arthroplasty (TKA) with respect to inter-rater agreement, confidence, prosthesis outcome, and biomechanical functioning.

Methods Retrospective study of bloodpool SPECT and planar control images. Four raters used the validated Bruderholz scheme and a 5-point scale to grade uptake. Inter-rater agreement and overall confidence scores were calculated. Variable cluster analysis was performed to identify patterns of uptake, and associations between patterns and prosthesis outcome and biomechanical functioning were examined.

Results In all, 55 knees in 43 patients were analyzed (median follow-up 17 months; revision rate 21.8%). SPECT significantly improved inter-rater agreement in 24% of regions (all $P < 0.05$) and overall confidence by 20% ($P < 0.001$). Regional uptake cluster analysis showed improved antero-posterior separation with SPECT, and distinct patterns associated with prosthesis survival in lateral femoral ($P = 0.041$) and medial tibial ($P < 0.001$) regions. The prognostic value of SPECT outperformed planar imaging for tibial ($P < 0.001$), patellar ($P = 0.009$), and synovial ($P = 0.040$) assessment. Internal femoral malrotation resulted in increased uptake in posteromedial ($P = 0.042$) and anterolateral ($P = 0.016$) femoral, and lateral patellar ($P = 0.011$) regions. Internal tibial malrotation increased uptake in posterolateral ($P = 0.026$) and posteromedial tibial ($P = 0.005$), and medial patellar regions ($P = 0.004$). Bloodpool SPECT improved the prognostic value of late-phase SPECT/CT for the assessment of the medial tibial region.

Conclusions Bloodpool SPECT outperforms planar assessment of painful TKAs and the identification of distinct uptake patterns make it a potentially clinically relevant biomarker of prosthesis survival and biomechanical functioning.

Keywords SPECT/CT · SPECT · Bloodpool · Bone scintigraphy · Total knee arthroplasty

Introduction

As a result of an ageing population, it is anticipated that the need for primary and revision total knee arthroplasty (TKA) in the United States will grow by 673% and 601% respectively between 2005 and 2030, with similar trends in Europe [1]. Even though TKA is accepted as a successful intervention for end-stage osteoarthritis, it is estimated that 20–30% of patients are not pain-free or satisfied after TKA [2]. A variety of causes can be responsible, ranging from septic loosening to aseptic mechanical intra-articular or extra-articular complications [3–6]. While overt instability, malpositioning, or acute infection can be diagnosed with clinical and first-line imaging, such as X-rays, the correct and timely identification of other frequent causes of recurrent pain remains challenging and may

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require advanced imaging techniques to select optimal patient management [7]. Radionuclide bone scintigraphy using technetium-99 m labeled bisphosphonates is a widely available and non-invasive imaging modality that with the introduction of hybrid SPECT/CT has been shown to be an important problem-solving tool in contemporary orthopedic decision-making [8]. In particular, bone SPECT/CT can be a valuable technique in the assessment of patients with recurrent pain after TKA. Over recent years, the group of Hirschmann and Rasch were able to link bone turnover uptake (BTU) patterns on late-phase bone SPECT/CT with the biomechanical functioning of the implant and causes of prosthesis failure, including the validation of a standardized localization method (the "Bruderholz" scheme) [9–12]. Moreover, the use of bone SPECT/CT in this population may also represent a dominant and cost-effective imaging strategy over CT and MRI using metal artifact reducing sequences (MARS) [13].

In addition to late-phase imaging, planar bloodpool acquisitions are routinely acquired as part of the bone scan technique and remain recommended for prosthesis assessment [14]. Yet, at this time it is unknown whether expanding the SPECT technique to early-phase imaging contributes additional information over planar assessment in TKA when using standardized localization methods. The potential advantage of SPECT bloodpool acquisitions is not limited to the more accurate localization of tracer uptake, due to the three-dimensional nature of the images and higher signal to background ratio, but also because of easier comparison of uptake with late-phase SPECT/CT [12].

The primary purpose of this study was to determine the inter-rater agreement and confidence when assessing bloodpool SPECT volumes compared with planar images. As secondary goals, we evaluated whether bloodpool SPECT data contained additional clinically relevant information relating to prosthesis outcome and biomechanical functioning.

Patients and methods

Imaging procedures

All patients received bone scintigraphy according to the guidelines of the European Association of Nuclear Medicine (EANM), consisting of a bloodpool acquisition and late-phase planar whole-body and SPECT/CT images of the knees [14]. Scans were acquired on a hybrid SPECT/CT system (Discovery NM/CT 670, GE Healthcare, Waukesha, WI, USA) consisting of a dual-head gamma camera, low-energy high-resolution parallel-hole collimators, and integrated 16-slice CT scanner. A step-and-shoot tomographic bloodpool acquisition was performed 2–7 min after injection, with the gamma camera positioned centered on the knees, with 60

projections of 7 s yielding a total acquisition time of 7 min. Anterior and posterior two-dimensional projections, serving as planar control image, were generated using a depth-shaded maximum intensity projection (MIP) algorithm from tomographic bloodpool data. No CT was performed during the bloodpool phase SPECT acquisition, as this would increase the overall patient radiation exposure. The acquisition settings for the late-phase SPECT 2–3 h after tracer injection were identical, except for a duration of 20 s per frame. For the CT part, the following tube settings were used: voltage 120 kVp, reference current 135 mAs. Images were reconstructed using adaptive statistical iterative reconstruction (ASIR) (512 × 512 matrix, planar pixel size of 0.98 mm, slice thickness and spacing 0.62 mm). All SPECT data were reconstructed using an ordered subset expectation maximization (OSEM) algorithm (Volumetrix MI, GE Healthcare): 128 × 128 matrix size, and a pixel size of 4.4 mm in every axis.

