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The Magazine for Molecular Imaging Innovation

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Tipping Points and Dramatic Change in the World of Molecular Imaging

Mario Zeiss
Vice President
Global Marketing and Sales
Molecular Imaging
Siemens Healthcare

Dear Reader,

At what point does tradition yield to a new norm? Whether it be ideas, trends or behaviors, new norms often occur over a series of incremental steps until becoming a significant change. This phenomenon is known as a tipping point.

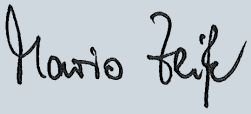
In this issue of *Imaging Life*, our cover story examines what could be the beginning of such a tipping point in molecular imaging, the exchange of a staid technique with a more effective one. In PET/CT, it is the replacement of traditional PET/CT bed positioning with continuous bed motion enabled through FlowMotion™ technology. In SPECT/CT, it is xSPECT's* quantitative capabilities that provide a numerical evaluation of pathology, so that even the smallest differences can be monitored and treated accordingly. Our feature article describes how the acceptance and adoption of these new techniques around the world is beginning to propel the molecular imaging community toward a new standard in both PET/CT and SPECT/CT, one that involves the dynamic collection and processing of data.

And just as FlowMotion and xSPECT are helping to redefine the utilization of PET/CT and SPECT/CT in patient care, other new technologies are helping frame molecular imaging's growing role in disease management. This includes powerful software solutions like *syngo*®.via for Molecular Imaging. Designed to manage unprecedented quantities of patient data, *syngo*.via for Molecular Imaging uses reference-based** quantification technology, called EQ•PET, to provide clinicians with harmonized SUVs across patient PET scans, permitting comparability of results from study to study.

Throughout this publication, you will read about the results of clinical teams and healthcare institutions that are leveraging these latest innovations to set new thresholds for the standard of care.

It is clearly an exciting time for our global molecular imaging community. Working together, we are transforming molecular imaging, and, in many ways, stimulating a positive tipping point for the future of healthcare.

Enjoy reading,



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* xSPECT is not commercially available in all countries. Due to regulatory reasons its future availability cannot be guaranteed. Please contact your local Siemens organization for further details.

**Based on MI EQ•PET and quantification tool functionality.

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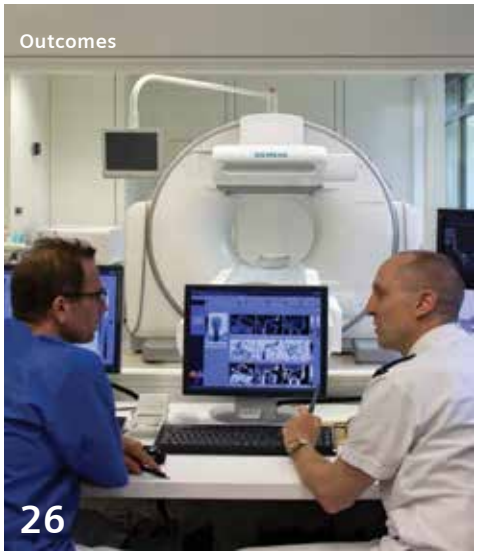

German Hospital Adopts xSPECT for Routine Bone Imaging

Cover Story

FlowMotion and xSPECT Propel Molecular Imaging Toward Tipping Point

In 2013, Siemens Healthcare debuted two ground-breaking molecular imaging systems designed to overcome the limitations of conventional molecular imaging and help propel the industry towards a new standard of practice. In PET, the agent of change is Biograph mCT Flow™*. In SPECT, it is Symbia Intevo™*. In this issue, read more about Siemens' new technologies and the results achieved by leading institutions that are leveraging these new innovations to more confidently diagnose, treat and monitor disease.

* Biograph mCT Flow, Symbia Intevo and xSPECT 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.

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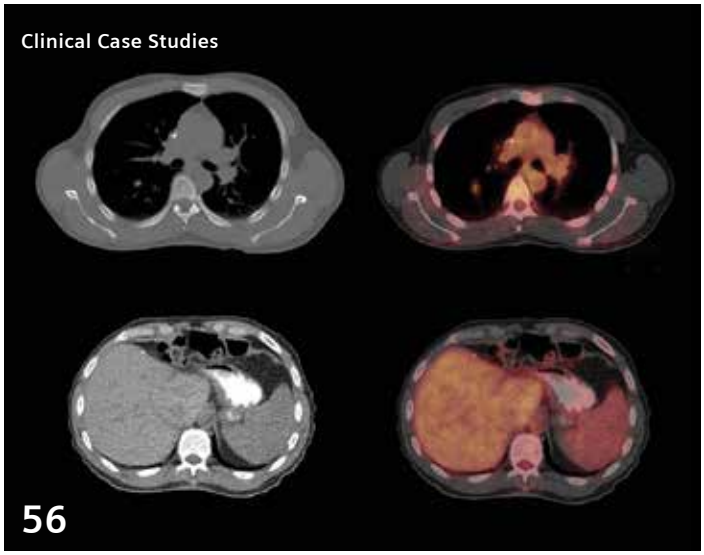

Improved Visualization of Small Liver Metastases Using HD•Chest and FlowMotion

Explore MIU 360 and Surround Yourself with Resources to Grow your Practice

Introducing *syngo*.via for Molecular Imaging: Transforming Big Data into Brilliant Results

Offering unique, automated tools to visualize, measure and report disease, Siemens announced at the Society of Nuclear Medicine and Molecular Imaging (SNMMI) 2014 Annual Meeting its latest molecular imaging software—*syngo*®.via for Molecular Imaging. The software transforms large amounts of data into brilliant results. As a result, physicians benefit from a regained focus on interpretation and can more easily produce high-quality reports.

Molecular imaging studies are typically performed once a disease has reached a critical point. As such, patients present to physicians with prior exams that require further investigation, and these prior examinations, in addition to new single- and/or multi-time point molecular imaging studies, create large amounts of diagnostic data. Consequently, managing this vast quantity of data can present a challenge for physicians who must produce high-quality reports within a reasonable timeframe.

To address this challenge, Siemens Molecular Imaging presents *syngo*.via for Molecular Imaging, an intuitive software solution that allows for organ-based reading*, reference-based quantification** and evidence-based reporting***.

Organ-based Reading

In order to arrive at a reliable and conclusive diagnosis from a study, reading physicians spend significant amounts of time and energy formatting diagnostic information into a layout specific to their personal preferences before moving forward with interpretation. With *syngo*.via for Molecular Imaging's SMART Layout, diagnostic information about the scan protocol, organ and study type are integrated into a Siemens DICOM header, and then automatically translated into the physician-specific layout. This helps ensure physicians can review all available data and focus on organ-specific readings immediately after opening the study—potentially reducing overall study-preparation time, fatigue and the risk of human error. Additionally, *syngo*.via for Molecular Imaging's ALPHA Landmark Registration technology includes algorithms that can automatically identify up to 28 anatomical landmarks, which allows for alignment of multiple studies, performed with CT, MR or PET/CT, for improved analysis and comparison of medical images.

Reference-based Quantification

Physicians diagnose diseases based on the results of molecular imaging studies. Therefore, their findings need to be accurate as well as specific in order to properly guide therapy decisions. However, an ambiguous continuum between what is "normal" and "abnormal" for patients, as well as prior examination data that can contain technology-induced SUV fluctuations can diminish physician confidence and lead to irregular conclusions. In order to remove ambiguity and create normalized, comparable results, *syngo*.via for Molecular Imaging not only offers standard quantification tools for oncology, cardiology and neurology, but it introduces EQ•PET—an innovative algorithm that converts all the non-uniform quantifiable data into harmonized numbers. Across the board, physicians can now compare results independent of imaging modality and source.

Evidence-based Reporting

Molecular imaging studies are often complex and abstract. This makes the traditional way of communicating findings to referring physicians difficult, as textual description lacks the confidence of objective data. This issue is made more difficult when reading physicians must also understand several prior examination textual descriptions before they can begin interpreting the current exam. With *syngo*.via for Molecular Imaging, automated tools generate structured, evidence-based reports, using customizable templates that can define the order and components of each report. Using the Findings Navigator feature, physicians can bookmark their findings for instant access to areas of interest. They can also easily transfer key images and quantification data into a report. Not only do reading physicians benefit from the Findings Navigator, but referring physicians will now have access to comprehensive visual and quantitative evidence, which makes a diagnosis easier to understand and a therapy decision more optimal.

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* Based on MI SMART Layout.

** Based on MI EQ•PET and quantification tool functionality.

*** Available with MI Oncology.

For more information on *syngo*.via for Molecular Imaging, please download the EQ•PET whitepaper on MIU 360 **(www.siemens.com/miu360)**, Siemens Molecular Imaging's customer portal.

Siemens Unveils New SPECT System: Symbia Evo Excel

At the 2014 congress of the European Association of Nuclear Medicine (EANM) in Gothenburg, Sweden, Siemens Healthcare unveiled its all-new Symbia Evo™ Excel*. Under the banner of "small is the new big," this cutting-edge SPECT system features the industry's smallest minimum room size in its class while offering a large, 102 cm (40.2 in) bore size and delivering high-resolution and high-sensitivity clinical images—a combination that positions Symbia Evo Excel as a smart investment for healthcare facilities and clinicians alike.**

Optimize Your Investment

Modernization of medical imaging equipment is essential to meet the demands of the changing healthcare environment. However, replacing conventional systems often comes at a price. Installing new systems typically requires renovations of existing infrastructures and other unplanned expenditures—both of which can add substantial costs. The minumum room size requirement for Symbia Evo Excel is up to 29 percent** smaller than conventional SPECT systems, with a minimum room size of 3.60 m (11 ft 8 in) x 4.57 m (15 ft). This allows the system to fit into virtually any existing nuclear medicine exam room. As such, healthcare institutions can minimize costs associated with room construction and system installation. Likewise, the system's simplicity in size could translate into a less-than-five-day installation, which allows healthcare facilities to minimize downtime and maximize workflow.

Image Every Patient

Providing high-quality care fundamentally resides in the ability to scan every patient***, regardless of size, weight or condition. Whereas many SPECT scanners are limited in their ability to image large patients and are often not flexible enough to accommodate critically ill patients who may not be able to move, Symbia Evo Excel provides a solution: a 30 percent** larger bore size [102 cm (40.2 in) tunnel opening]; a shorter tunnel length, compared to prior systems; a high-capacity, low-height bed that supports patients up to 227 kg (500 lbs); and gurney and hospital bed imaging capabilities—all enabling healthcare facilities to expand their imaging services to a wider population as well as improve patient satisfaction.

