Author's response to reviews

Title: Clinical value of SPECT/CT for evaluation of patients with painful knees after total knee arthroplasty- a new dimension of diagnostics?

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Author's response to reviews: see over
Dear Prof. Hartwigsen,

Thank you very much for giving us the opportunity to submit a revised version of our original article entitled “Clinical value of SPECT/CT for evaluation of patients with painful knees after total knee arthroplasty- a new dimension of diagnostics.” from the Kantonsspital Bruderholz, Switzerland by Hirschmann MT, Konala P, Iranpour F, Kerner A, Rasch H and Friederich NF. We would like to resubmit this manuscript to your attention for possible publication in the Journal “BMC Musculoskeletal Disorders”.

The final manuscript has been seen and approved by all authors and they have taken due care to ensure the integrity of the work. We declare that all authors have contributed to the paper and are familiar with the contents of the final draft. We hereby affirm that the submitted manuscript is our original work, has not been published or is being considered for publication elsewhere. Looking forward to hearing from you, yours sincerely,
Response to reviewer’s comments:

Reviewer: Kinner Davda

Reviewer’s report:

This is a well written study of an interesting and valuable use of new technology. The paper is written well and the primary hypothesis is justly answered. The methodology and statistical analysis is appropriate, followed by a well judged and balanced discussion of the study versus the literature. Papers regarding the use of SPECT/CT remain limited in number and this current study will surely be a helpful contribution.

Discretionary Revision

There were however several points regarding methodology:

1. The focus of this article hinges on the use of SPECT/CT as an adjunct to a clinical diagnosis. It is unclear whether a single investigator or senior author reviewed each of these patients prior to SPECT/CT. Some form of multiple investigator agreement would be of value to reduce observer bias.

The classification system of SPECT/CT in patients with painful total knee arthroplasty has been validated and published previously. It showed near perfect inter- and intra-observer reliability. Hence, we believe this is not a problem for this series. See references.
The cases in the present study were reviewed by one orthopaedic surgeon and one radiologist/nuclear medicine specialist. The measurements of component position were done by two orthopaedic surgeons.

2. Regarding 'Table 1', 'anterior knee pain' cannot be considered a preoperative diagnosis, but rather a description of a symptom. 
We entirely agree. It was changed as suggested.

3. The author refers to the use of a high ICC as a measure of method agreement. A Bland Altman analysis would be a more revealing examination of inter and intra observer reliability. A high ICC does not necessarily equate to high level of observer agreement.

Bland-Altman analysis (also known as the method of differences) has been proposed for measuring the degree of agreement. In this method, the differences in the measurements made by two readers are plotted against the average values of these measurements. According to Bland and Altman, if 95% of the differences are within ±1.96 standard deviations of the mean of the differences, then this denotes good agreements between the two sets of measurements. These limits are also known as the "limits of agreement". Note that hypothesis testing for equivalence and the ICC method provide quantitative measures of the agreement between the measurements whereas the Bland-Altman analysis technique provides a qualitative assessment.

In summary, ICC values are the most widely and accepted measures for inter- and intra-observer agreement. In contrast to others ICCs take the absolute difference into consideration.
4. The authors use a Mann Whitney test to examine non parametric data, hence median and not mean values should be stated in the subsequent results tables. 
We entirely agree. The table 4 was changed as suggested.

5. A figure demonstrating the CT measurements made would be of value to the reader who is unfamiliar of how such measurements are made in 3D reconstructed images.
The figure is shown in the former publications demonstrating and evaluating the SPECT/CT classification system and figure 1.

6. It is unclear what contribution the second (PK) and third author (FI) made from the 'Contribution' statement at the end of the paper.
Information was added.

A future study would be strengthened by the use of a functional outcome scores, such as the Oxford, pre and post surgery.
We currently perform a prospective study including functional outcome scores.

Reviewer's report

Reviewer: Robert Teitge

This paper is a preliminary report which investigates the use of a reasonably new technology (SPECT/CT) in the diagnostic evaluation of a particularly difficult group of patients – those with painful total knee arthroplasty. Twenty-three consecutive patients with painful total knee arthroplasty were subjected to SPECT/CT study. In 19 of these 23 (83%) the diagnosis was changed or amended. This is a rather
remarkable finding which clearly deserves more extensive study as it may pave the way for a new standard in the evaluation of these patients.