Image scoring

For each TKA, four nuclear medicine physicians with a varying number of years of clinical experience (range 5–24 years) assessed regional tracer uptake using the Bruderholz scheme on both bloodpool SPECT reconstructions and planar controls, using a 5-point scale (1 = definitely absent; 3 = equivocal; 5 = definitely present) [12]. An additional variable was added to capture synovial uptake. In addition, the overall confidence of localizing uptake on the bloodpool SPECT reconstructions and planar controls was scored using a 5-point scale (1 = not confident; 3 = equivocal; 5 = confident). Except for knowledge of the presence of painful knee arthroplasty, raters were unaware of the findings from clinical examination or other imaging modalities. Patient management and follow-up was based on all available clinical and imaging data as part of routine clinical practice but did not include bloodpool SPECT findings, as this analysis was performed at the time of this retrospective study.

Component alignment

The rotational alignment of the prostheses components was assessed on the CT part of the SPECT/CT study by measuring the angle between the anatomic transepicondylar axis (TEA) and the posterior bicondylar axis of the femoral prosthesis (PBCf), and the angle between the TEA and the posterior marginal axis of the tibial prosthesis (PMAt) [15, 16]. Positive angle values were used for internal rotation, and negative values denoted external component rotation. Alignment in the frontal plane of the mechanical and anatomic axis of the lower limb was retrieved from the medical file of the patient as measured on full-leg standing X-ray, if available. Valgus TKAs were assigned positive values, whereas negative angles represented varus knees.

Study endpoints

For the primary endpoint of inter-rater agreement, the study hypothesis was that the use of bloodpool SPECT results in higher agreement and confidence between raters because of better spatial localization of tracer uptake and image contrast. For the secondary endpoint of clinically relevant information captured by bloodpool SPECT imaging, the hypothesis was that the use of SPECT would contribute independent prognostic information on prosthesis survival compared to planar imaging. Prosthesis survival from the time of imaging was used as a composite and dummy end-point to assess the capability of bloodpool SPECT to capture clinically relevant conditions leading to revision surgery. While this endpoint precludes a formal analysis of diagnostic test characteristics for a specific root cause (because of a lack of optimal reference standard due to the retrospective nature of the study), it does represent an important clinical endpoint from a patient and healthcare provider perspective. In addition, the biomechanical functioning of the prosthesis as determined by component alignment was assessed as predictor of patterns of tracer uptake on bloodpool SPECT.

Statistical methods

For the primary endpoint, the agreement between raters was assessed using Gwet's method for multiple raters and multiple categories [17]. Differences in the agreement between SPECT reconstructions and planar control images were assessed by paired t-tests of the differences between correlated agreement coefficients [18]. A mixed linear model was estimated to compare the confidence scores between SPECT reconstructions and planar controls, accounting for the repeated (i.e., SPECT versus planar score for every TKA) and clustered (i.e., multiple observers of every TKA) nature of observations [19].

For the secondary endpoint, correlation matrices of regional tracer uptake scores were constructed for each prosthesis component to identify variables representing regions with highly correlated scores on the blood pool images. In case of correlation (as tested using Bartlett's test of sphericity), a variable cluster analysis was performed as a dimension-reduction method to subsequently identify clinically relevant patterns of uptake. Briefly, this method is based on principal component analysis, but uses an iterative process to create a new set of variables consisting of clustered components or the most representative variable in a cluster, to explain most of the observed variation in the original data. These cluster variables, even though non-orthogonal, are more interpretable compared to the original principal components [20]. Binary logistic regression and linear regression were used as methods to identify associations between imaging characteristics and prosthesis survival, and prosthesis alignment and tracer uptake, respectively. Means with standard deviations, and odds ratios (OR) and unstandardized regression coefficients (b) with 95% confidence intervals (CI) are reported.

Given the exploratory nature of the study, no formal sample size estimation was performed. A sample of at least 50 patients was deemed appropriate as benefits requiring a larger sample size to be detected were considered not clinically relevant. A value of $P < 0.05$ was considered statistically significant without adjustment for multiplicity. Statistical analyses were performed using Stata 14.2 (StataCorp, College Station, TX, USA) and JMP Pro 13.2 (SAS Institute Inc., Cary, NC, USA).

Results

Patient population

A total of 55 TKAs in 43 patients inserted because of osteoarthritis were analyzed (Table 1). All patients were referred because of painful TKA. Of the included TKAs, seven (12.7%) were contralateral asymptomatic arthroplasties that were included as controls. The median duration of follow-up was 17 months (range 7–26 months). At the time of last follow-up, 12 out of the 55 TKAs were revised (revision rate 21.8%; 95% CI 11.8–35.0%).

