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Accurate, Reproducible and Standardized Quantification

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Content

• Symbia Intevo, xSPECT and xSPECT Quant are not commercially available in all countries. Due to regulatory reasons, their future availability cannot be guaranteed. Please contact your local Siemens organization for further details.

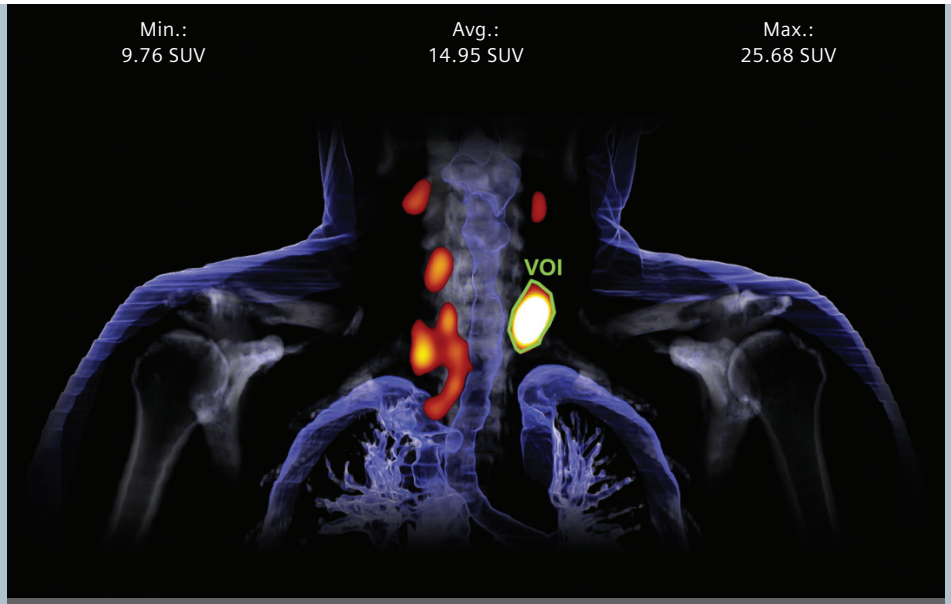

Figure 1

Figure 1: Clinical example of a patient scanned on a Symbia SPECT/CT system using xSPECT Quant. The image on the right shows a ^{99m}Tc thyroid scan revealing a hyper-funtioning thyroid adenoma and the standard uptake values (SUVs) for defined volume-of-interest (VOI).

Image courtesy of Friedrich Alexander University, Erlangen, Germany

Introduction

Accurate and reproducible quantification has been a key objective since the early days of nuclear medicine. The ability to accurately quantify total radionuclide uptake in SPECT imaging has a number of increasingly important applications.

However, there are a number of physical, patient and technical factors that limit the quantitative reliability of nuclear medicine images.[1] Many current applications that involve quantification of nuclear medicine images use relative quantification only. This relative quantification involves ratios of image intensity values simply assuming that the effects of physical, patient and technical factors like attenuation and scatter will cancel each other out. This is an erroneous assumption because the magnitudes of these factors are both spatially varying and patient-dependent.[2]

Absolute quantification addresses these limitations by accurately measuring the system physical characteristics as well as accurately incorporating the imaging physics.

One important benefit of using images that are quantitative in an absolute sense is standardization and consistency. Some clinical applications, for example, require established benchmarks or thresholds often derived from normal databases; absolute quantification will ensure that reference values derived from databases are consistent across healthcare institutions, scanners and time, and are independent of patient variability.

In June 2013, Siemens Molecular Imaging introduced the Symbia Intevo™* and with it, xSPECT Quant*, the first and only solution capable of delivering absolute quantification—paving the way for accurate, reproducible and standardized quantitative clinical studies.