Specific comments to the authors:

(1) How does SPECT/CT differ from combining the separate studies of SPECT and CT? Does the study with SPECT/CT generate different data from that which could be obtained from combining the separate studies? [Background pp2]

The SPECT/CT machine generates SPECT and CT information, which could be looked at as combined or single dataset. Clearly, only the combined dataset localizes the tracer uptake of SPECT within the CT. Ten years ago no hybrid machines were on the market. In that time coregistration of the SPECT and CT information was based on anatomical landmarks, was done manually and neither accurate nor precise enough to be used as diagnostic tool.

(2) The two largest post study diagnostic groups were (a) patellar OA and (b) prosthetic mal-position. Could the diagnosis of these been determined by (a) SPECT alone and (b) CT alone?

Indeed, this is a very good point. The diagnosis of symptomatic patellofemoral OA can be established by SPECT alone, but SPECT is less sensitive and specific. In addition only SPECT/CT is able to precisely localize the tracer activity. For evaluation of component position 3D-CT alone could also be used, but the combine analysis of SPECT and CT in one hybrid imaging modality offers the chance to a better understanding of the painful knee after TKR.

(3) Were all of these TKA’s performed without resurfacing of the patella?

Yes, all of them had not primary patella resurfacing.
(4) If so would you suggest that all painful TKA without patellar replacement be assessed with SPECT/CT to rule out patellar OA progression? 

Due to this preliminary study, it seems that SPECT/CT is indeed really promising for the assessment of patellofemoral pain after TKR. In another ongoing study on 100 prospective patients this impression has also been proven.

(5) In the cases in which the final diagnosis was determined at surgery n=8 [Methods pp3] what were the specific surgical findings which confirmed the diagnosis. In the case of Patellar OA this is clear, but in the case of malposition were any objective measurements possible? 

Indeed, assessment of malposition at revision surgery is sometimes difficult. For determination of rotational alignment the surgical and transepидondylar axis was determined. Flexion and extension as well as varus valgus was judged based on the mechanical axis (given by an alignment rod) and the surgeon`s impression.

(6) Did microbiological and histological examination from surgery (n=8) provide any useful diagnostic information? [Methods pp 3] 

All of them were unremarkable.

(7) Would you comment on the fact that while there were two suspected infections, there were no infections in any of this group of patients with painful TKA? This is impressive as usually infection is a common consideration in the painful TKA. This is only a group of 23 patients, a rather small sample size. In an ongoing study we investigate the use of SPECT/CT in a group of 100 prospective patients. We also believe that there also might be a regional bias in this group of patients.
Please comment on the use of CT for measuring limb alignment. I am not aware of any study which compares standing alignment while (a) standing on one foot which represents the mid-stance position of gait with (b) standing on both feet which does not measure the limb alignment during mid-stance with (c) CT measurement of alignment. Based on personal observation comparing intraoperative navigation measurements of limb alignment with post-operative single limb standing, I suspect that CT measurements of alignment are not accurate in reflecting limb alignment during gait. Do you have references on this question?

We entirely agree on the fact that measuring alignment on non-weight bearing CT images does not reflect the mechanical limb alignment. However, to date there is no imaging modality available offering standing CTs. Flat panel CT might in future be available. With the CT measurement we only aligned the CT images obtained with regards to the Mikulicz line, reflecting the mechanical line. Using 3D-CT for assessment of component position we cannot comment on the stability and mechanical alignment, but the position of the implant in relation to anatomical landmarks.

CT measurements of limb alignment can certainly not reflect malalignment due to abnormal ligament laxity. Would reliance on SPECT/CT for evaluation of total knees underestimate or completely miss pain as a result of ligament instability?

See above. Using SPECT/CT we cannot comment on instability. In our used diagnostic algorithm for painful knees after arthroplasty SPECT/CT represents only one part of the diagnostic armamentarium. Fluoroscopy or stress radiographs are necessary to comment on stability after arthroplasty.

The CT used for limb alignment in this study did not include the ankle or the
femoral head. Please comment on how do you know that your method of modeling to compensate this was accurate?

Striving to reduce the radiation dose of the CT, we decided not to include the ankle and hip joint. As we assessed the component position of the TKR with regards to local anatomical landmarks (e.g. epicondylar axis) on 3D-CT we could adjust the CT images in terms of the patient’s leg position.

(11) Please comment on how the diagnosis of component mal-position was determined at surgery. As it is know that the surgical landmarks for component positioning are less than accurate, the landmarks for revision surgery must be even more inaccurate. If the intra-operative assessment of component mal-position was only a guess, please state that? [Results paragraph 4]

See above.

(12) How would you use markers to transfer the position of components on CT to the patient during surgery?