Prosthesis rotational and coronal alignment

The mean TEA-PBCf and TEA-PMAt angles were $3.8 \pm 3.0°$ and $3.2 \pm 6.0°$ respectively. A total of 11 knees (20.0%; 95% CI 10.4–33.0%) had an internal rotation of the femoral component (TEA-PBCf angle) in excess of 7°, which was associated with an approximately 2.5 times higher odds of revision surgery (OR 2.6; 95% CI 1.2–5.3; $P = 0.011$). In contrast, external rotation (< 0°) was present in seven knees (12.7%;

Table 1 Summary of patient characteristics and demographics

Characteristic	N (%), median (range)
Number of patients/TKAs	43/55
Age at time of bone scintigraphy	64.9 years (42.8–94.3)
Gender	
Male	11 (25.6%)
Female	32 (74.4%)
Type of TKA	
Primary	44 (80.0%)
Revised	11 (20.0%)
Side of TKA	
Left	27 (49.0%)
Right	28 (51.0%)
Interval between last surgery and bone scintigraphy	5.2 years (0.4–15.6)

95% CI 5.2–24.5%), yet this did not affect prosthesis survival. Coronal alignment data was available for 25 knees (45%) and showed on average $0.5 \pm 2.9°$ valgus between the mechanical axis of the leg relative to the anatomical axis of the tibia. Varus malalignment in excess of 2° (OR 2.9; 95% CI 1.0–7.6; $P = 0.031$) and valgus positioning larger than 4° (OR 4.3; 95% CI 1.0–18.1; $P = 0.045$) were associated with an increased likelihood for revision surgery.

Inter-rater agreement and confidence

The mean tracer uptake scores in each anatomical region for both planar and SPECT bloodpool images are presented in Table 2. Collectively, raters scored all TKA regions as having definitely absent uptake in 65 planar bloodpool scans (29.6%), compared to 90 SPECT studies (40.9%). In planar scans read as negative, SPECT/CT had at least one region with probable uptake (or higher) in seven scans (10.8%; 95% CI 4.4–

Table 2 Summary of planar and SPECT regional bloodpool scores

Region	Planar	SPECT
F1ia	1.30 ± 0.766	1.20 ± 0.700
F1ip	1.15 ± 0.529	1.05 ± 0.340
F1sa	1.12 ± 0.432	1.06 ± 0.359
F1sp	1.10 ± 0.437	1.02 ± 0.177
F2ia	1.80 ± 1.203	1.55 ± 1.155
F2ip	1.46 ± 0.999	1.37 ± 0.964
F2sa	1.55 ± 1.057	1.36 ± 0.971
F2sp	1.24 ± 0.677	1.03 ± 0.189
Fshaft	1.01 ± 0.116	1.01 ± 0.116
P1i	1.23 ± 0.680	1.20 ± 0.752
P1s	1.23 ± 0.725	1.20 ± 0.738
P2i	1.26 ± 0.818	1.28 ± 0.902
P2s	1.32 ± 0.896	1.36 ± 0.995
T1a	1.39 ± 0.966	1.21 ± 0.814
T1p	1.23 ± 0.731	1.13 ± 0.591
T2a	1.50 ± 1.018	1.23 ± 0.774
T2p	1.30 ± 0.800	1.24 ± 0.812
T3a	1.26 ± 0.736	1.10 ± 0.478
T3p	1.17 ± 0.576	1.09 ± 0.445
Tshaft	1.05 ± 0.306	1.02 ± 0.223
Ttip	1.17 ± 0.560	1.04 ± 0.292

Abbreviations: F1ia = femoral medial inferior anterior; F1ip = femoral medial inferior posterior; F1sa = femoral medial superior anterior; F1sp = femoral medial superior posterior; F2ia = femoral lateral inferior anterior; F2ip = femoral lateral inferior posterior; F2sa = femoral lateral superior anterior; F2sp = femoral lateral superior posterior; F shaft = femoral shaft; P1i = patella medial inferior; P1s = patella medial superior; P2i = patella lateral inferior; P2s = patella lateral superior; T1a = tibial medial anterior; T1p = tibial medial posterior; T2a = tibial lateral anterior; T2p = tibial lateral posterior; T3a = tibial peg anterior; T3p = tibial peg posterior; T shaft = tibial shaft; T tip = tibial tip

20.9%). Overall, the inter-rater agreement was moderate to high and statistically significant for all regions, both on SPECT reconstructions and planar controls (Table 3). The numerical value of Gwet's AC was higher in 17 out of 21 regions (81%; 95% CI 58–95%) on SPECT, with statistically significant differences in five regions (24%; 95% CI 8–47%) compared to planar images. All four regions in which agreement was numerically lower or equal on SPECT compared to planar controls were localized in the patella, even though none of these differences were statistically significant. The confidence score for localizing tracer uptake on the bloodpool images was on average one category higher on the five-point scale for SPECT (4.41; 95% CI 4.09–4.73) compared to planar (3.34; 95% CI 2.99–3.68) controls ($\Delta b = 1.07$; 95% CI 0.93–1.21; $P < 0.001$), when accounting for the repeated nature of observations and trends within raters.

Uptake patterns and prosthesis survival

Crude correlations between regional tracer uptake scores for each prosthesis component on bloodpool images are shown in Fig. 1 as color maps, demonstrating distinct patterns for the SPECT and planar data (all Bartlett's $P < 0.001$). After variable reduction, two clusters were identified for the femoral regions, three for the tibial zones, and one for the patella.