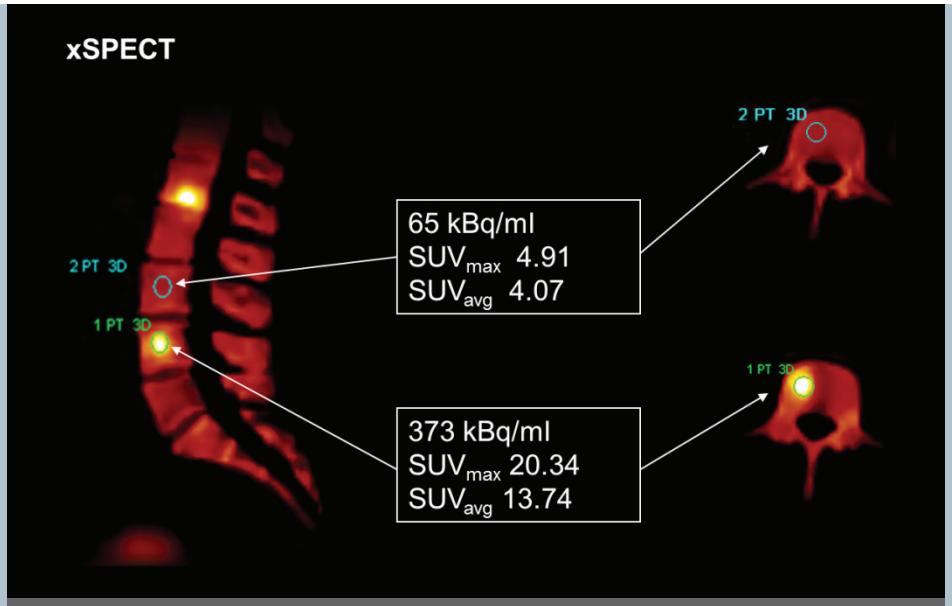

Figure 2

Figure 2: Lumbar vertebral metastases in a patient with lung cancer. xSPECT Quant confirms hot lesions are metastatic with high SUV but also uncovers zones with very low SUV in uninvolved vertebrae, suggesting osteoporosis.

Data courtesy of Johns Hopkins University, Baltimore, Maryland, USA

Clinical Applications

There are several applications of nuclear medicine that require images to be quantitatively accurate in an absolute sense.

Although SPECT imaging has emerged as a well-established modality in the past decades, accurate and absolute quantification is only now gaining momentum. Therefore, therapy planning and treatment response evaluation has been a PET and PET/CT domain for the last decade. With the advent of precise and robust quantification using xSPECT Quant, the quantitative domain in SPECT is becoming more and more a reality in clinical practice.

Today, there are several clinical applications in nuclear medicine that will benefit from accurate, reproducible and standardized quantification.

Orthopedics

Osseous inflammation such as Osteomyelitis often forces the surgeons and orthopedists to perform secondary or even multiple surgeries, increasing patients' overall number of interventions and overall incident levels.The reporting of conventional SPECT images relies heavily on the visual interpretation and the expertise of the reading physician.

A quantitative approach using xSPECT Quant can help to differentiate a reactive focal increase in bone metabolism from significant uptake derived from inflammation. In a follow-up setting, reporting physicians can precisely inform referring clinicians of quantitative changes in the focal uptake and precisely monitor disease response to therapy. Shear stress related to joint pathology and prosthesis implantation defined quantitatively with xSPECT Quant may help in orthopedic decisions. This is worth mentioning as a part of quantitative possibilities.

Oncology

Treatment of liver cancer and/or liver metastases from other cancers using nuclear medicine has become a daily routine.

For shunt volume measurement, the standard practice approach is still to use ratios defining the relative fraction of tracer to pulmonary tissue and identifying possible shunts that may hamper therapy or even be hazardous to a patient's lungs.

A 3D quantitative approach like xSPECT Quant could replace the ratio standard practice with a more precise way of measuring the shunt fraction in each patient.

During or after therapy, xSPECT Quant is capable of exact metabolic description of each of the lesion's responses. Initial values can be compared to follow-up scans and, using this quantification method, physicians can identify responders from non-responders, demonstrate clear changes to the referring clinicians and give the patient an opportunity for treatment optimization.

Figure 3: 1. Measure the total radionuclide activity in the syringe using a dose calibrator.

2. Insert tracer information including the measured activity to the processing software workstation.

3. Perform a regular system scan using either a syringe or a dedicated phantom with the radionuclide dose of step 1.

4. Insert the system sensitivity in counts per second measured in step 3.

5. Set up the patient and perform the scan.

6. Provide patient information and compute estimated proportional counts per activity concentration based on steps 1-5.

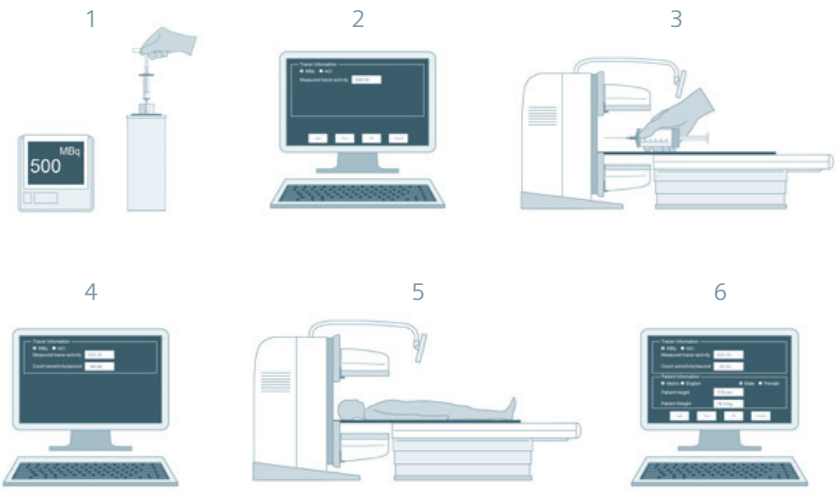

Figure 3: Traditional method A calibrates the scanner using the dose calibrator as reference source.