For rotational alignment of the TKR the surgical or anatomical transepicondylar axis is marked using pins and then compared to the position and orientation of the TKR. For assessment of the mechanical axis we use an alignment rod.

(13) [Results Paragraph 6] You state that “patients with externally mal-rotated tibial tray showed significantly higher tracer activity”. How much tracer uptake is significant?

I agree that to date we are not able to explain every increased tracer uptake. In future we will look at specific uptake patterns which could reflect with regards to the prosthesis shape and design different pathologies. The intensity of tracer uptake of
SPECT/CT is only valid for each individual, as long it is not a ratio of the uptake region in relation to the midshaft of the femur, which represents the normal background activity. To deal with these problems I developed an analysing software, which offers the possibility of using the 3D information, thresholding, quantitative data.

(14) On Table 4 patient #14 had a higher tracer uptake (equal medially and laterally) than many other patients yet there was no anatomic cause of pain determined. In this case would you comment on this high uptake…is it significant? We again reviewed this case and found that the cause of the patient’s pain remains unclear. Currently the patient is pain free. We suggested a follow-up SPECT/CT if pain returns. With the new analysis software we believe to become more specific in such cases.

(15) [Table 4] What is the significance that 5 of the 12 patients without a diagnosis of patellar OA had mean tracer activity in the patella which was equal or greater than the mean tracer activity in the patella of 2 patients diagnosed as patellar OA? We believe that not the mean or median value might be decisive, but the highest value on the medial or lateral patella region. Therefore, we developed a new method of analysing for future studies. This new method takes into consideration the 3D intensity values of each uptake cloud separating different regions.

(16) Does Table 2 refer only to activity in the tibia and femur and not the patella? Does Table 4 refer only to activity in the patella and not to any femoral or tibial tracer activity?
That is correct. See figure 1.

(17) On table 4 there is listed “medial” and “lateral”...does this mean medial and lateral refer to medial and lateral patella?
Correct.

(18) Figure 1 needs a label.
Information was added. „Figure 1  - The previously published and used SPECT/CT classification system“.

(19) [Table 1] There were 14 (of 23 total = 61%) cases of pre-op loosening which were not confirmed by SPECT/CT. That is an impressive change in diagnosis. Can you comment on the confidence of this finding? That is, that in 48% of the entire series the pre-op diagnosis was incorrect. [Table 1] How was it determined by the SPECT/CT that there was no loosening?
SPECT has been shown to be a very sensitive diagnostic imaging modality, in particular when combined with all 3 phases. When no uptake is present someone could be certain that no loosening is present.

(20) What are the specific SPECT/CT findings that indicate loosening? (Or can you give a specific reference).
See above.
Also see-
Henderson et al. 1996, „The value of skeletal scintigraphy in predicting the need for revision surgery in total knee replacement“, Orthopedics
Soininvaara et al. 2008 Clin Physiol Funct Imaging
Hirschmann et al. found in references.

(21) [Table 1 & 3] Equally impressive is the fact that there were 11 (of 23 cases = 48%) cases of mal positioning of the prosthesis. What are the specific findings of prosthetic mal-position seen with SPECT/CT? (Or specific reference which validates the measurement technique used to make this determination).

The method of measuring component position and orientation has been validated in a former published paper (Hirschmann et al.- see references). 3D-CT is used. We currently have another study under review comparing assessment of component position on radiographs, 2D-CT and 3D-CT. Clearly, it shows that the used 3D algorithm is highly reliable.

(22) [Discussion] Are you able to assign any role to SPECT in the diagnosis of mal-positioned prostheses?

See above and below. Malposition is shown on 3D-CT, but the clinically significant malpositioned TKR also shows increased tracer uptake, which indirectly might be able to show the metabolic reaction of altered knee kinematics.

(23) [Discussion] Is there a study to suggest the percentage of painful TKA which are due to mal-position of components?


(24) [Discussion] Should every painful TKA have evaluation with SPECT/CT?

We believe that SPECT/CT is a helpful part of the orthopaedic surgeon’s diagnostic armamentarium. in particular in patients with painful knees after arthroplasty.
(25) [Discussion] Would CT alone be sufficient to diagnose mal-position of components and what type of CT? (Or can you give a specific reference). See above. We recommend 3D-CT for assessment of component position after TKR. Only 3D-CT can adjust for patient’s leg rotation and is less prone to observer bias.