Planar imaging of the femoral prosthesis component showed strong clustering of ipsilateral regions as well as anterior and posterior regions. In contrast, there is clear separation of anterior and posterior uptake on SPECT imaging, suggesting improved assessment of these regions (Fig. 2a). Variable clusters representing femoral lateral uptake regions on bloodpool imaging were associated with increased likelihood of requiring revision surgery, both on planar controls (OR 1.2 per unit increase; 95% CI 1.0–1.4; $P = 0.032$) and SPECT (OR 1.2 per unit increase; 95% CI 1.0–1.5; $P = 0.041$) reconstructions. Transposed back to the original anatomic regions, this translates to a 3- to 4-fold increase in the need of revision surgery if "probably present" or "definitely present" uptake was scored in lateral regions (F2sa, F2sp, F2ia, F2ip) on bloodpool planar or SPECT images compared to less intense uptake. In a multivariable comparison, both planar and SPECT femoral uptake scores performed comparably in predicting component outcome ($P = 0.335$).

For the tibial component, similar clusters of uptake were seen on planar controls and SPECT, capturing both anterior and posterior tibial regions with similar loading coefficients (Fig. 2b). Interestingly, only clusters representing medial regions on bloodpool imaging were associated with increased revision surgery on planar (OR 1.4 per unit increase; 95% CI 1.1–1.7; $P = 0.003$) and SPECT (OR 1.8 per unit increase; 95% CI 1.3–2.4; $P < 0.001$) imaging. Transposing to regional scores, this means that any uptake scored as "probably present" or "definitely present" below the medial compartment

Table 3 Interrater reliability for all regions both on planar and SPECT images using Gwet's AC

Region	Planar		SPECT		Planar vs SPECT	
	Gwet's AC (95% CI)	P	Gwet's AC (95% CI)	P	Δ Gwet's AC	P
F1ia	89% (77%– 100%)	< 0.001	92% (85%– 99%)	< 0.001	3%	0.256
F1ip	95% (89%– 100%)	< 0.001	98% (96%– 100%)	< 0.001	3%	0.103
F1sa	97% (92%– 100%)	< 0.001	98% (94%– 100%)	< 0.001	1%	0.250
F1sp	97% (91%– 100%)	< 0.001	99% (98%– 100%)	< 0.001	3%	0.252
F2ia	65% (27%– 100%)	0.012	75% (53%– 96%)	0.002	10%	0.277
F2ip	80% (54%– 100%)	0.002	84% (69%– 98%)	< 0.001	3%	0.675
F2sa	76% (61%– 91%)	< 0.001	84% (73%– 95%)	< 0.001	8%	**0.046**
F2sp	91% (83%– 100%)	< 0.001	99% (97%– 100%)	< 0.001	8%	**0.048**
Fshaft	100% (99%– 100%)	< 0.001	100% (99%– 100%)	< 0.001	0%	0.966
P1i	92% (80%– 100%)	< 0.001	91% (89%– 93%)	< 0.001	−1%	0.863
P1s	91% (79%– 100%)	< 0.001	91% (85%– 97%)	< 0.001	0%	0.941
P2i	89% (75%– 100%)	< 0.001	87% (74%– 100%)	< 0.001	−2%	0.693
P2s	86% (72%– 100%)	< 0.001	83% (77%– 90%)	< 0.001	−3%	0.538
T1a	83% (79%– 87%)	< 0.001	90% (83%– 97%)	< 0.001	7%	**0.015**
T1p	91% (83%– 99%)	< 0.001	95% (92%– 97%)	< 0.001	4%	0.220
T2a	78% (67%– 89%)	< 0.001	90% (87%– 94%)	< 0.001	12%	**0.035**
T2p	88% (79%– 98%)	< 0.001	90% (80%– 100%)	< 0.001	1%	0.770
T3a	90% (79%– 100%)	< 0.001	97% (88%– 100%)	< 0.001	6%	0.112
T3p	94% (87%– 100%)	< 0.001	97% (88%– 100%)	< 0.001	3%	**0.049**
Tshaft	99% (94%– 100%)	< 0.001	99% (98%– 100%)	< 0.001	1%	0.667
Ttip	95% (86%– 100%)	< 0.001	99% (96%– 100%)	< 0.001	4%	0.127

Abbreviations: see footer for Table 2

Bold type indicates significance

(T1a, T1p) was associated with 6- to 24-fold increase in the odds for revision surgery on the bloodpool planar or SPECT images compared to less intense uptake. It should be noted that tibial uptake scores on SPECT outperformed those on planar imaging for predicting revision surgery ($P = 0.014$), with an 16% improvement in area under the curve of the receiver operator characteristic (AUROC) (86% versus 70%), when late-phase medial uptake was present.

The identified clusters of patellar uptake were comparable between planar and SPECT images (Fig. 2c) and no additional patterns of uptake with respect to side or location could be identified. Nevertheless, SPECT outperformed planar scoring in identifying the need for patellar revision surgery ($P = 0.001$) with an 6% improvement in AUROC (64% versus 58%) when assessing bloodpool imaging alone. This suggests that the benefit of SPECT in this region lies in the better localization of uptake to the patellar region rather than its specific pattern.

Finally, analysis of synovial uptake revealed that probable or definite synovial uptake on SPECT reconstructions was associated with a 2-fold higher revision rate (OR 2.0; 95% CI 1.0–4.1; $P = 0.040$), but not on planar images (OR 1.7; 95% CI 0.8–3.4; $P = 0.166$).