Traditional Quantification

The concept of quantification in nuclear medicine is not new. [3-7] We seek to estimate activity concentration of the radio pharmaceutical in Bq/ml *in-vivo*. Given the vast range of possible isotopes used in nuclear medicine, it is a very complex task, one that has eluded satisfactory solution in clinical practice. Quantification is inherently a volumetric problem which requires tomography to solve it. The principle solution for quantification only became tractable once computing power was high enough to allow for iterative reconstruction with all the needed corrections to be performed in a clinical setting. The key requirement for reliable patient-specific attenuation correction (AC) was essentially solved with the advent of hybrid SPECT/CT systems with fast rotating and diagnostic-quality CTs. Numerous publications have demonstrated the advantage of quantification, e.g., [8-10], but there is no standardized approach.

The base unit in a gamma camera is the count. Traditionally, SPECT acquires, reconstructs and delivers a 3D image in units of counts. A conversion method is then needed to compute Bq/ml, the simplest of which is to use a simple conversion factor post-reconstruction. Thus, acquiring a test source for a known amount of time with SPECT, and then reconstructing that data with the method of choice, one can determine a conversion factor between the activity (in Bq) of the test source measured in the reference device (i.e., dose calibrator) and the resulting counts in a 3D image of that test source. Once that conversion factor is obtained, one assumes that one can use the same conversion factor to convert data from the patient scan.

Ritt et al. [5] summarizes not only the basic steps needed to quantitatively measure the activity distribution, but also briefly describes common methods used to reconstruct and compensate for the various effects affecting the SPECT image formation. Zeintl et al. [6] describes a conversion method based on the dose calibrator as the reference device. The method essentially boils down to applying conversion factors from a list based on the volume sensitivity and the appropriate imaging condition (acquisition, collimator, counts and reconstruction) and lesion size. Beauregard et al. [7] expands on the approach when focusing on a ^{177}Lu application at high count rates, and thus including a system dead-time correction method. Please note that the conversion factors and dead-time correction tables have to be measured on-site and are strictly only valid on that machine at that point in time.

Methods relying on the dose calibrator can only be as accurate and precise as the dose calibrator itself, in the sense that they may work well at a site under a certain protocol but may be hard to translate to other sites and users yielding the same accuracy and precision.

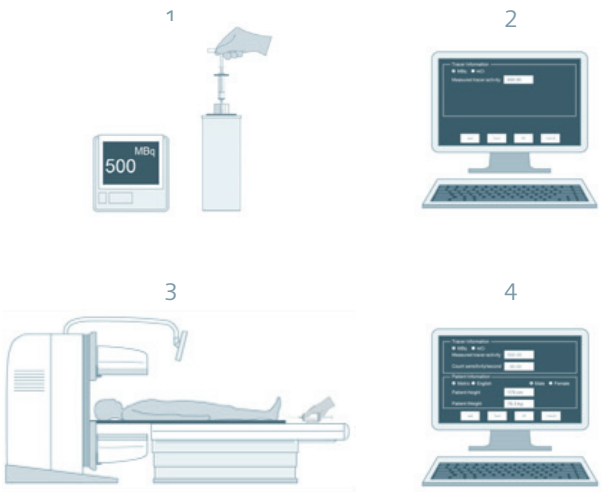

Figure 4: Traditional method B calibrates each scan with a syringe.

Figure 4: 1. Measure the total radionuclide activity in the syringe using a dose calibrator.

2. Insert tracer information including the measured activity to the processing software workstation.

3. Set up the patient and place the measured radioactive syringe from step 1 at the patient's feet. Perform the scan.

4. Provide patient information and compute estimated proportional counts per activity concentration based on steps 1-3.

Limitations of Absolute Quantification Using a Relative Reference

Relative quantification is an important aspect in nuclear medicine imaging analysis. "Relative" could indicate a comparison of uptake in different regions of the body, such as a left and right kidney, using a ratio of uptake. Clearly, in this case the unit of the voxel being either count or Bq/ml is irrelevant. Another "relative" measure is SUV, where the activity in a region is normalized to the injected dose assuming that the dose in the background is in first approximation uniformly distributed, yet often such measure is referred to as "absolute".