Read with Confidence

Having access to reliable, reproducible clinical information is essential to physicians' patient-management decisions and their ability to ultimately initiate the appropriate course of treatment early on or modify existing treatment that may not be effective. The basis for this is exquisite image quality. To achieve this, Symbia Evo Excel uses Siemens AUTOFORM® collimator that delivers up to 26 percent** more counts in sensitivity—the industry's highest**. Additionally, with Symbia 3D iterative reconstruction, the spatial resolution of the collimator is modeled to maintain the precise shape of the lesion. As a result, images are reconstructed with more counts in the correct volume, increasing image contrast. With advanced HD detector technology, combined with the lowest** pallet attenuation, highest** collimator sensitivity and industry-leading** reconstruction algorithms, this system delivers high-quality SPECT images to assist physician decision making.

* Symbia Evo Excel is not commercially available in all countries. Due to regulatory reasons its future availability cannot be guaranteed. Please contact your local Siemens organization for further details.

** Based on competitive literature at time of publication. Data on file.

*** Patients up to 227 kg (500 lbs).

Meet the CFO of Siemens Molecular Imaging

By **Rhett Morici, Molecular Imaging Business Unit, Siemens Healthcare**

Ask most people what healthcare and the IT/telecommunications revolution have in common, and they may just laugh it away. Ask Nitin Gupta, the new chief financial officer (CFO) of Siemens Healthcare Molecular Imaging (MI) since February, 2014, and he will explain how the history of "life-changing" innovation can be used to predict dramatic shifts in healthcare.

Gupta's knack for connecting seemingly unrelated events began early in his life.

"Since my school days, I have liked 'connecting the dots' to see the underlying story," said Gupta, who earned a bachelor's degree in commerce from the University of Delhi, India.

After graduation in 1994, Gupta went to work for Siemens telecommunications in Italy. From there, Gupta has held a wide variety of roles within Siemens from sales and contract administration to business development, performing corporate functions related to strategy development, mergers and acquisitions, and asset/risk management. Additionally, he has held executive management positions. During that time, Gupta earned his MBA degree from the University of Warwick, UK, where he specialized in strategy, finance and start-ups.

"I have enjoyed working within diversified industries over multiple geographies." Gupta said. "It has given me the opportunity to manage similar business challenges that occurred in different business cultures, through unique approaches to problem solving."

These 20 years of far ranging experiences have helped prepare him to be the new CFO of Siemens' MI business.

"In my view, molecular imaging is a mix of diverse business segments," Gupta said of his initial impressions, referencing Siemens' PETNET Solutions and the hybrid modalities that this business unit brings together.

As the CFO, Gupta oversees the unit's financial activities around the world. From this post he will provide financial leadership as well as reinforce Siemens MI's approach to business.

"Siemens focuses heavily on two things: one is quality; we strive very hard to deliver on quality," he said. "Second, we put customers first; it is in our organizational DNA."

Referencing Soviet economist Nikolai Kondratiev, Gupta brings a sense of history, connecting seemingly unrelated subjects to draw hypotheses that can be applied in the healthcare business. Through this, he has forged a connection between future advances in healthcare and the early days of the industrial revolution.

"Historic innovations from as early as the 18th century are extremely insightful," Gupta said. "Some of them have transformed human life, the way we do business and shaped the global economy. The introduction of the steam engine, the steel industry and the laying of railways, together revolutionized transportation. Then there was the automobile, whose true impact was possible because of advances in the petrochemical industry. Much of our life today is based on advances in IT and telecommunications that took shape in the early 2000s."

This continuum of technological advancement is cyclical, he said, rendering historical and life-changing events every 30 to 40 years. According to Gupta, we are due for the next big transformation in the next decade.

"The next big thing," he said, "will come from healthcare and its delivery to the patient, using the IT/telecommunications infrastructure backbone."

Nitin Gupta, CFO, Siemens Healthcare Molecular Imaging

Historically, the advances in medical imaging have been fragmented, he said. But that will change. Our industry, he said, is "moving toward a consolidated and comprehensive approach that will not only benefit the patient but reduce healthcare costs."

In discursive fashion he lists the possible innovations that could reshape the healthcare industry, explaining how consumer electronics might be leveraged to change the delivery of medical images and the reports that help explain them.

Gupta is excited about the story unfolding in healthcare, noting how Siemens' history of innovation and its pioneering spirit has put the MI business unit in position to help lead this changing landscape.

"I see molecular imaging as one step beyond the traditional imaging business," he said. "We help physicians actually follow the disease. This is so much different than taking a snapshot. And I see people [at Siemens] who are very competent, confident, credible and passionate about what they do, and that gives me a good feeling about where we are as a business and the pivotal role molecular imaging will play in transforming the future of imaging, and healthcare."

U.S. Medicare Reimbursement for PET

In 2013, the Centers for Medicare and Medicaid Services (CMS) issued a final decision memorandum on Positron Emission Tomography (PET) for Solid Tumors.[1] This decision memorandum was in response to the National Oncologic PET Registry's (NOPR) request to lift the requirement for Coverage with Evidence Development (CED) for NOPR-covered Fludeoxyglucose F 18 (^{18}F FDG)* PET indications on all subsequent PET scans for oncologic purposes. To confirm, there were three specific elements of this decision.

First, CMS ended the requirement for CED for ^{18}F FDG PET for oncologic indications. This removes the requirement for prospective data collection by the NOPR for cancers or cancer types that had been covered under CED. Second, CMS determined that, after completion of initial anti-cancer therapy, three ^{18}F FDG PET scans are nationally covered when used to guide subsequent management of anti-tumor treatment strategy. Coverage of any additional ^{18}F FDG PET scans for subsequent management will be determined by local Medicare Administrative Contractors. Third, CMS will nationally cover ^{18}F FDG PET when it is used to guide subsequent anti-tumor treatment strategies of prostate cancer. (*See chart below for more information regarding PET/CT indications and reimbursement.*)

Effective for claims with dates of service on or after June 11, 2013, the National Coverage Determination allows and considers four ^{18}F FDG PET scans per patient per unique diagnosis when "medically necessary and appropriate." This includes one initial treatment strategy (ITS), formerly known as "diagnosis" and "staging" and three subsequent treatment strategies (STS), formerly "restaging" and "monitoring response to treatment," for the same cancer diagnosis. Coverage for additional ITS and/or STS exams is determined and controlled by the regional Medical Administrative Contractors (MAC). MACs are not limiting reimbursement to three STS scans, but they require documentation of medical necessity for all STS PET scans beyond three.

References:
1. Final Decision Memorandum on Positron Emission Tomography (PET) for Solid Tumors (CAG-00191R4). (2013, June 11). Retrieved from http://www.cms.gov/medicare-coverage-database/details/nca-decision-memo.aspx?NCAId=263

* Indications and important safety information on Fludeoxyglucose F 18 Injection can be found on pages 53 and 73. The full prescribing information can be found on pages 78-80.

The following table is taken from Appendix C of the National Coverage Determination for ^{18}F FDG PET/CT for oncologic conditions effective June 11, 2013.

Tumor Type	Initial Treatment Strategy	Subsequent Treatment Strategy
Colorectal	Covered	Covered
Esophagus	Covered	Covered
Head and Neck (not thyroid or CNS)	Covered	Covered
Lymphoma	Covered	Covered
Non-small cell lung	Covered	Covered
Ovary	Covered	Covered
Brain	Covered	Covered
Cervix	Covered with exceptions	Covered
Small cell lung	Covered	Covered
Soft tissue sarcoma	Covered	Covered
Pancreas	Covered	Covered
Testes	Covered	Covered
Prostate	**Not covered**	Covered
Thyroid	Covered	Covered
Breast (male and female)	Covered with exceptions	Covered
Melanoma	Covered with exceptions	Covered
All other solid tumors	Covered	Covered
Myeloma	Covered	Covered
All other cancers not listed	Covered	Covered

Image data courtesy of Ludwig-Maximilians University, Munich, Germany; University of Michigan, Ann Arbor, MI, USA; Keio University, Tokyo, Japan

FlowMotion and xSPECT Propel Molecular Imaging Toward Tipping Point

By **Greg Freiherr**

Major societal changes often appear to occur in sudden leaps. Yet this is seldom the case. Instead, new norms generally emerge over a series of steps. While not sufficient in themselves, these incremental advances when compounded, can bring about great change. Change which then appears to be a force that suddenly sweeps across society. This phenomenon is known as a tipping point.

For example, the miniaturization of high-powered computers may have been the basis for the transformation of radiography into computed tomography (CT), but it would not have been enough on its own. Its development required progress in detector electronics, algorithms for processing recorded data and technologies for displaying the reconstructed images.

Led by Sir Godfrey Hounsfield, engineers, scientists and mathematicians put those pieces together. But, as important as Hounsfield and his team were to building the first CTs, the clinicians who made sense of the images contributed as much or more towards tipping the scale from engineering curiosity to medical reality.

It was 1979 when Hounsfield looked into a CT monitor at Northwestern Memorial Hospital in Chicago, IL, USA, and exclaimed: "My word, what is that?" "That" was a large hematoma in the brain of a comatose elderly woman. She had been scanned with a machine descended from the one Hounsfield had developed and would later receive the Nobel Prize.

Clearly Hounsfield's innovations were an initial step, but the routine use of CT imaging resulted from subsequent actions, which took place in a relatively short time period: key researchers and clinicians embraced this new approach early on, propelled its development and then shared their findings with the rest of the medical community, who then created the critical mass needed for these new approaches in medicine to "stick." As a result of these steps, within a few years, CT was validated by the medical community and clinically accepted as a new norm in medical imaging.

In many ways, molecular imaging's future can also be viewed as a series of advances that are leading the

modality towards becoming the new standard of care.

In 2013, Siemens Healthcare, in concert with luminaries around the world, sought to stimulate the next step, with the belief that by introducing new approaches to PET and SPECT image acquisition and processing, the industry could break through existing imaging limitations and unlock the door for further advancement. In PET, the agent of change is Biograph mCT Flow™*. In SPECT, it is Symbia Intevo™*.

Agents of Change

Positive change enables people to do more with less effort while producing higher quality results. Biograph mCT Flow and Symbia Intevo are agents of such change.

With Biograph mCT Flow, physicians benefit from the finest** image resolution in every organ and every scan. By continuously moving the patient through the detection system, FlowMotion™ technology eliminates overlapping bed acquisitions and maintains uniform noise sensitivity across the entire scan range. Building on proven in-plane quantitative accuracy, FlowMotion expands precise quantifiable results to all dimensions. As such, outcomes are achieved more efficiently and effectively, potentially minimizing patient radiation and enhancing patient comfort.