Prosthesis biomechanics and bloodpool SPECT uptake

When linking prosthesis rotational alignment with bloodpool SPECT uptake scores, femoral internal rotation was associated with higher bloodpool uptake scores in posterior medial (b = 0.21; 95% CI 0.01–0.41; $P = 0.042$) and anterior lateral regions (b = 0.71; 95% CI 0.14–1.28; $P = 0.016$) of the femur. Comparable reciprocal associations were seen for the lateral patellar regions with internal femoral malrotation (b = 0.76; 95% CI 0.17–1.34; $P = 0.011$) (Figs. 3a, 4). The inverse phenomenon with external femoral rotation was not observed. In addition, femoral internal (b = 1.64; 95% CI 0.69–2.60; $P = 0.001$) or external (b = 0.54; 95% CI 0.09–0.98; $P = 0.019$) rotation resulted in higher synovial uptake scores on bloodpool SPECT.

Tibial internal rotation was associated with increased uptake in posterior lateral (b = 0.31; 95% CI 0.04–0.58; $P = 0.026$) and posteromedial regions (b = 0.21; 95% CI 0.06–0.36; $P = 0.005$) of the tibia, and the medial superior (b = 0.35; 95% CI 0.11–0.60; $P = 0.004$) and inferior (b = 0.50; 95% CI 0.26–0.74; $P < 0.001$) regions of the patella (Fig. 3b). There was no association between synovial uptake and tibial rotational alignment. It should be noted that none of

these tibial patterns of uptake could be identified using the planar uptake scores.

Finally, coronal valgus alignment resulted in increased uptake in the lateral inferior (b = 0.41; 95% CI 0.16–0.60; $P < 0.001$) and superior (b = 0.54; 95% CI 0.27–0.81; $P < 0.001$) patellar regions.

Discussion

The introduction of hybrid SPECT/CT as an integral part of bone scintigraphy has opened up a very promising field in orthopedic imaging, fully unlocking the power of metabolic and morphological information in a single study [21, 22]. With respect to the knee, it has been demonstrated that SPECT/CT outperforms planar bone imaging both in patients with and without arthroplasty [23, 24]. Moreover, data also suggest that bone SPECT/CT is on par with magnetic resonance imaging (MRI) in patients with chronic medial knee pain or recurrent pain after knee arthroplasty [25, 26]. In particular, the recognition of bone SPECT/CT as a biomarker of prosthesis biomechanics and alignment has driven much of this recent progress [27]. However, this effort has almost exclusively focused on late-phase imaging, with no data currently available on the potential additional information captured

by the bloodpool phase of the study, while the benefit of bloodpool SPECT has been suggested in other indications [28].

In this study, we first aimed to validate the use of bloodpool SPECT compared to conventional planar images. This showed that the use of SPECT improved inter-rater agreement in 81% of assessed areas, and significantly improved rater confidence by 20%. Importantly, statistically significant gains in agreement were observed in 24% of regions, including those that convey clinically relevant information on prosthesis biomechanics and failure modes, such as the superior lateral femoral regions. Indeed, increased bloodpool uptake in these regions was associated with a 3- to 4-fold increase in the need for revision surgery, which is in keeping with the results from Hirschmann et al. showing an association on late-phase imaging uptake in these regions with component loosening [9]. Our findings hence strengthen the observation that lateral femoral uptake is an important marker of biomechanical prosthesis failure increasing the need for revision surgery.

The use of SPECT was superior for the assessment of the tibial and patellar regions when predicting prosthesis survival on bloodpool images, even though the patterns of uptake identified on SPECT and planar imaging were comparable. This suggests that the correct attribution of uptake to these regions instead of any superimposed structures — rather than the

Fig. 1 Color maps of correlations between regional uptake scores on **a** planar and **b** SPECT bloodpool images
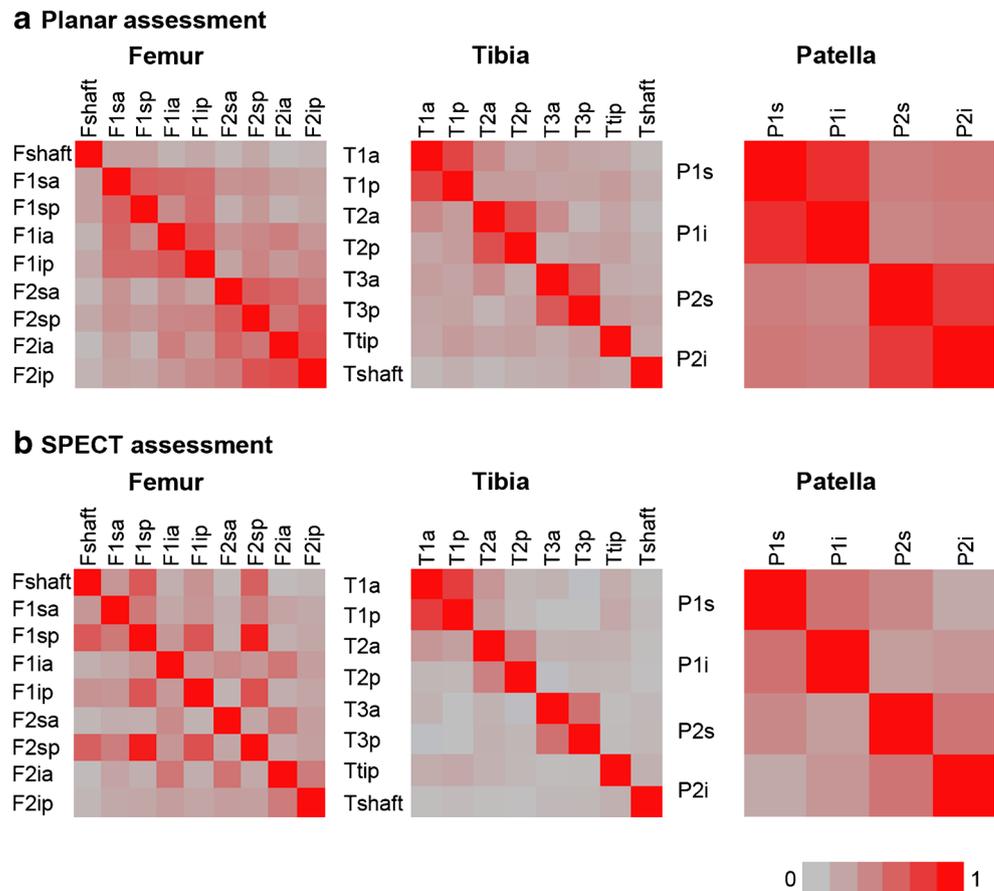
Fig. 2 Standardized coefficients for each variable in identified clusters for **a** femoral, **b** tibial, and **c** patellar regional uptake