In this case, the bias in the dose calibrator is not relevant as long as one uses the same dose calibrator to determine the calibration factor and the injected dose, as the bias in the SUV will cancel out. Inherently, all these measures imply a relation to the calibration source used to do the count-to-Bq conversion and thus to the dose calibrator used to calibrate the calibration source. For such quantification with a relative reference, the variability of the dose calibrators doesn't matter. This relative quantification involves ratios of image intensity values simply assuming that the effects of physical, patient, and technical factors such as attenuation and scatter will cancel each other out. This is an erroneous assumption because the magnitudes of these factors are both spatially varying and patient-dependent.[2]

However, if we envision using the SPECT system to assess biological variability in a patient over time, or to compare or pool patient populations with the same disease or to perform internal dosimetry estimations, one needs to have a reference standard that has small variability and allows reliable measurement of absolute activity distribution *in-vivo*. Dose calibrators can have biases in excess of 10%, e.g., [11] and should not be the reference standard, when the goal is to achieve highly accurate absolute quantification, with errors ultimately below 10%.

Figure 5: Description of xSPECT quantification workflow:

Monthly activities:
1. Calibrate the scanner once every month (12-20 minutes).

2. Calibrate the dosimeter once every month.

Per scan activities:
1. Measure the total radionuclide activity in the syringe in the calibrated dosimeter.

2. Scan the patient and retrieve automatic SUVs in your reconstruction console.

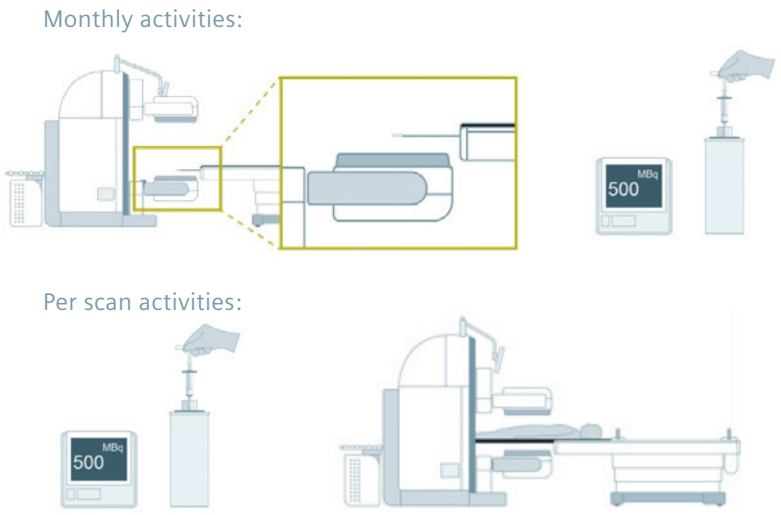

Figure 5: xSPECT method calibrates the scanner and the dosimeter once a month.

Introducing xSPECT Quant

Siemens Molecular Imaging introduced xSPECT Quant in 2013, laying the foundation for quantitative SPECT imaging. The goal is to create a NIST traceable approach to deliver accurate and reproducible quantification of nuclear medicine tracers for such enabled SPECT systems.

A NIST traceable calibrated sensitivity source (CSS) is used as the gold standard. The goal of the CSS calibration is to standardize the system sensitivity so that quantitative results can be compared across systems and time. Each CSS contains ^{57}Co with an activity accurate to within a 3% (99% confidence level (CL) or 2.56s) traceable uncertainty of the known manufactured strength, which itself resides within a 15% acceptance range of the nominal 111 MBq. Following proper SPECT calibration, the CSS should be extended once a month into the field of view (FOV) at a precise location to calibrate out system-specific sensitivity variation. The xSPECT* system is designed to estimate the activity concentration as an integral part of the reconstruction process and the result is an image in units of Bq/ml. No further conversion is needed. The CSS should also be placed in a dose calibrator within a holder that specifies the geometry and allows for a cross-check between the system, the dose calibrator and the CSS.

The xSPECT method is described in detail in reference [12]. Here, the key highlights of xSPECT are summarized:

1. measure system characteristics, either as a class standard or for an individual component (“fingerprint”), 2. iterative reconstruction using an additive update scheme using Mighell’s modified X_g^2 [13] as the objective function and a pre-conditioned conjugate gradient as the minimizer, 3. data is uncorrected and corrections are applied in image space, where the reference coordinate system is the CT Frame-of-Reference.

The characterization of the image formation is anchored by the PSF as measured over the entire FOV and at different distances, where for ^{99m}Tc and LEHR about 90% of the counts are inside the purely geometric footprint (i.e., the region without septal penetration).

All compensations, conversions and use of calibration data occur within the reconstruction, preserving the Poisson nature of the data and, in itself, represent a paradigm shift from the traditional approach that attempts to “correct” projection data. xSPECT reconstructs the activity concentration in Bq/ml at injection time. Currently, only ^{99m}Tc imaging is supported, yet a library of other supported isotopes is being built. Extra modal information (EMI) can also be incorporated in an additive update mechanism, allowing for multi-modal reconstruction, such as xSPECT Bone.