By comparison, conventional PET/CT can be slower and less efficient. It relies on stop-and-go imaging, assigning several bed positions to scan the adult body.

Such whole-body scans are typical in oncologic studies, which comprise more than 90 percent of PET/CT exams. The limitations are especially apparent for physicians seeking higher resolution in the head and neck or respiratory gating to nullify movement artifacts. Scans for these must be performed separately.

FlowMotion completes them in a single, head-to-toe exam. The patient moves continuously through the detector rings at varying speeds, optimizing number of counts for specific body parts and organs and gating to reduce artifacts. A typical oncologic exam may start with a slow moving table, acquiring additional counts for high-resolution images of the head and neck. Table speed may remain slow over the chest to allow respiratory gating. The slow pace may continue over the abdomen to provide the extra counts needed to record small metastases in the liver, for example. Then table speed increases over the pelvis and down through the extremities, making up time when covering areas where metastases are less likely to be found.

Symbia Intevo is the only system to integrate SPECT and CT data. This new innovative technology, xSPECT*, creates images of greater clarity than ever before. Symbia Intevo digitally integrates the two data sets by leveraging the 512 x 512 matrix of the CT to enhance the SPECT matrix which is now acquired in 256 x 256. This is not the case in traditional SPECT/CT systems, which "down sample" the CT data set to the lower resolution afforded by SPECT.

Image quality improves when using xSPECT thanks in large part to the Symbia Intevo's novel algorithm. But the advanced technologies of Symbia Intevo underlie the success of this software.

Through Symbia Intevo's digital detectors, accurate patient contouring, that will ultimately result in an increase in resolution, can be achieved. Mechanical sources of error that cannot be eliminated, for example, those related to detector motion, are corrected by algorithms that also account for the size and shape of collimator holes and distance of the patient from the detectors.

Luminaries of Flow Motion

Early adopters and champions are the ones who lay the foundation for the adoption of new ideas. In medicine, through their work, these luminaries

"Our sense is that FlowMotion provides a more accurate and sensitive acquisition."

Kirk A. Frey, MD, PhD, Director of the PET Center, University of Michigan Hospitals, Ann Arbor, MI, USA

establish the clinical value of new equipment. The early development and clinical testing of FlowMotion was done by a handful of such experts around the world.

This core group of thought leaders helped develop the FlowMotion protocol and validate its key components. Since then, they have adopted the FlowMotion technique for routine use and helped blaze the path towards widespread acceptance of this new approach.

Kirk A. Frey, MD, PhD, director of the PET Center at the University of Michigan Hospitals in Ann Arbor, MI, USA, and his colleagues helped perform the acceptance testing of the new technology in April 2013. They have been using FlowMotion routinely for more than a year. Today they operate two PET/CT scanners, a Biograph™ mCT and a Biograph mCT Flow, and image as many as 10 patients per machine per day.

The Michigan team established early that FlowMotion studies at a high resolution can help discover tiny lesions in the head and neck that might otherwise escape detection. Frey and his colleagues now have made 400 x 400 matrix scans of this body region a building block of the scans for these patients.

"We do our head and neck cancer patients with FlowMotion because it permits us to efficiently acquire better images," Frey said. "We believe this gives us more accurate nodal staging. Our sense is that FlowMotion provides a more accurate and sensitive acquisition."

Also sent for FlowMotion scanning at the University of Michigan are patients who require respiratory gating, primarily to characterize lung nodules. Respiratory gating is also ordered for patients with colorectal and pelvic tumors, as their cancers frequently metastasize to the liver. The appearance of such metastatic disease, Frey said, directly impacts patient management.

Like Frey, Helmut Rasch, MD, is among the early pioneers of FlowMotion. A senior doctor at the Kantonsspital Bruderholz near Basel, Switzerland, Rasch helped establish the utility of FlowMotion when evaluating patients for signs of small pulmonary nodules in a way that minimizes radiation risks to the patient.

Small nodules are found in as many as 30 percent of all CT scans of the lung, according to Rasch. Traditionally CT follow-ups are scheduled at three, six, 12, 18 and 24 months after the initial finding.

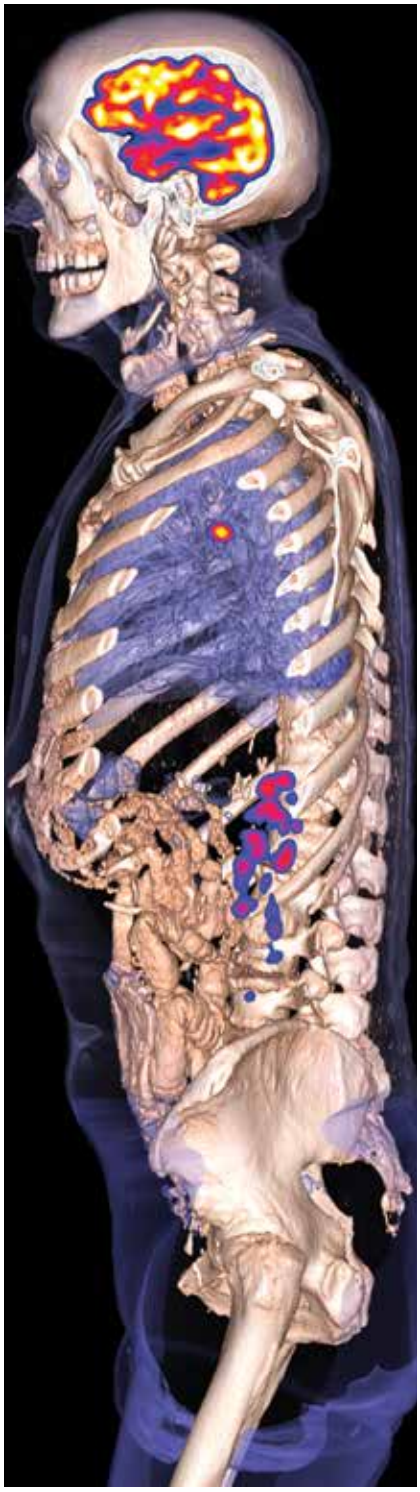
"That is a lot of radiation dose," Rasch said. "We have been trying to do PET scans instead."

Rasch explains that respiratory gating has become a routine part of FlowMotion exams for every patient suspected of lung cancer. Positive results trigger an aggressive diagnostic workup, followed by aggressive therapy, that may involve lung resection. But, when the PET is negative, the staff are confident enough in the absence of cancer that they will hold off ordering a follow-up CT for 12 months, sparing patients the time, expense and radiation of several exams.

"Our confidence is going up in the smaller lesions," he said. "We are getting better results."

Frey concurs with the power of respiratory gating. Motion correction appears to improve the negative predictive value of PET, he said. The Michigan radiologist describes PET/CT with respiratory gating as "the most sensitive approach you can take" when evaluating lung nodules.

At the Medizinische Hoschshule in Hannover, Germany, Frank M. Bengel, MD, and colleagues are using FlowMotion for single organ coverage, assessing the use of FlowMotion as it might be applied at the beginning of a whole-body scan, then truncating the scan after gathering data on just the brain. The goal behind their ongoing research is to look at how FlowMotion acquisitions compare with those done in a single-bed position.



FlowMotion's high-resolution 400 x 400 matrix and HD•Chest for motion management provides physicians with critical data for early lesion detection. *Data courtesy of University of Michigan, Ann Arbor, MI, USA.*

Early Adopters of xSPECT

The value of quantitation has been evident for decades in PET/CT. The combination of SPECT and CT raised the prospect of quantitation. But until the release of Symbia Intevo, the numerical evaluation of pathology could be achieved with SPECT/CT only in research laboratories following substantial enhancement of scanners. With xSPECT, quantitation is possible for the first time using a commercial system right out of the box.

Torsten Kuwert, MD, chair of nuclear medicine at the Friedrich-Alexander-Universität Erlangen-Nürnberg, is validating Symbia Intevo for this purpose, using xSPECT to quantify absolute radioactivity concentration in patients referred for bone scintigraphy. Presenting results at the Siemens Molecular Imaging World Summit 2014, Kuwert reported the calculation of standard uptake values with xSPECT "that correlated rather nicely to the values you would get with PET/CT."

Kuwert described several cases in which quantitation helped determine the correct diagnosis. A patient with prostate cancer presented with metabolic activity in the bone. Quantitation with xSPECT of the radioactivity within vertebral bodies demonstrated higher radioactivity when compared to control patients.

In another case, quantitation with xSPECT allowed tumor response monitoring during radioreceptor therapy. Radioactivity in liver metastasis was quantitated and compared with values obtained in a volume of interest of the liver unaffected by disease. Values obtained with xSPECT showed a substantial decrease of activity in the metastasis after a single cycle of radioreceptor therapy in the context of a much smaller decrease in the healthy tissue.

"This then proved the patient response," Kuwert said. "This is quite analogous to what we have been doing with ^{18}F-labelled PET radiopharmaceuticals for some time."

The images with limited spatial resolution that commonly result from the fusion of SPECT and CT can be particularly vexing in the evaluation of oncology patients both diagnostically and prognostically. In these patients, localization of the metabolic abnormality uncovered with SPECT is critically important. Diagnosticians must determine whether the lesion is inside or outside the bone.

Improved localization helps in drawing the correct conclusion. Lesions caused by joint degeneration, for example, may look like inflammation of the surrounding tissue or even a soft tissue cancer near the bone. This is where xSPECT can help.

Symbia Intevo uses the CT data set to define the density of tissues. Hard and soft tissues are easily distinguished, producing a map of the tissues. This map then serves as the basis for interpreting SPECT values.

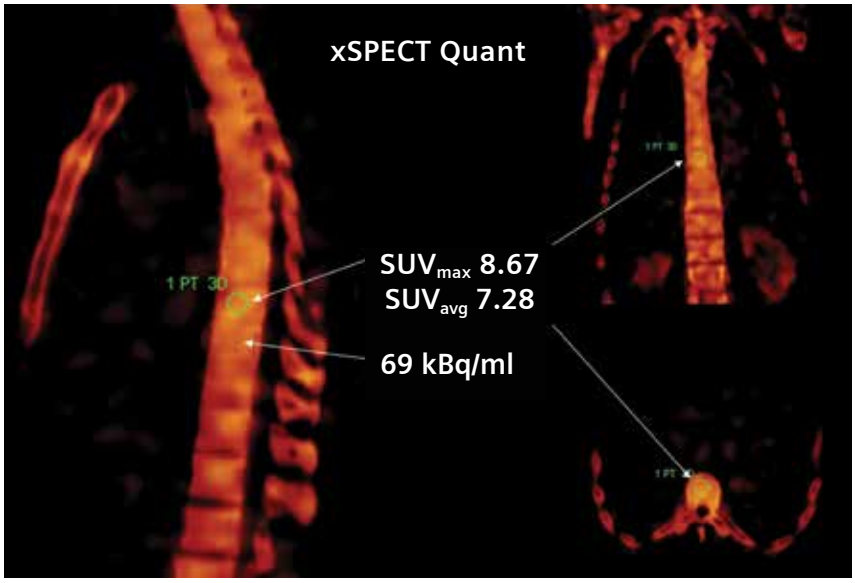
Harun Ilhan, MD, at the Department of Nuclear Medicine at the University Hospital of Munich is comparing 3D iterative reconstructed images made through conventional SPECT/CT processing to xSPECT images. Until xSPECT, younger radiologists at the university were regularly overruled by veteran diagnosticians who relied more on their experience when drawing conclusions than images provided by gamma cameras, according to Ilhan.