(26) [Discussion] Does SPECT or SPECT/CT currently help with the diagnosis of mal-position of components?
Clearly, SPECT has only poor ability to localize tracer uptake. Along with its precise localization of the tracer uptake SPECT/CT offers the possibility of correlation of type, design and shape of the prosthesis with mechanical alignment and component position. From this data a better understanding of biomechanics in relation to prosthesis type could be gained in future. Hence, we evaluate this issue in several ongoing study projects.

(27) [Fig 3] Could you comment on the findings indicative or consistent with femoral loosening? [Discussion] Is it possible to have loose prosthesis with just uptake under one portion of the prosthesis? Is it possible to have a painful prosthesis with just one portion being loose? i.e. In Fig. 3 there is no image of isotope uptake under the anterior flange or on the side opposite the increased uptake. Is this still consistent with a loose prosthesis? In Figure 3 does the increased uptake beneath the tibial component indicate it is also loose?
See above. As stated above you have to evaluate all 3 phases of SPECT/CT and the diagnosis is not only assessed qualitatively on the coloured SPECT/CT images. Looking only at the SPECT/CT images might lead to an incorrect diagnosis. This is the first series presenting data on SPECT/CT in painful TKR. Hence, we cannot fully answer this question. However, to date we believe that it is possible that
only parts of the femoral or tibial component show tracer uptake, although being loose.

(28) [Fig 4] states “mechanical loosening of the tibial component”. Would you give the findings (or reference) that confirms the diagnosis of ‘mechanical’ loosening?

*The diagnosis of mechanical loosening in SPECT/CT is historically defined as positive tracer uptake in all three phases of imaging. With SPECT/CT also specific regional uptake patterns, which depend on the design and shape of the implant, have to be taken into consideration.*

(29) Is it possible to differentiate, with imaging, mechanical loosening from other types of loosening (infection, particulate driven osteolysis, etc.)?

With the use of different SPECT tracers (such as leucocyte tracers or diphosphonates) it is possible to differentiate infection and loosening.

(30) [Discussion Paragraph 8] There were 6 patients diagnosed with PF OA and tibial component mal-rotation [Table 1]. Could these patients have been symptomatically improved with revision of the tibial component or with patellar replacement or would both be necessary?

Clearly, the type of prosthesis as well as the position of the femoral component influences tracking of the patella. The tibial component is not known to affect patellar maltracking. Revision of the patellar is less invasive then revising the tibial or femoral component. Hence, secondary replacement of the patella is indicated.

(31) Why is a tibial slope of $<3^\circ$ or $>10^\circ$ considered in Table 1 as cut offs of
abnormal? How much tibial slope is desired?

*This range is considered to be a normal value. Matsuda et al. (Am J Knee Surg. 1999 Summer;12(3):165-8) evaluated the posterior tibial slope in 30 normal and 30 varus knees using magnetic resonance imaging. The mean tibial posterior slope in the medial plateau was 10.7 degrees in the normal knees and 9.9 degrees in the varus knees.*

For TKR an anterior posterior slope should be avoided. A posterior tibial slope of 3-10 degrees is considered to facilitate flexion after TKR. One could speculate how far the tibial slope can be increased by the surgeon in an attempt to maximize flexion (J. Bellemans et al., Knee Surg Sports Traumatol Arthrosc (2005) 13: 193–196

(32) [Discussion Paragraph 4] “All except one of our patients with Patellofemoral problems presented within the first five years after TKA” Did these patients with PF problems present with PF or Anterior Knee Pain or were they diagnosed as having “PF Problems” only after the SPECT/CT study?

*Most of these patients presented with diffuse symptoms, not clearly indicating patellofemoral problems. The diagnosis of patellofemoral hyperpression or OA was made after SPECT/CT.*

(33) [Conclusions] Do you state the SPECT/CT is of great clinical value “particularly in patients with Patellofemoral problems” because there were 8 of 23 patients with (35%) with Patellar OA not suspected prior to surgery? Why would the 11 cases (48%) diagnosed as mal-positioned components or the 14 (61%) diagnosed as *not* loose when the clinical diagnosis was loosening not be just as important to the clinical value of SPECT/CT?

*We entirely agree, this was added in the conclusion section.*
Last and important, how much can we conclude that the findings revealed by SPECT/CT are the cause of the patient's pain?

We currently work on another ongoing project investigating this issue. Here we correlate the patient's pain level with the SPECT/CT tracer uptake.

Reviewer's opinion. I think this technique offers a potentially great improvement in diagnosis and thus this data which I regard as preliminary appears very significant. This should lead to the development of more important studies ultimately yielding great patient benefit and a greatly improved understanding of the interplay between mechanics and biology.