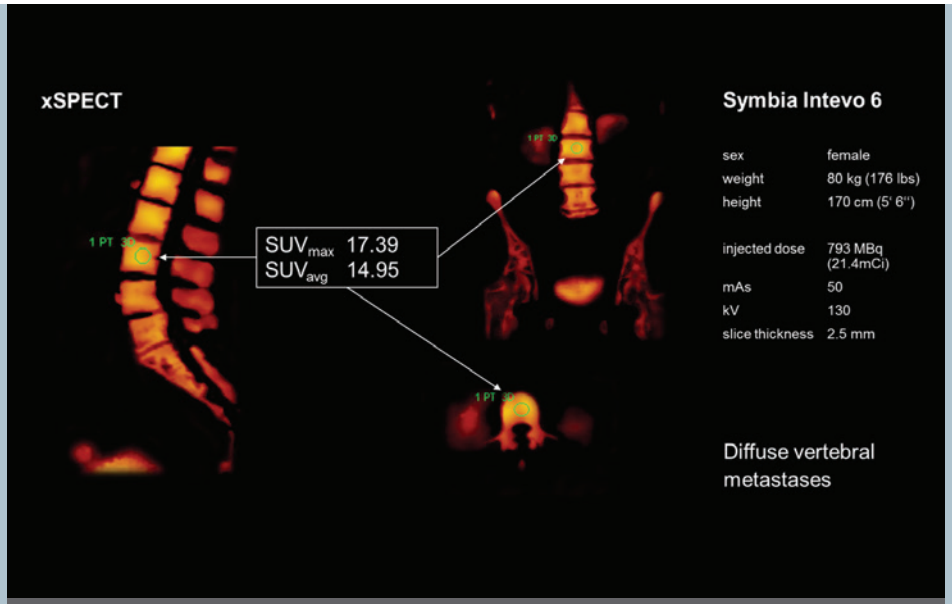

Figure 6

Figure 6: Diffuse vertebral metastases.

Data courtesy of University of Minnesota, Minneapolis, Minnesota, USA

The Benefits of xSPECT Quant

By establishing an accurate, reproducible and standardized quantitative method with xSPECT Quant, the clinical utilities are endless. Here's an example of where xSPECT Quant was able to support the diagnosis of diffuse vertebral metastases.

Background Information

A 70-year-old woman with a history of breast carcinoma treated with surgery and chemotherapy underwent ^{99m}Tc MDP bone scintigraphy for routine follow-up. The planar study was followed by a SPECT/CT study of the lumbar spine performed on a Symbia™ T2.

Findings

The planar whole-body scan showed normal tracer uptake throughout the spine, except for degenerative changes in lumbar vertebrae. xSPECT showed uniform distribution of the tracer throughout the lumbar vertebrae with increased uptake in the right facet joint in L5 vertebrae secondary to facet arthropathy, as well as clear and sharp delineation of lamina, spinous process and spinal canal. Visual evaluation of the CT and fused (CT+xSPECT bone) images, however, shows a different clinical picture. CT shows diffuse sclerosis involving all the lumbar vertebrae including the body of the sacrum and the lamina and spinous processes. Such diffuse sclerosis could potentially reflect diffuse osseous metastases. Visually, the ^{99m}Tc MDP uptake in the sclerotic vertebrae appears uniform without any focal increase. Visualization of kidneys and bladder activity exclude a superscan appearance.

The Benefits of xSPECT Quant

Using xSPECT Quant, the tracer concentration in kBq/ml could be obtained and, using injected dose and patient height and weight information, the SUV of individual voxels as well as volumes could be calculated.

Absolute quantification of tracer concentration in the lumbar with xSPECT Quant shows SUV_{avg} of 14.95 in the center of the body of L3 vertebrae (arrow) which is more than 2 times higher than that of normal (SUV average of 5.91). This high SUV within the lumbar vertebrae along with the diffuse sclerosis on CT is reflective of diffuse osseous metastases. However, the planar bone study did not show diffuse vertebral hypermetabolism and both kidneys were visualized, excluding a "superscan" appearance. This can be explained by the response of the diffuse vertebral metastases to chemotherapy, but with a persistently higher level of vertebral metabolism due to the increased bone turnover within the sclerotic component, as evident in the increased tracer concentration and SUV within the vertebrae.

Quantitative measurements using a technique similar to xSPECT Quant in lumbar vertebrae of 50 normal female patients yielded an average bone tracer activity concentration (AC) of 48.15±13.66 kBq/ml which corresponded to average SUV of 5.91±1.54. [14]