"Novel techniques like xSPECT are making it easier for us to make our diagnoses," he said.

Ilhan and colleagues began evaluating Siemens' novel reconstruction algorithm in 2012. At the Siemens Molecular Imaging World Summit 2014, Ilhan presented several cases demonstrating the value of xSPECT. In one, a 51-year-old female with breast cancer, the extent of bone metastasis was not apparent on 3D iterative reconstructed images but required the separate interpretation of images prepared from the CT data set.

"But if we look at the xSPECT reconstruction we actually don't need the CT images to see where the accumulation is in the vertebral body," he said.

Similarly, diagnosis was simplified in the xSPECT of a 65-year-old male with prostate cancer, when xSPECT images showed that a finding suggestive of bone metastasis on 3D iterative



xSPECT measurments in lumbar vertebrae of a patient with normal tracer distribution in thoracic and lumbar vertebrae show tracer concentration of 69 kBq/ml and average SUV of 7.28 in the center of the T9 vertebral body. *Data courtesy of University of Erlangen, Germany.*

reconstruction was actually an osteoporotic fracture.

"The xSPECT alone speaks for itself," he said. "We see the end plate deformity; we see the uptake between the end plates; and we can say it is due to an osteoporotic fracture."

Greater clarity in single photon molecular imaging is arriving, just as the tools for effective palliative therapy for osteosarcoma and bone metastases are emerging that involve the use of novel SPECT tracers.

In peptide receptor radionuclide therapy (PRRT)***, a synthetic analogue of somatostatin binds to receptors on the surface of tumor cells as would the naturally occurring hormone. But, unlike the natural hormone, it carries a radionuclide, whose high-energy radiation kills the tumor cells with low-energy gamma rays that allow the SPECT/CT to localize the radionuclide.

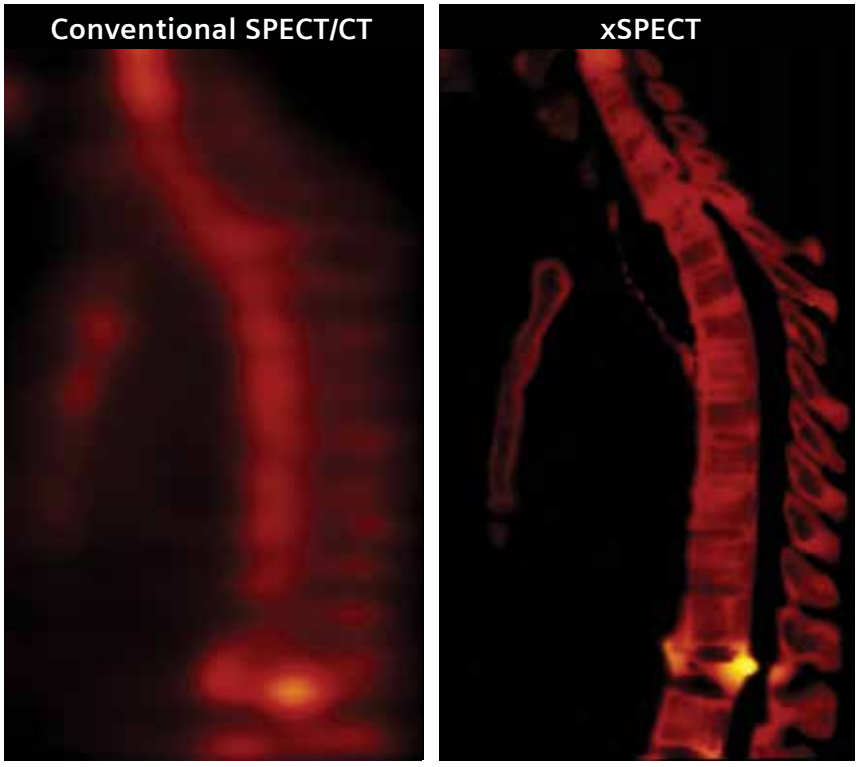
Ideally physicians would like to tailor the dose of octreotate to the patient. This is possible using gallium and PET/CT. It may also be possible using SPECT quantitation, according to Jean-Mathieu Beauregard, MD, Assistant Professor in the Department of Radiology at Université Laval, CHU de Québec, Quebec City, Canada. Beauregard demonstrated the potential of SPECT/CT quantitation, performing dosimetry studies on patients undergoing PRRT.

"I think quantitative SPECT could be useful in the PRRT pre-therapy evaluation to better characterize this disease and it could also provide some prognostic information, but for the most part quantitative SPECT will be about monitoring absorbed radiation dose. This would allow personalized radiation radionuclide therapy. There's also a role for therapeutic molecular response assessment during therapy."

This assessment, conducted after each cycle, would indicate the relative radiation activity of the tumors and, in doing so, indicate subtle changes that may be predictive of outcome, according to Beauregard.

"...techniques like xSPECT are making it easier for us to make our diagnoses."

Harun Ilhan, MD, Department of Nuclear Medicine
University Hospital of Munich, Munich, Germany



With Symbia Intevo, physicians are now able to have more diagnostic information to aid them in drawing correct conclusions. *Data courtesy of the Ludwig-Maximilians University, Munich, Germany.*

Results achieved with SPECT/CT were comparable, he said, to those achieved using PET/CT. One drawback, however, is the time involved. Gallium PET/CT studies can be done in an hour or less. SPECT/CT dosimetry requires 24 hours, according to Beauregard.

But quantitative SPECT has the potential to evolve into "what I think is the radionuclide medicine of the future—personalized nuclear medicine," he said. "I am thrilled that Siemens introduced its xSPECT package, fulfilling a long-standing need for quantitation in monophotonic nuclear medicine."

Fast-Growing Community

Not surprisingly, the community of users who have since joined the pioneers of FlowMotion are leveraging this new technique to perform whole-body imaging, either for clinical applications or as part of research projects.

Physicians at Keio University School of Medicine in Tokyo, Japan, began using FlowMotion routinely in mid-February 2014. It is used primarily in oncology.

"FlowMotion allows us to visualize the tiniest lesions in head and neck cancer patients," said Koji Murakami, MD, PhD, head of the Division of Nuclear Medicine, Department of Radiology at Keio University School of Medicine. "For these patients, we perform precise imaging using slow table speeds, followed by a faster table speed for the pelvis and extremities, which have a lower probability of metastases."

Murakami and his staff scan patients with a wide range of cancers. The majority are lymphoma, lung cancer and gastrointestinal cancers, including colorectal and gastric.

Respiratory gating is an important part of scans involving suspected thoracic and abdominal metastasis. In past research, Murakami and his colleagues have confirmed the utility of respiratory gating. The drawback to its use then, he said, was the need to do a separate, respiratory gated scan in addition to the whole-body stop-and-go scan. Biograph mCT Flow resolves this issue.

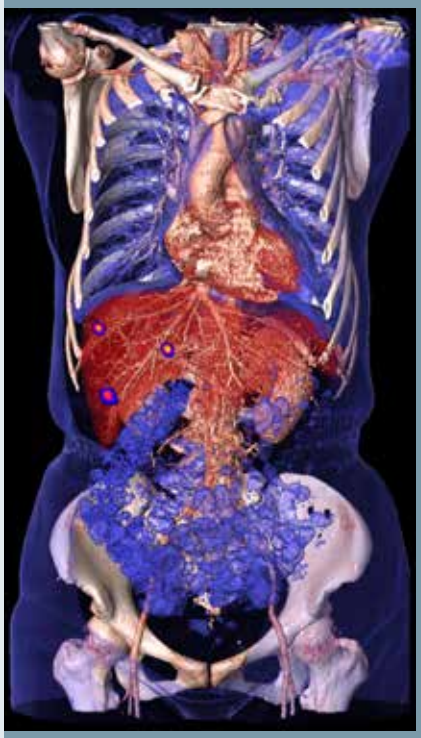
"The merit of FlowMotion is that we can vary the acquisition time and integrate respiratory gating into a single exam," he said.

When staging cancer of the head and neck, a slow table speed is chosen for those regions of the body, followed by a faster acquisition over the pelvis and the extremities.

"This is the optimal way to use FlowMotion," Murakami said.

"FlowMotion allows us to visualize the tiniest lesions in head and neck cancer patients."

Koji Murakami, MD, PhD, Head of the Division of Nuclear Medicine
Department of Radiology Keio University School of Medicine
Keio, Japan



FlowMotion's variable table speed allows physicians to tailor scans specifically for each patient that not only minimizes the overall exposure to radiation, but delivers image resolution suited for specific regions. *Data courtesy of Keio University, Tokyo, Japan.*

He and his colleagues are among a broadly growing community of Biograph mCT Flow users.

Just as FlowMotion gains traction around the world, a growing number of Symbia Intevo users are beginning to document the advantages of this new system's unique imaging capabilities. Pierre-Yves Salaun, MD, PhD, head of the Department of Nuclear Medicine at University Hospital in Brest, France, is using xSPECT to take on some of the most challenging cases in bone scintigraphy, ones addressing carpal fractures of the wrist.

The metabolic and anatomic information provided by xSPECT offers the potential to determine the presence of fracture among the small bones of the wrist. Located inside the bone, a metabolically active area may indicate fracture. Outside it may be a sign of inflammation. Proper management of the patient depends on making the right call.

Since the delivery of Symbia Intevo in February 2014, Salaun has been comparing images obtained through traditional 3D iterative reconstruction with those generated by xSPECT. Both types are reconstructed for each patient, ensuring that what is seen is real and not an artifact.

"If both show the same, we send the beautiful (images) to the clinician," said Salaun who notes that xSPECT delivers the most impressive images. Interpretation is easier with xSPECT, he said, and faster because the lesions are more apparent.

"I am sure that, using xSPECT Bone*, it is easier to see the abnormalities than with 3D iterative reconstruction," Salaun said. "The images appear very focused and with higher intensity."