|	Planar			SPECT		
	Cluster 1	Cluster 2	Cluster 3	Cluster 1	Cluster 2	Cluster 3
a Femur						
Fshaft	0.00	0.22	–	0.40	0.00	–
F1sa	0.00	0.51	–	0.33	0.00	–
F1sp	0.00	0.47	–	0.53	0.00	–
F1ia	0.00	0.47	–	0.00	0.49	–
F1ip	0.00	0.51	–	0.42	0.00	–
F2sa	0.47	0.00	–	0.00	0.49	–
F2sp	0.51	0.00	–	0.52	0.00	–
F2ia	0.50	0.00	–	0.00	0.58	–
F2ip	0.51	0.00	–	0.00	0.43	–
b Tibia						
T1a	0.71	0.00	0.00	0.68	0.00	0.00
T1p	0.71	0.00	0.00	0.68	0.00	0.00
T2a	0.00	0.00	0.65	0.00	0.00	0.71
T2p	0.00	0.00	0.66	0.00	0.00	0.71
T3a	0.00	0.66	0.00	0.00	0.70	0.00
T3p	0.00	0.68	0.00	0.00	0.70	0.00
Ttip	0.00	0.00	0.37	0.27	0.00	0.00
Tshaft	0.00	0.32	0.00	0.00	0.18	0.00
c Patella						
P1s	0.51	–	–	0.51	–	–
P1i	0.50	–	–	0.50	–	–
P2s	0.49	–	–	0.52	–	–
P2i	0.50	–	–	0.47	–	–

0 ▭ 1

Fig. 3 Illustration of distinct patterns of regional bloodpool SPECT uptake linked with biomechanical profiles of prosthesis alignment: **a** internal rotation of the femoral component, and **b** internal rotation of the tibial component. *Blue clouds* illustrate areas of expected increased regional uptake on bloodpool SPECT. The *green and red rectangles* show the plane of rotational alignment of the native bone and prosthesis component, respectively. Abbreviations: *M* = medial; *L* = lateral