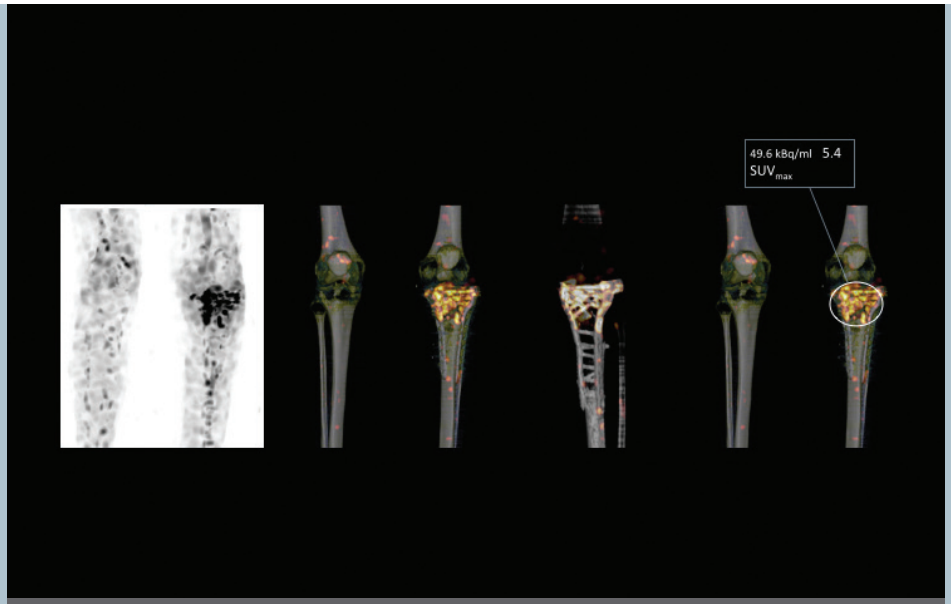

Figure 7: SPECT/CT imaging of infection in tibial fracture with internal fixation with ^{99m}Tc anti-granulocyte antibody with xSPECT Quant evaluation of SUV of leucocyte accumulation.

Data courtesy of Bundeswehrkrankenhaus, Ulm, Germany

Figure 7: Pre-surgery

Quantitative Clinical Case Study

A 74-year-old female with open comminuted fracture of upper part of left tibia was treated with surgical reduction of fracture and internal fixation with flap reconstruction surgery for the surface wound. The tibial plateau fracture was treated with internal fixation using a dual plate. Subsequent to the surgery, the patient experienced persistent pain, wound discharge and non-union of the fracture fragments. In view of the suspicion of osteomyelitis of the tibial fracture fragments, the patient underwent infection imaging with ^{99m}Tc-labelled antigranulocyte antibodies (Leukoscan) and SPECT/CT. The study was performed on Symbia Intevo at 5- and 24-hours after injection with absolute quantification of tracer uptake using xSPECT Quant. SPECT/CT acquisition was performed at 5- and 24-hours following injection. SUV_{max} values were obtained using xSPECT Quant and compared across 5- and 24-hour acquisitions. SPECT/CT images show focal areas of intense inhomogeneous accumulation of ^{99m}Tc-labelled antigranulocyte antibodies within the fracture fragments in the proximal end of left tibia as well as the internal fixation plates, especially the intercondylar plate. The pattern of uptake is suggestive of active osteomyelitis. SUV_{max} comparisons showed that there was a significant increase in SUV_{max} between the 5- and 24-hour acquisitions in all areas of focal uptake (SUV_{max} increase from 2.61 to 4.55 in one foci shown in Figure 7) suggestive of progressive accumulation of radiolabelled antigranulocyte antibodies, which reflect progressive leucocyte accumulation within the infective foci involving the fracture fragments and internal fixation pins and plates of the proximal tibia, suggestive of active osteomyelitis.

In view of the extent of active osteomyelitis, the patient underwent a revision arthroplasty with complete removal of all metal internal fixation plates, resection of the majority of the proximal tibia including the condyles, and replacement of the proximal tibia with gentamicin impregnated bone cement spacer along with external fixation of the femoral and tibial shafts. A delayed arthrodesis once the bone is free from infection was planned. Microbiological evaluation of the resected tibial bone fragment demonstrated Propionibacterium acnes infection.