Experiences by Salaun and colleagues are building the foundation of a critical mass that may eventually tip SPECT/CT practice in favor of xSPECT. Broader and more widespread adoption will depend, however, on documenting the technical advantages of this new technology, validating claims of improved clarity in the fused images.

The improved resolution offered by xSPECT was the subject of a scientific poster presented at the Society of Nuclear Medicine and Molecular Imaging (SNMMI) 2014 meeting. Data gathered by Siemens documented that xSPECT Bone has higher resolution at the edges, where boundary is delineated by the CT and that xSPECT recovers resolution about four times faster than the conventional reconstruction algorithm used to produce 3D iterative reconstructed images.

A recent multi-center scientific study demonstrated increased physician reading confidence in both lesion detection and lesion characterization with Siemens xSPECT Bone technology, versus conventional methods. Participating physicians evaluated more than 75 anonymized scans, including over 2,000 individual lesions, in four different formats—conventional OSEM 3D iterative reconstruction and SPECT/CT fusion methods, and xSPECT Bone reconstruction and xSPECT/CT fusion methods. During their evaluation, physicians responded to two questions using a five-point scale rating: "Is the lesion present?" (lesion detection) and "Is the lesion benign or malignant?" (lesion characterization). Results showed that physician reading-confidence in lesion detection and characterization without CT when evaluating images reconstructed using xSPECT Bone was 41 percent higher and three-times higher, respectively, versus conventional OSEM 3D reconstruction. Additionally, reading confidence for lesion detection and characterization with CT when evaluating xSPECT/CT fused images was 21 percent and 32 percent higher, respectively, in comparison to conventional SPECT/CT fusion.

The study, involving exams done on 76 patients, was performed by nine reading physicians at MD Anderson Cancer Center, the Johns Hopkins University, University of Minnesota, Friedrich-Alexander University of Erlangen and Ludwig-Maximilians University of Munich.

Everyday Routine

One reason behind the strong foothold these new technologies have taken is the fact that they are helping to meet daily clinical needs. When characterizing lung nodules with Biograph mCT Flow, quantitative measurements are routinely used at the University of Michigan Hospitals. Data obtained using respiratory gating, according to Frey, reliably translates into standardized uptake values

(SUVs) of lung lesions, even when the lesions are located in the mid- or lower zones of the lung.

"This is where respiratory motion is most vigorous," he said. "We think, but we have not yet completed data analysis, that these measurements will impact the assessment of therapeutic response."

This is particularly important when external radiation beam therapies are applied, according to Frey. This type of therapy, often prescribed for patients who are not surgical candidates, typically results in lung scarring or fibrosis around the radiated lesion. This, in turn, changes the way in which that part of the lung moves during respiration.

"It usually restricts it so much that the post radiation therapy scan has less confounding expiratory motion than the scan done at initial diagnosis," he said. "We think this could lead to an inaccurate estimate of residual metabolic activity, unless respiratory gating is done for both examinations. We, therefore, believe that respiratory gating will give us a better and more accurate estimate of what the tumor's actual response has been to therapy."

According to Rasch's observations, he sees the possible advantages of FlowMotion with respiratory gating over stop-and-go imaging when it comes to quantitation. "It has a great benefit especially in cancer where we need to accurately measure uptake to make the right therapeutic decision," he said. The wrong one exposes patients to unwarranted costs, less than optimal therapies and potentially unnecessary imaging exams.

In their routine clinical work, Rasch and his colleagues have little margin for error. They are competing with three other PET scanners operating within 10 miles of their facility.

"FlowMotion is a great marketing instrument," Rasch said. "We have faster scans with the potential for more precision. And we have quantitation that we can rely on."

The precision of FlowMotion comes from the use of a continuously moving table. All PET/CT scanners are susceptible to a loss of sensitivity near the edge of the detector. Stop-and-go imaging relies on static bed positions. Consequently, tissues near the edge of the detector may not be assessed as accurately as those in the center or "sweet spot" of the axial field of view (FOV). FlowMotion does not suffer from this shortcoming. It pushes every point in the patient through the center of the FOV.

The problem has been long known in PET/CT. This is why, in stop-and-go imaging, bed positions are commonly overlapped to compensate. It is not possible to do so, however, for the first and last bed positions. And, typically based on the technologist's decision, there are no clear guidelines regarding the degree of bed position overlap.

"The problem is that the user doesn't know exactly where the overlap begins and ends," said Yong C. Bradley, MD, who helped in the early development and testing of FlowMotion. "The count values actually changed quite a bit, before we got our Biograph mCT flow."

Bradley, an associate professor of radiology at the University of Tennessee Medical Center in Knoxville, recalls evaluating cases done with stop-and-go imaging in which SUV_{max} calculations were calculated for points in the liver. These varied significantly.

"Values could be from 2.5 to 10.8 on the same lesion," he said. "I always had to look closely at the rest of the scan to see if there was a qualitative difference, which meant the quantitative values became less and less important."

This variability raised issues with referring physicians who would ask Bradley how the patient could be getting better when the SUVs were higher after the most recent scan compared to the previous one.

Shortcomings associated with overlapping bed positions can be a problem qualitatively, as well. Insufficient or improperly set overlaps can lead to blurring, especially of small or low-grade lesions. This can compromise diagnostic accuracy.

"You want sensitivity to be as uniform as possible throughout the scan," Bradley said. "You want to take your measurements in the so-called sweet

spot of each detector, which is about 60 percent toward the center," Bradley said. "The other 20 to 30 percent near the edges may not show activity as uniformly as the center."

Biograph mCT Flow begins scanning before the specified start point and slightly after the defined scan range. This ensures that data otherwise on the edge of the detector are acquired in this sweet spot. The result is uniform data collection, "edge-to-edge" image quality, and the accuracy of quantitative measurements.

FlowMotion also ensures the reproducibility of repeat scans, because data are gathered in exactly the same way. Follow-up scans are commonly performed in oncologic cases to gauge patient response to therapy. Accurate readings are essential, if the patient is to receive the best possible management.

Value for Patients

Image quality is inherently beneficial to the patient, as it increases diagnostic confidence. Qualitatively, xSPECT produces "images of unheard quality for SPECT," Kuwert said. "You can appreciate how sharp the different bones are delineated. Pathology can be much better appreciated than when you only have the 3D iterative reconstructed images."

In a case presented at the Siemens Molecular Imaging World Summit 2014, Kuwert pointed out a compression fracture of the first lumbar vertebral body that was immediately apparent on xSPECT, which he describes as representing "a breakthrough for spatial resolution."

Minimizing patient radiation dose is important, especially when managing cancer patients who typically undergo repeat PET/CTs. By eliminating bed positions, Biograph mCT Flow eliminates the over scanning with CT that commonly occurs during stop-and-go exams.

The bed positions in conventional PET/CT require CT over scanning because the PET acquisitions cover body areas beyond the actual target regions. This is not so in FlowMotion, which allows the technologist or physician to truncate the CT scan when the target organ is covered. This precision leads to the lowest possible patient radiation dose, while it speeds the exam, boosting workflow. At the University of Michigan, an FDG study including radiotracer and CT exposure typically totals 10 mSv, according to Frey.

Dose minimization is especially important when imaging pediatric cases and young adults who have lifelong concern about ionizing radiation exposure, he noted. For example, a 17-year-old with Hodgkin's disease would be assigned a FlowMotion scan because the patient would likely receive between four and six PET scans over the coming three years, depending on how the lymphoma response to therapy.

Because FlowMotion is very efficient at counting coincidence events, radiation dose from the radiopharmaceutical can be minimized. The operator can administer a low dose of radiopharmaceutical. Frey and his colleagues routinely administer just 8 mCi injection for an adult patient weighing 70 kg.

"This is the lowest I am aware of in our geographic environment," he said. "To give much less I think would require us to extend the imaging time such that the exam might not be as well tolerated by patients who might then begin to move because they have become uncomfortable. This would compromise the data collection."

Protocols with high resolution and respiratory-gated regions can be routinely performed using FlowMotion within the same time slots as would be used for standard stop-and-go exams. Frey and his colleagues schedule the acquisition for a time slot between 20 and 24 minutes.

The ability to accelerate an exam can come in handy when fast exams are needed to win the cooperation of anxious patients. FlowMotion substantially reduces the sources of patient movement that can introduce motion artifacts.

"[With FlowMotion] we have faster scans with the potential for more precision. And we have quantitation that we can rely on."

Helmut Rasch, MD, senior doctor
Kantonsspital Baselland, Bruderholz, Switzerland

"...the flexibility of FlowMotion is beneficial."

Frank M Bengel, MD
Director, Dept. of Nuclear Medicine
Medizinische Hochschule, Hannover, Germany

Growing Momentum

Biograph mCT Flow and Symbia Intevo address challenges affecting healthcare now and for decades to come. Efficiency and clinical effectiveness; diagnostic confidence and patient comfort—these increasingly are the metrics by which molecular imaging will be judged. Gone are the days of sprawling decision trees with multiple modalities intertwined in their branches. Physicians are seeking quick and sure answers.

Experience has shown that what is already possible with FlowMotion and xSPECT offers substantial advantages over the status quo. A PET/CT showing brain metastatic disease, a finding especially likely when performing a FlowMotion high-resolution brain scan, may obviate the need for MRI to confirm the presence of metastases, according to Frey.

"A contrast-enhanced CT may be all that is necessary and if the patient has symptomatic CNS disease, and even that may not be a requisite," he said.

Symbia Intevo with xSPECT offers similar advantages, as seen in work carried out by Salaun. MRI is the gold standard, when it comes to evaluating the scaphoid bone, one of the most common carpal bones to break, as happens when falling on an outstretched hand.

Correct diagnosis and prompt treatment are essential for the well-being of the patient. Treatment involves an arm cast worn to the elbow for two to three months. Sometimes surgery is needed.

To judge the clinical value of xSPECT, Salaun is comparing xSPECT bone and 3D iterative reconstructed images to MR images. "This way we will know whether xSPECT is the best (for this indication)", he said.

Quantitation may help. Salaun is obtaining SUVs for scaphoid bones in both wrists of each patient examined. The one not traumatized provides base values for comparison against ones in the traumatized wrist.

"Currently we do not have an idea of what the thresholds may be but I am pretty sure that in the future, when we have more clinical follow-up, xSPECT Quant will be great tool for evaluating patients. "

With FlowMotion, providers can efficiently and effectively perform an otherwise complex and time consuming protocol. This is so when considering that physicians who practice stop-and-go imaging can do high resolution and respiratory gated imaging, but these require additional effort and time.