a Internally rotated femoral component
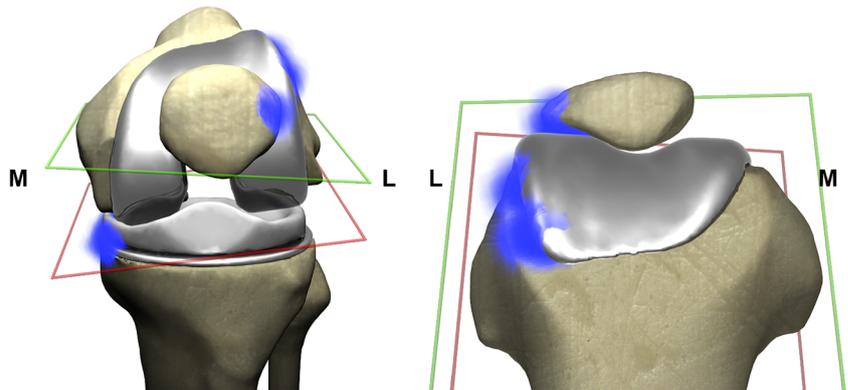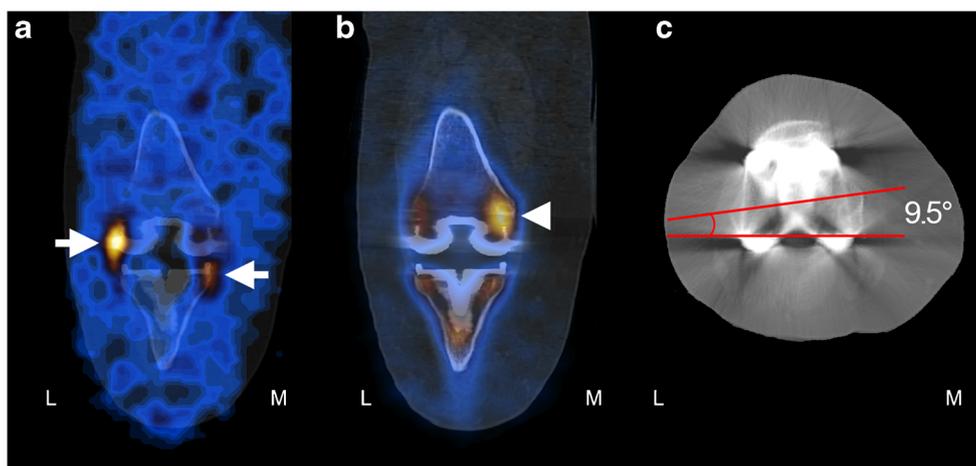
b Internally rotated tibial component
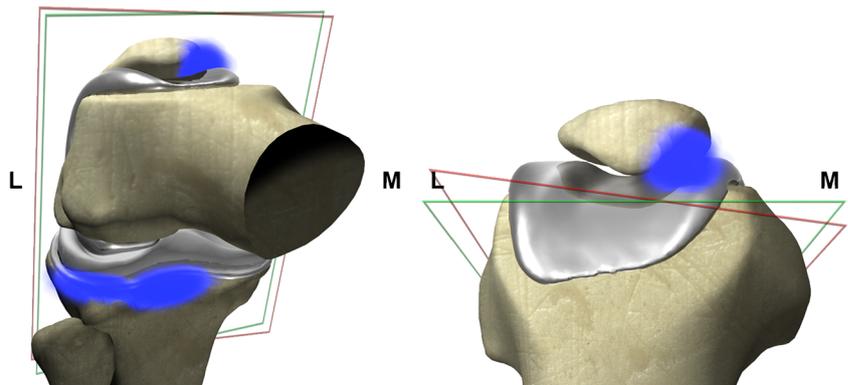
Fig. 4 Illustration of increased focal bloodpool SPECT uptake at the lateral femoral and medial tibial prosthesis components (**a**: *arrows*), without corresponding late-phase SPECT/CT uptake (**b**: *arrowhead* showing increased medial femoral uptake without prosthesis–bone interface contact) in a patient with severe internally rotated femoral component (9.5°) (**c**: summed axial CT images with measurement of angle between anatomic transepicondylar axis and posterior bicondylar axis). Revision surgery was performed. Abbreviations: M = medial; L = lateral. Note: for illustrative purposes, fused bloodpool SPECT images are shown after rigid registration with the CT performed during late-phase SPECT/CT, but during the study only non-fused bloodpool SPECT images were assessed

pattern of uptake itself — may be driving the superiority of SPECT in this region. It is of interest that bloodpool uptake in the medial tibial regions conferred a 6- to 24-fold increase in the need for revision surgery. This finding is clinically relevant, as increased uptake in the medial tibial regions on late-phase imaging is a frequent finding, and no specific pattern for loosening other than increased uptake in any tibial region has so far been identified on late-phase imaging [9]. For that reason, bloodpool SPECT may offer the ability to differentiate between local stress and loosening of the tibial component (Fig. 5). This interpretation is supported by an analysis of BTU on the late-phase SPECT/CT acquisitions in our cohort, showing that increased tibial BTU in the lateral part (OR 4.2; 95% CI 2.0–8.7; $P < 0.001$) and below the tip (OR 2.6; 95% CI 1.3–5.3; $P = 0.007$) were most strongly associated with prosthesis survival, but not the late-phase BTU in the medial part (OR 1.2; 95% CI 0.7–1.9; $P = 0.488$) when uptake in that region on bloodpool imaging (OR 2.4; 95% CI 1.5–4.1; $P = 0.001$) was added in a multivariable analysis. This finding illustrates the complementary nature of bloodpool and late-phase bone SPECT/CT imaging of painful TKAs.

When linking prosthesis outcome and regional uptake on SPECT with rotational and coronal alignment, the results of this study underscore the relevance of bone SPECT/CT as an imaging biomarker of prosthetic biomechanical functioning. In line with other clinical and cadaveric studies, we could confirm the detrimental impact of internal femoral rotation — as opposed to the external rotation — on prosthesis outcome. [29] In particular, Berger et al. examined a group of 30 patients with isolated patellofemoral complications and compared these to a control group of 20 patients with well-functioning total knee replacements. They underlined the direct correlation of combined excessive internal rotation to the severity of patellofemoral complications in these patients with otherwise correct axial alignment. In contrast, the control group of 20 patients without patellofemoral complications and normal axial alignment had combined excessive external rotation [30]. The pattern of bloodpool uptake with internally rotated femoral components consisted of increased uptake in the posterior medial and anterior lateral femoral regions and lateral patellar regions. This can be explained biomechanically by increased local stress caused by lateral patellar maltracking and increased contact with the medial tibial plateau during flexion [16]. In particular in patients presenting with anterior knee pain, recognition of this pattern may assist in identifying the underlying cause.

Similarly, we show that this concept can be extended to the case of tibial internal rotation, where bloodpool SPECT shows increased uptake in posterior lateral and posteromedial tibial regions, and the medial superior and inferior patellar regions. These findings reflect the biomechanical effect of the internal rotation of the tibial component, which increases peak contact stress during flexion in the posterolateral region of the tibia and medial patellofemoral interface [31, 32]. Coronal TKA malalignment resulted in increased patellar bloodpool SPECT uptake, which is consistent with late-phase imaging findings reported by Slevin et al. [33]. Moreover, this uptake pattern provided clinically relevant insights into patellar maltracking and prosthesis survival.