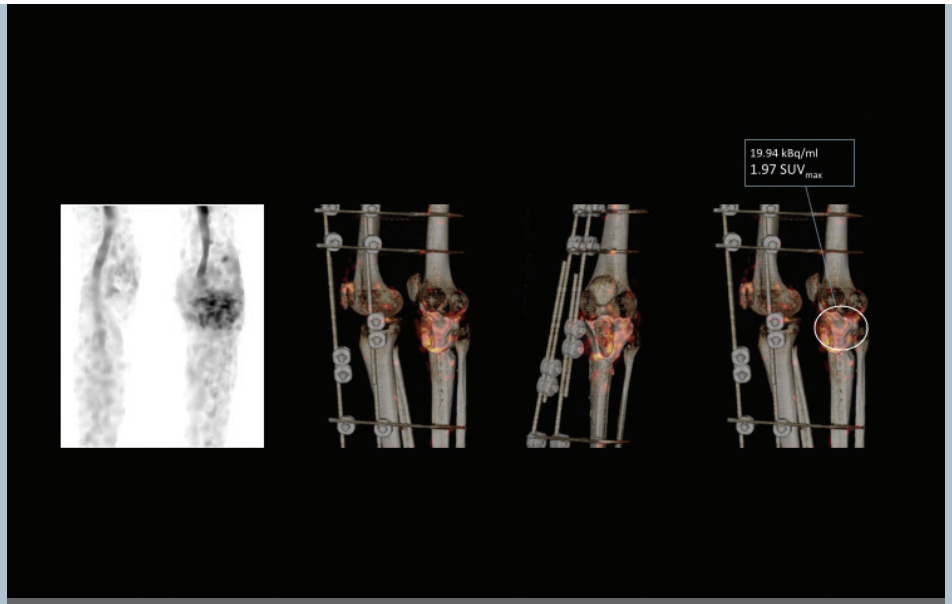

Figure 8: Post-surgery

Figure 8: Follow-up SPECT/CT infection imaging with ^{99m}Tc anti-granulocyte antibodies with SUV quantification using xSPECT quant.

Data courtesy of Bundeswehrkrankenhaus, Ulm, Germany

Two months after surgery, the patient underwent SPECT/CT imaging for evaluation of the presence of infection using ^{99m}Tc-labelled antigranulocyte antibodies (Leukoscan) in order to assess the feasibility of arthrodesis. A similar protocol of SPECT/CT acquisition at 5- and 24-hours after tracer injection was followed with SUV comparison using xSPECT Quant.

CT shows a radiodense mass at the proximal end of the tibia which reflects the cement spacer inserted following resection of the majority of tibial head. The cement fits between the femoral articular surface and the upper end of the tibial shaft. The junction of cement spacer and tibial shaft is irregular, suggesting pseudoarthrosis. The external fixation devices are well-delineated. Fused images show a small area of mildly increased uptake at the junction of the dense cement spacer and the tibial shaft reflecting mild accumulation of leukocytes secondary to reactive changes which are secondary to pseudoarthrosis at the bone cement junction. SUV_{max} in the junction between the radiodense cement spacer and the shaft of the tibia was 1.31 in the 5-hour study but increased only slightly to 1.82 in the 24-hour study. This very mild increase in an extended time period suggested the absence of active infection which is usually associated with much higher leucocyte migration and accumulation in infected bone. SUV_{max} estimation using xSPECT Quant thus provided an objective measurement to evaluate granulocyte migration inside the suspected foci. Moreover, the initial SUV_{max} of 1.31 was also very low which corresponded to the visual impression of only mild uptake which reflects reactive changes at the level of pseudoarthrosis.

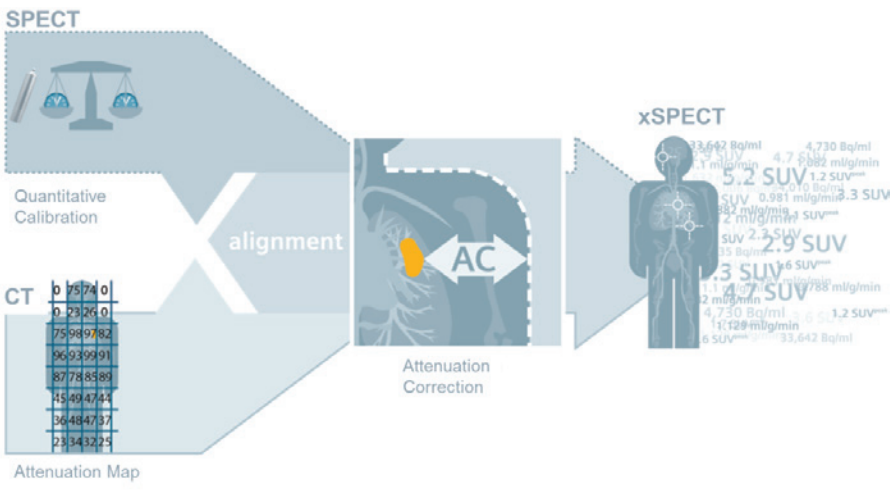

Figure 9: Symbia Intevo with xSPECT Quant is the only nuclear medicine system capable of delivering absolute quantification that is both accurate and reproducible.

Figure 9

Conclusion

The introduction of xSPECT by Siemens represents a paradigm shift for the industry, as clinicians try to carefully construct calibration, acquisition and reconstruction to meet the stringent needs of absolute quantitation in SPECT, whereby an independent gold standard (3% traceable NIST source) from both the dose calibrator and the imaging system itself is also introduced. xSPECT incorporates an additive update mechanism, a more accurate model of the image formation physics using a measured LEHR PSF over the entire FOV of the detector at various heights, and the capability to use extra-modal information to enhance nuclear reconstructions.

In summary, as compared to conventional reconstruction techniques which use relative quantification methods, xSPECT Quant not only improves image quality but introduces for the first time in nuclear medicine a standardized approach to produce accurate and reproducible quantitative values that will further support clinical decision-making and help monitor disease response to therapy.