This added protocol is time consuming and challenging for the technologist. It also sometimes exposes the patient to excessive radiation from repeat administrations of the radiotracer and the accompanying CT if the scans are not performed back-to-back. For these reasons, this protocol typically is not performed.

The widening appeal of FlowMotion is that, with a single click, technologists launch algorithms that automatically integrate scans with varying resolutions and respiratory gating, simplifying the workflow so that otherwise challenging data acquisitions can be done routinely and exposing the patient to no extra radiation.

Done separately, respiratory-gated acquisitions with conventional PET/CT typically require between one and three bed positions, depending on the size of the patient and on whether data needed to be acquired from the liver. Accommodating such scans could turn into a scheduling nightmare and an interpretive challenge for the physician.

The PET Center at the University of Michigan Hospitals maintains a rigid schedule for its PET scans. Fixed times are set for the injection of patients with radiotracer and when the patients are brought to the scanner. As a result there is an absolute time for each scan beyond which technologists cannot continue imaging.

Delaying the next patient on the itinerary would impact the overall schedule, impeding throughput. As importantly, adding an acquisition to perform respiratory gating could affect the quantitative values due to the short half-life of the positron emitter, Frey said.

"The real advantage of FlowMotion is to limit the anatomic extent of its gated use and to allocate no more—and no less—time than is needed to collect the data where motion is expected," he said.

Simplicity is at the root of FlowMotion's popularity among technologists, according to Frey, as its continuous table motion eliminates the complexity of configuring and adjusting individual bed positions.

Biograph mCT Flow also provides a standardized scan that fits the clinical needs of the individual patient.

"We can standardize acquisitions for patients who have a defined type of malignancy or an unknown anatomic abnormality," Frey said. "In the past the only options were to add extra standalone acquisitions to a whole-body scan for gating or for high resolution brain imaging and those almost always caused us to spend additional time on the scanner."

The Catalyst for Further Discovery

Naturally, FlowMotion and xSPECT are still in their infancy. Currently the benefits of xSPECT, for example, are available only when performing bone scintigraphy. The users of this technology, however, want more.

"We are keen on increased sensitivity and resolution not only for bone but for all applications," Kuwert said. "We would be interested in getting advanced software for data evaluation that allow us to perform clinical studies much more quickly."

When performing dedicated heart and brain scans at the University of Michigan, Frey and colleagues scan patients in a fixed position. But Frey has an idea that would change that, one that would take advantage of the inherent strengths of FlowMotion.

"FlowMotion could theoretically be an advantage for acquisitions of the heart and brain, but to do this properly we would need to implement a 'hover' mode whereby the scanner would traverse back and forth across a limited region of interest," Frey said.

This hovering, or shuttling back and forth across the brain, would ensure that there is no temporal bias over the course of the exam. Such bias can be imposed by ^{18}F-labelled radiopharmaceuticals whose short half-life and tissue clearance can cause a measurable loss of activity during even a relatively short, 15-minute acquisition. Frey envisions a hover mode in which brain would be traversed as many as six times during the examination with the table pushing the patient back and forth through the FOV. It might be applicable to cardiac as well as neurologic studies.

Murakami and his Japanese colleagues are examining the development of a dynamic whole-body PET/CT scan. The goal of such a scan would be to produce an evolving view of radiotracer diffusion throughout the body over a set period of time.

This might be done by scanning the patient from head to toe at one minute increments. To do so, the patient table would have to push the patient completely through the detector rings multiple times. Murakami suggests that the scan might be composed of up to ten such whole-body acquisitions.

The approach would involve "additive cumulative reconstruction," whereby the 10 one-minute images are acquired and then compiled dynamically. "This could be very important in discriminating between normal and pathological tissue," Murakami said.

Ongoing research at the Hannover facility involves the use of FlowMotion to plot time-activity curves of experimental radiotracers in different organs. For these radiotracers to have clinical value, the curves must be determined to support interpretations that distinguish between normal and pathologic processes. The details are proprietary, but Bengel noted that the studies have clinical potential in looking at cancer metabolism.

"Melanoma, for example, involves not just one organ but usually the whole body," he said. "That is where you need whole-body images and that is where the flexibility of FlowMotion is beneficial."

FlowMotion, with its unique approach to whole-body scanning, and xSPECT with its improved image quality and ability to quantitate, appear today at the crossroads of medicine. Their widespread use could potentially lead the way to an age of value-based medicine, and serve as the tipping point for the molecular imaging community in becoming the new standard of care.

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* Biograph mCT Flow, Symbia Intevo and xSPECT 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.

** Based on volumetric resolution available in competitive literature for systems greater than 70 cm bore size. Data on file.

*** The concepts and information presented for PRRT are not commercially available. Its future availability cannot be ensured.

The statements by Siemens' customers described herein are based on results that were achieved in the customer's unique setting. Since there is no "typical" hospital and many variables exist (e.g., hospital size, case mix, level of IT adoption) there can be no guarantee that other customers will achieve the same results.

syngo.via for Molecular Imaging Reduces Labor, Speeds Interpretations

Increasing the volume of patients at a PET facility may come with many challenges. The need for greater efficiency is fundamental as physicians interpret more images each day. At the Sand Lake Imaging Center in Orlando, Florida, USA, Siemens' new reading solution, *syngo*.via for Molecular Imaging, paved the way for this transition.

By **John Hayes**

With capabilities in both clinical practice and academic research, Sand Lake Imaging Center was primed to move from a mobile PET/CT service to a fixed operation. Demand for PET/CT in oncology and potentially neurology was growing. Installing a Biograph mCT PET•CT system on-site would handle patient volume. But that was only part of the challenge facing the Orlando, Florida, center.

PET/CT scans were taking 45 to 50 minutes to read. This was fast enough when handling the low patient volume of a mobile service. But not the increased rate possible with a high-performance, fixed PET/CT, which demanded greater efficiency.

The staff at Sand Lake Imaging met the challenge in November 2012 with the installation of Siemens' *syngo*®.via. This early-version software assisted in the collection, presentation, analysis and reporting of imaging studies. An upgrade to Siemens latest reading solution *syngo*.via for Molecular Imaging, promised to markedly boost the center's productivity, automating the technical aspects of collecting and presenting scan data and speeding interpretations.

"We sought a software solution that would enable us to be more efficient and accurate in delivering information to our referring doctors," said Stephen Bravo, MD, medical director of Sand Lake Imaging Center.

Now in commercial form, *syngo*.via for Molecular Imaging easily handles routine and time-consuming tasks, allowing reading physicians to concentrate on making interpretations, just as it helps analyze quantitative data. The software also helps produce a report that referring physicians can easily understand and trust to accurately guide therapy decisions.

syngo.via for Molecular Imaging does this by leveraging three functions. The first involves image alignment. The software aligns images from past and current studies performed with CT, MR or PET/CT, using organ-based, anatomical reference points. Second, algorithms compute normalized quantifications of SUVs (standard uptake values) obtained from current and prior studies. With this, SUV calculations are scanner independent and comparable for longitudinal trending, for example, as part of therapy assessment. Third, special reporting tools supplement the narrative report with automatically generated tabular information related to the images.

Cutting the Labor

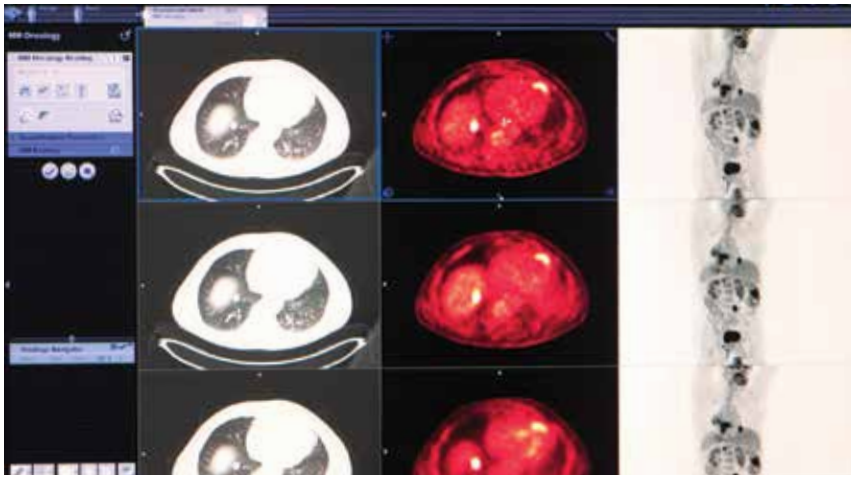
Before *syngo*.via for Molecular Imaging, physicians who read PET/CT scans had to spend substantial time preparing the case for interpretation. This preparation was particularly fatiguing when reading cases with two or more time points, Bravo said.

"*syngo*.via software takes out the pre-processing and allows us to set up organ-specific protocols that ensure we make a very thorough evaluation," Bravo said.

Two features are key. One is SMART Layout, which automatically loads physician-specific organ-based reading protocols. The other is automated image registration based on ALPHA technology, which registers images from prior studies even when they have been done with other PET/CT scanners or over different scan ranges.

"SMART Layout allows us to automatically translate the raw data of the PET/CT into a physician-specific layout that is constant and reproducible," Bravo said. "Doing so allows physicians to start reading immediately with their own process."

SMART Layout makes it so radiologists can click on the most recent study and compare it to prior ones. *syngo*.via tools allow them to see the anatomic CT information, along with the PET information, Bravo said. Images from the two studies appear next to each other.



ALPHA Landmark Registration and SMART layout enable organ-based reading.

The ALPHA technology handles registration, between current and prior studies. This takes manual pre-processing out of the equation. Bravo describes ALPHA-based Anatomical Registration as "transformative."

"Independent of the alignment or source, you have immediate registration," he said. "The pre-process work drops from minutes to instantaneous."

Anatomy-based Registration

With *syngo*.via for Molecular Imaging, reading physicians no longer have to go through the laborious process of bringing up an image, scrolling to the region of interest, reviewing it, repeating the process for the comparison image and then clicking back and forth between them. Even with images obtained over multiple time points, it is possible to click on one study and see images from studies taken at other time points exactly aligned, so that comparisons can be easily made.

"As you scroll through one study, you scroll through the images for the other studies as well," Bravo said.

The ALPHA Anatomical Registration technology, which is proprietary to Siemens, automatically lines up the images using a set of up to 28 landmarks. A sophisticated algorithm then performs an integrity check between the landmarks.

Unlike traditional registration systems, which focus on low-level information such as grayscale, edges, patterns or regions of an image, ALPHA operates like a human interpreter, recognizing high-level struc-

"syngo.via software takes out the pre-processing and allows us to set up organ-specific protocols that insure we make a very thorough evaluation."