Finally, the increased synovial uptake on bloodpool SPECT imaging occurred in the case of femoral internal or external rotation, and was associated with 2-fold higher revision rates. A similar finding was reported with ^{18}F-fluorodeoxyglucose (FDG) PET/CT imaging of TKA,
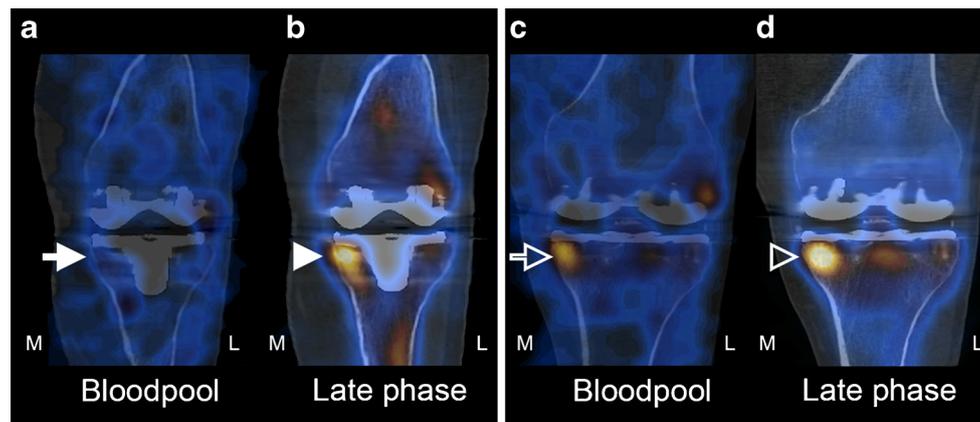
Fig. 5 Example of complementary information provided by bloodpool SPECT in a patient imaged 9 months after left TKA without uptake on bloodpool SPECT (**a**: *arrow*) but increased focal uptake on late phase SPECT/CT below the tibial component on the medial side reflecting bone stress (**b**: *arrowhead*). Resolution of symptoms was seen with conservative management. Another patient imaged 14 months after left TKA showing increased uptake on the medial side below the tibial component on bloodpool SPECT (**a**: *arrow outline*) and late phase SPECT/CT (**b**: *arrowhead outline*). Loosening of the tibial component was confirmed during revision arthroplasty. Abbreviations: M = medial; L = lateral. Note: For illustrative purposes, fused bloodpool SPECT images are shown after rigid registration with the CT performed during late-phase SPECT/CT, but during the study only non-fused bloodpool SPECT images were assessed

possibly providing mechanistic insight and supporting inflammation as a cause of increased uptake, which can be due to chronic synovitis, postoperative inflammation at the bone–prosthesis interface, reaction to fixating cement or reaction to polyethylene inlay wear [11, 34].

This study has some limitations that need to be considered. As with any retrospective analysis, the follow-up of patients was not standardized, resulting in a suboptimal reference standard. An attempt was made to mediate this by using prosthesis survival as dummy end-point for diagnoses requiring revision surgery. While appropriate for this preliminary technical validation study, further trials should investigate whether specific patterns can be linked to the final diagnosis at the time of revision or during follow-up. The same holds true for the use of the 5-point scale, which was used as a research instrument but is not validated for clinical use. The comparator in this study consisted of planar projections from tomographic data. However, a dual-acquisition protocol was not possible due to the rapidly changing kinetics of radiotracer uptake during this early phase of imaging. In addition, no CT was performed during the bloodpool SPECT acquisition, in order not to increase the overall patient radiation exposure. Nevertheless, it can be argued that the adult knee region does not contain particularly radiosensitive tissues (e.g., no red marrow), as demonstrated by the very low dose length product over effective dose (DLP/ED) conversion coefficient (0.0004 mSv/mGy.cm). [35, 36] This may warrant further adaptations of the scan protocol, in particular switching to bloodpool SPECT/CT followed by late-phase SPECT/CT with diagnostic-quality CT, if the incremental diagnostic benefit of this modification can be validated.

In summary, replacing planar bloodpool imaging with SPECT increases inter-rater agreement and confidence, without penalty in overall acquisition time or radiation exposure. Moreover, bloodpool SPECT offers incremental value over planar imaging in assessing biomechanically important prosthesis regions, and is essential to interpret the findings on late-phase SPECT/CT imaging. Another specific advantage is that bloodpool SPECT can reveal unique patterns associated with synovitis, or malrotation leading to maltracking and increased peak contact stress, ultimately causing premature prosthesis failure.

Conclusions

The use of bloodpool SPECT instead of planar imaging improves inter-rater agreement and confidence when reporting TKA bone SPECT/CT studies, with significant improvements in regions linked with clinically relevant information on prosthesis outcome. Our results provide important insights into understanding bloodpool SPECT findings from a biomechanical perspective. In addition, they add to the growing body of evidence showing that bone SPECT/CT is a true imaging biomarker of prosthetic biomechanics, not only in late-phase acquisitions but, as we demonstrate here, also in the bloodpool phase. Further work will focus on identifying uptake patterns that associate with particular clinical or surgical diagnoses during follow-up or revision surgery, and how to integrate these with findings with late-phase SPECT/CT.

Compliance with ethical standards

Ethical approval All procedures were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. For this type of study formal consent is not required.

Conflict of interest The authors report no conflict of interests.

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