What the Future Holds

With the introduction of xSPECT Quant, the future looks promising with another step forward towards the development and implementation of standardized evidence-based medicine. xSPECT Quant for ^{99m}Tc is just the beginning and lays the foundation for future developments in the area of accurate and reproducible quantification. At the time of this white paper release, Siemens Molecular Imaging is collaborating with key institutions worldwide to apply the concept of absolute and standardized quantification to other radiopharmaceuticals, such as but not limited to, ^{123}I, ^{111}In and ^{177}Lu.*

*Absolute quantification is not commercially available for ^{111}In, ^{123}I and ^{177}Lu. Due to regulatory reasons, their future availability cannot be guaranteed.

List of References

[1] Frey EC, Humm JL, Ljungberg M, "Accuracy and precision of radioactivity quantification in nuclear medicine images." Semin Nuclear Medicine 2012 May;42(3):208-18. doi: 10.1053/j.semnuclmed.2011.11.003.

[2] International Atomic Energy Agency, "Quantitative Nuclear Medicine Imaging: Concepts, Requirements and Methods," IAEA Human Health Reports No. 9, Vienna, 2014

[3] D. L. Bailey and K. P. Willowson, "Quantitative SPECT/CT: SPECT joins PET as a quantitative imaging modality," *European Journal of Nuclear Medicine and Molecular Imaging*, vol. 41, pp. S17-S25, 2014.

[4] D. L. Bailey and K. P. Willowson, "An Evidence-Based Review of Quantitative SPECT Imaging and Potential Clinical Applications," *Journal of Nuclear Medicine*, vol. 54, pp. 83-89, January 1, 2013.

[5] P. Ritt, H. Vija, J. Hornegger, and T. Kuwert, "Absolute quantification in SPECT," *European Journal of Nuclear Medicine and Molecular Imaging*, vol. 38, pp. S69-S77, 2011.

[6] J.-M. Beauregard, M. S. Hofman, J. M. Pereira, P. Eu, and R. J. Hicks, "Quantitative ^{177}Lu SPECT (QSPECT) Imaging Using a Commercially Available SPECT/CT System," *Cancer Imaging*, vol. 11, pp. 56-66, 2011.

[7] J. Zeintl, A. H. Vija, A. Yahil, J. Hornegger, and T. Kuwert, "Quantitative Accuracy of Clinical ^{99m}Tc SPECT/CT Using Ordered-Subset Expectation Maximization with 3-Dimensional Resolution Recovery, Attenuation, and Scatter Correction," *Journal of Nuclear Medicine*, vol. 51, pp. 921-928, 2010.

[8] M. Elschot, J. F. W. Nijsen, M. G. E. H. Lam, M. L. J. Smits, J. F. Prince, M. A. Viergever, M. A. A. J. van den Bosch, B. A. Zonnenberg, and H. W. A. M. de jong, "^{99m}Tc-MAA overestimates the absorbed dose to the lungs in radioembolization: a quantitative evaluation in patients treated with ^{166}Ho-microspheres," *European Journal of Nuclear Medicine and Molecular Imaging*, vol. 41, pp. 1965-1975, 2014.

[9] R. de Nijs, V. Lagerburg, T. L. Klausen, and S. Holm, "Improving quantitative dosimetry in ^{177}Lu-DOTATATE SPECT by energy window-based scatter corrections," *Nuclear Medicine Communications*, vol. 35, pp. 522-533, 2014.

[10] G. El Fakhri, M. F. Kijewski, M. S. Albert, K. A. Johnson, and S. C. Moore, "Quantitative SPECT leads to improved performance in discrimination tasks related to prodromal Alzheimer's disease," *Journal of Nuclear Medicine*, vol. 45, p. 2026, 2004.

[11] D. E. Bergeron, J. T. Cessna, D. B. Golas, R. K. Young, and B. E. Zimmerman, "Dose calibrator manufacturer-dependent bias in assays of ^{123}I," *Applied Radiation and isotopes*, vol. 90, pp. 79-83, 2014.

[12] A. H. Vija, "Introduction to xSPECT Technology: Evolving Multi-modal SPECT to Become Context-based and Quantitative," Siemens Medical Solutions USA, Inc., Molecular Imaging, White Paper 2013.

[13] K. J. Mighell, "Parameter Estimation in Astronomy with Poisson-Distributed Data. I. The Chi-Square-Lambda Statistic," *The Astrophysical Journal*, vol. 518, pp. 380-393, 1999.

[14] Cachovan M, Vija AH, Hornegger J, Kuwert T. "Quantification of ^{99m}Tc-DPD Concentration in the Lumbar Spine SPECT/CT," *European Journal of Nuclear Medicine and Molecular Imaging*. 2013;3:1-8.

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