Stephen Bravo, MD
Medical Director, Sand Lake Imaging Center, Orlando, FL, USA

tures using a process its inventor, Xiang "Sean" Zhou, PhD, calls "recognition before registration." In essence, the system "understands" what is in the image before it tries to determine which part of one image can be matched up with another image.

Zhou, head of technology and research at Siemens Healthcare, explains that traditional registration algorithms work well if two whole-body PET/CT images are comparable in coverage (e.g., image field of view) or patient posture. They fail, however, if one image was acquired with the patient's hands up and the other with hands down, or if the shared body coverage was relatively small. The reason? Comparable image regions are "contaminated" with non-comparable regions. This can often throw the conventional algorithm off. But not the one developed by Zhou and his team.

ALPHA "recognizes" the neck, for example, or the base of the spine regardless of hand position. It achieves this "understanding" of human anatomy by learning from hundreds of annotated training images, specific to the modality. These images are acquired using systems from a variety of vendors.

Because ALPHA dependably registers images, reading physicians don't have to click back and forth between images to reorient themselves when comparing current and prior studies. This is a huge time saver. And it reduces error.

"Any system that takes 30 to 45 minutes to generate a report is prone to user error," Bravo said. "It's very difficult to maintain concentration for that long a time. Inevitably, if you are interrupted in the flow of the case by busy work processes, there will be a time when you say, 'Oh, there was a lung lesion I forgot to look at because I was too busy processing something else'."

Apples-to-Apples Quantitation

Molecular imaging is an inherently quantitative modality. But, until now, using quantitative measurements obtained over multiple studies has been a challenge. One problem is that different PET scanners use different methods to calculate SUVs. To interpret them accurately, reading physicians had to know how to compensate for these differences. Doing so was especially important when assessing patient response to therapy, as changes in SUVs may indicate response —or lack of response—to therapy.

Siemens tackled this problem by developing two techniques and integrating them into *syngo*.via for Molecular Imaging. One, called PERCIST (PET response criteria in solid tumors), references SUV_{peak} with SUVs associated with liver and blood pool background. Together, these SUVs establish a baseline for follow-up studies. As well, to speed up the quantitation, ALPHA offers automatic placement of the reference regions of interest (ROI) in the liver and the descending aorta.

The second, called EQ•PET, harmonizes SUVs to a NEMA reference independently of scanner make, model or reconstruction algorithms. This harmonization provides confidence that the quantitative values obtained through multiple studies are comparable at different time points and across different equipment.

"It makes sure that the reading physician is actually comparing apples to apples," Bravo said.

EQ•PET, which is a new technology and currently applicable only in oncology, was particularly useful when calculating tumor growth rates over the period of time two or more studies were performed. The technique is useful in drawing conclusions regarding routine cases as well as those conducted during clinical trials. Sites in a multi-center trial typically use different PET/CTs.

ALPHA operates like a human interpreter, recognizing high-level structures using a process called "recognition before registration."

Xiang "Sean" Zhou, Head of Technology and Research at Siemens Healthcare, ALPHA Inventor

About three-fourths of the PET/CT scans performed at Sand Lake Imaging Center relate to oncology. One quarter are in neurology.

Patients suspected of having Alzheimer's disease, for example, are evaluated according to the prevalence and location of neurofibrillary tangles in the brain. These tangles are comprised of amyloid plaque to which radiotracers specifically attach.

Qualitative assessments are susceptible to inter-reader variation. One physician may evaluate a PET scan as normal. Another, looking at the same images, may judge the scan to be abnormal.

Siemens has pioneered the implementation of SUV ratio analysis and further integrated into *syngo*.via for Molecular Imaging databases that define the distribution of amyloid binding radiotracers in a "normal" brain. These data were drawn from images acquired during clinical trials using FDA approved amyloid radiotracers for the assessment of patients suspected of Alzheimer's disease and other causes of cognitive decline. Users of *syngo*.via for Molecular Imaging also have the option to add their own data indicating normal results.

When evaluating patient scans, the software compares the distribution of isotope in the patient scan to those in the databases, then calculates a standard deviation for the patient scan data above or below the norm.

"Instead of saying this is consistent with high quantities of beta amyloid plaque pathophysiologically, with *syngo*.via for Molecular Imaging I can say the deposition in the frontal lobe is 6.5 standard deviations above the norm," Bravo said. "With this comparison, I can feel more confident concluding that the scan is abnormal."

Pulling the Report Together

Molecular imaging reports can be long, complex and difficult for time-pressed referring physicians to digest. Here, *syngo*.via for Molecular Imaging also helps.

"The software allows us to create objective quantification charts, graphs and other data that auto-populate the report and summarize all the wordy text in a form that is quickly and easily assimilated by the referring doctor," Bravo said.

This is done through a Findings Navigator, which tracks the results obtained during the interpretation, places them into the report, then relates them to the image. Referring physicians reading the report can see the findings in context by clicking on the Findings Navigator, which relates them to the images. Using this navigator, they can also retrieve and toggle among findings regarding a lesion appearing, for example, in multiple images taken over a series of time points.

"This evidence-based report allows us to contribute data points that are reproducible, objective and scientific," Bravo said. "It has helped us in our relationships with referring doctors, facilitating their acceptance of the data that we present to them. And that has generated more business for us."

German Hospital Adopts xSPECT for Routine Bone Imaging

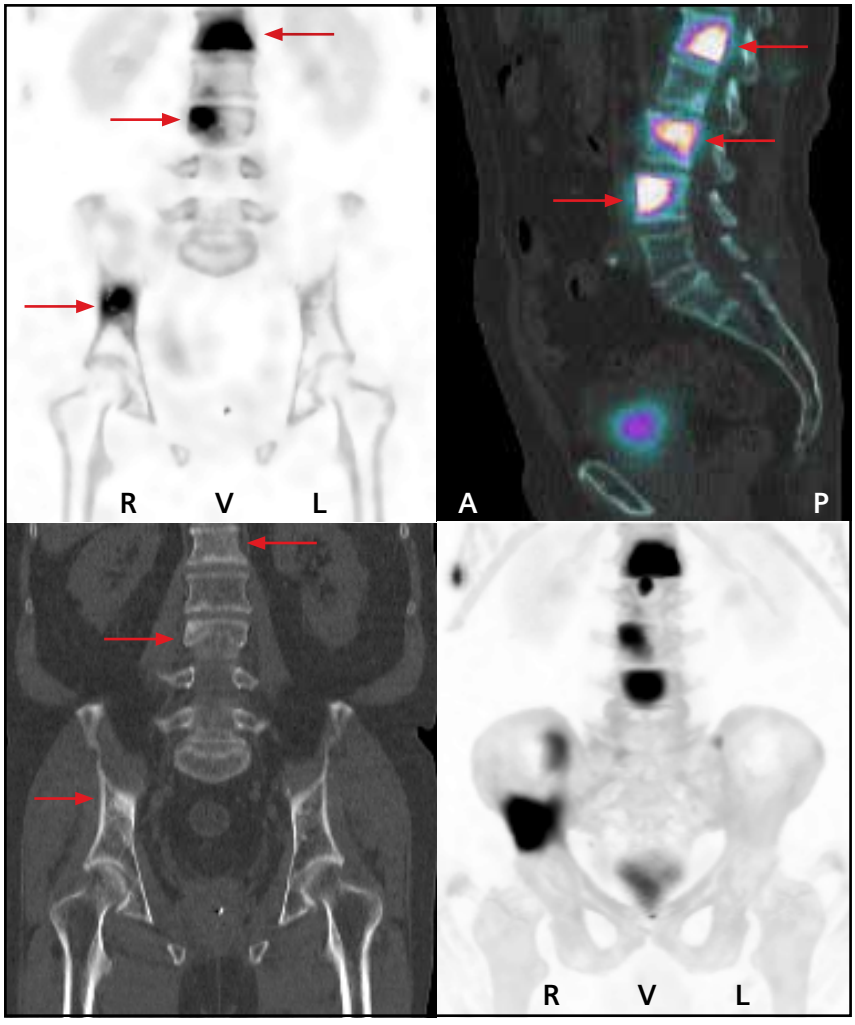
The nuclear medicine department at the German Federal Armed Forces Hospital in Ulm, Germany, likes being first. It was the first in Europe to install a Symbia T gamma camera for routine clinical applications. Nearly a decade later, it is among the first to install Siemens' Symbia Intevo for routine patient assessment. The innovative system fully integrates SPECT and CT data, during reconstruction and, for the first time, delivers quantitative SPECT images. At the Ulm hospital, Symbia Intevo is making an immediate impact on a daily basis.

By **Greg Freiherr**

Bone scintigraphy is among the most widely practiced nuclear medicine procedures in the world. Through its combination of functional and anatomical data, SPECT/CT should localize metabolic hot spots so lesions on the bone can be differentiated from those in the surrounding soft tissue. Historically, this hybrid has fallen short.

Symbia Intevo™* is the first to reach its potential, delivering integrated images from which diagnostic interpretations can be made. With its true integration of SPECT and CT data, it generates images unlike any conventional system of its kind.

"They look like CT images," said Burkhard Klemenz, MD, head of the nuclear medicine department at the German Federal Armed Forces Hospi-



xSPECT shows osteoblastic metastases in a 78-year-old patient with an increasing PSA-value (>100 ng/ml) after radiation of a prostate carcinoma seven years ago. xSPECT Bone coronal images of the lumbar spine and pelvis (left upper image); metastases in the right acetabulum and lumbar spine (L1, L3 and L4) (*red arrows*). The xSPECT Quant SUV_{max} in L4 is 93.3 compared to 8.3 (L2, reference value). *Data courtesy of German Federal Armed Forces Hospital, Ulm, Germany.*

"We can recognize disease localization now with xSPECT Bone. The images are very, very good."

Burkhard Klemenz, MD,
Head of the Nuclear Medicine Department,
German Federal Armed Forces Hospital,
Ulm, Germany

Above: German Federal Armed Forces Hospital in Ulm.

tal in Ulm. "The outlying border is extraordinary; the brilliance is very good. This is due to the fact that the CT data are implemented in the reconstruction procedure."

Symbia Intevo, the world's first xSPECT* system, fully integrates SPECT and CT data during reconstruction to deliver higher resolution and anatomical clarity, allowing physicians to differentiate between cancer and degenerative disease.

"Now, for the first time, I look at the xSPECT Bone* images and I talk to my colleagues about the quality of those images; it's because the images are so convincing," Klemenz said. "We can recognize disease localization now with xSPECT Bone. The images are very, very good."

The German Federal Armed Forces Hospital is among the first in the world to adopt Symbia Intevo. The spur to do so came from a sense of duty.

"We are obligated to our clinical colleagues to get the best images and do the best nuclear medicine procedures," Klemenz said.

Everyday Use

Klemenz began routinely scanning patients with xSPECT in early April 2014. The hospital took delivery of the system in late March. Symbia Intevo joined the hospital's existing Siemens Symbia™ T, installed in 2005. At the time, Symbia T was the first such installation in Europe, according to Klemenz. The German Federal Armed Forces Hospital also operates a Siemens Biograph™ mCT PET•CT scanner.

In addition to the ambulatory and inpatient treatment of civilian and military patients, the Ulm hospital is responsible for the training and continuing education of armed forces medical personnel. Among its specialties are orthopedics and the surgical treatment of patients with traumatic injuries requiring prostheses, Klemenz said.

"We often get questions about whether a prosthesis is loose or is infected," he said.

Until xSPECT, hybrid scans had to be interpreted by reading CT and SPECT images separately. In traditional SPECT/CT, the fused images offer only general localization of the metabolic information. Accurately interpreting these images is difficult, which is why diagnosticians typically read the CT and SPECT images separately.

Like the rest of the nuclear medicine community, Klemenz previously could read SPECT/CT scans only from images rendered using the separately acquired data sets. That has changed with Symbia Intevo.

"I can now see complicated structures on the xSPECT images," he said. "We can see osteoblastic activity—activity within the bone. This is quite brilliant and very sharp."

By completely integrating SPECT and CT data during reconstruction, Symbia Intevo leverages the high-resolution 512 x 512 matrix of the CT to increase the resolution of the SPECT matrix from 128 x 128 to 256 x 256. This is not the case for traditional SPECT/CT fusion.

Unable to fuse images with limited spatial resolution, mainstream SPECT/CT systems use a process, called "down sampling," reducing the resolution of the CT image to that of the SPECT. This provides a common denominator by which the two images can be combined. Unfortunately, the process degrades the CT information, devoid of the edge information that gives high-quality images their crisp look.

Changing Patient Management

By comparison, xSPECT images are sharp enough that interpreters can determine whether a lesion is in bone or in the surrounding soft tissue. This can dramatically change patient management. Bone lesions caused by degeneration of the joint can be misinterpreted as inflammation or even cancer tumors in soft tissue near the bone.

Knowing that a hot spot is in a particular region of the bone, for example, may indicate trauma or osteoporosis rather than metastasis, a critical distinction when doing the initial work

up or following a cancer patient undergoing therapy. Similarly, knowing the exact location of a hot spot in relation to a prosthesis can make a big difference in diagnosis, as well as therapy.

When interpreting traditional SPECT/CT bone scans, diagnosticians try to work around the shortcomings by factoring in the patient's age. Degenerative changes, for example, are common in the spines of older patients but not in their long bones. Lesions seen in long bones, therefore, are more likely metastases. But this is not always so. Degenerative changes can occur along with metastases. Infection can be similarly confounding.

At the German Federal Armed Forces Hospital, Klemenz and his staff regularly are asked to evaluate patients for osteitis of the skull base, an inflammation of bone associated often with bacterial infection. After diagnosis, patients with bacterial osteitis may undergo therapies combining hyperbaric oxygen therapy with surgery and antibiotics. In osteitis, after bone fracture and osteosynthesis, surgery is performed to explant osteosynthetic material. In case of soft tissue infection, the osteosynthetic material need not be changed and only a minor surgical intervention is necessary. In the past, Klemenz had used standard SPECT/CT to evaluate patient response. These patients will now likely be followed using xSPECT, he said.

"Symbia Intevo has an advantage in bone imaging because the image quality with xSPECT Bone is very good," he said.

Symbia Intevo replaces subjectivity with objectivity. With xSPECT, the origin of metabolic information—such as bone or soft tissue—can be determined. The answer can substantially change patient management, just as it reduces cost and patient discomfort due to additional and unnecessary tests such as biopsy. The potential for the adoption of this new modality is enormous.

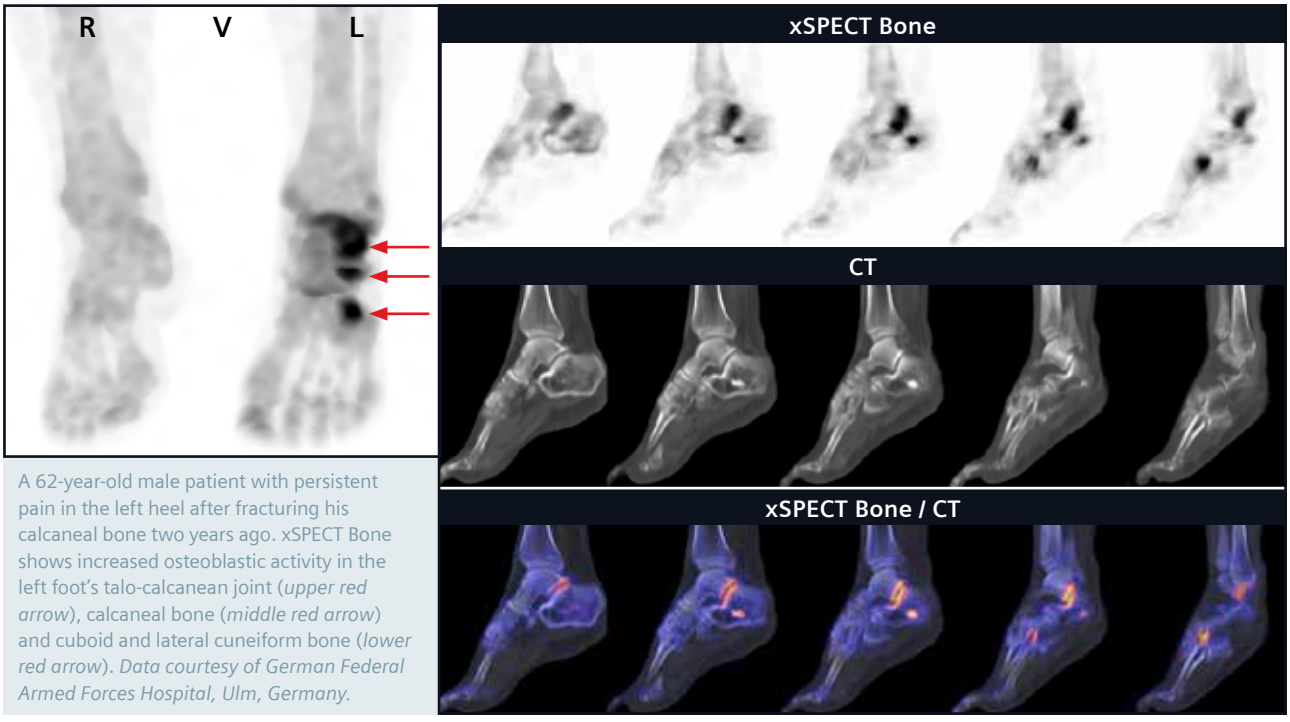
SPECT and its hybrid combination with CT are popular around the globe, largely due to their cost efficiency. The radionuclides used in SPECT and SPECT/CT are relatively inexpensive and easy to obtain. The problem has been a propensity toward false positives, which has caused diagnosticians to resort to additional studies, such as MRI, high-resolution CT, PET/CT or biopsy to characterize suspicious lesions.

xSPECT identifies CT data associated with bone and maps those values onto the accompanying SPECT voxels. The software then adjusts the SPECT voxels so that they accurately represent bone.

This transformation occurs when data are segmented. CT draws a sharp distinction between bone and soft tissue. In xSPECT, the CT data are used to define the density of tissues. Bones can be contoured, just as the density of bone and soft tissue can be mapped according to the variable absorption of photons emitted by the radiotracer. This process, a type of CT segmentation, is called zoning, whereby SPECT data are weighted using CT data to indicate the likelihood of where the radiotracers were located in the body.

Quantitation with SPECT

In addition to truly integrated SPECT and CT images, for the first time, clinicians can accurately quantitate radiotracer uptake. Until xSPECT, such quantitation was possible only with PET/CT. This modality has been a pathfinder for quantitation. Its



A 62-year-old male patient with persistent pain in the left heel after fracturing his calcaneal bone two years ago. xSPECT Bone shows increased osteoblastic activity in the left foot's talo-calcanean joint (*upper red arrow*), calcaneal bone (*middle red arrow*) and cuboid and lateral cuneiform bone (*lower red arrow*). *Data courtesy of German Federal Armed Forces Hospital, Ulm, Germany.*

decade of routine clinical use has proven the utility of using measurements in the evaluation of patient response to therapy.

In PET/CT, high uptake values are commonly associated with the active metabolism of cancer tumors, as well as some other pathologies. Dropping values following the administration of therapy indicates a positive therapeutic effect. Now this kind of measurement is possible with xSPECT.

"Quantitation on the Symbia Intevo could potentially be similar to the SUV (standard uptake values) of PET/CT," Klemenz said. "I intend to use quantitation in my routine clinical patients and I will look to examine therapy response in patients with cancer and those with infections."

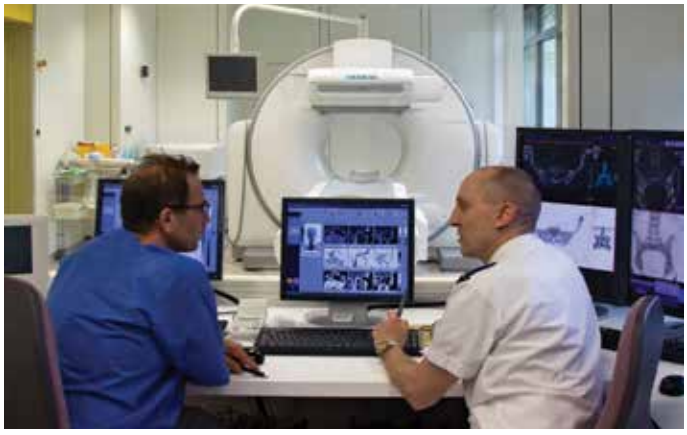
Determining the efficacy of therapy—whether it affects the metabolism of the tumor or infection and to what degree—can change the way patients are treated. The value of such information is hard to overestimate. Extended use of an ineffective treatment places substantial burdens on the patient, as it delays the application of a potentially better treatment and imposes the financial cost of an ineffective one. It can also cause collateral damage to healthy tissue that might otherwise be avoided.

Patients may benefit further by a reduction in the overall radiation burden. The acquisition and processing by xSPECT minimizes the need for radiotracer, just as low-dose CT tools, including iterative reconstruction algorithms, minimize patient exposure to CT radiation.

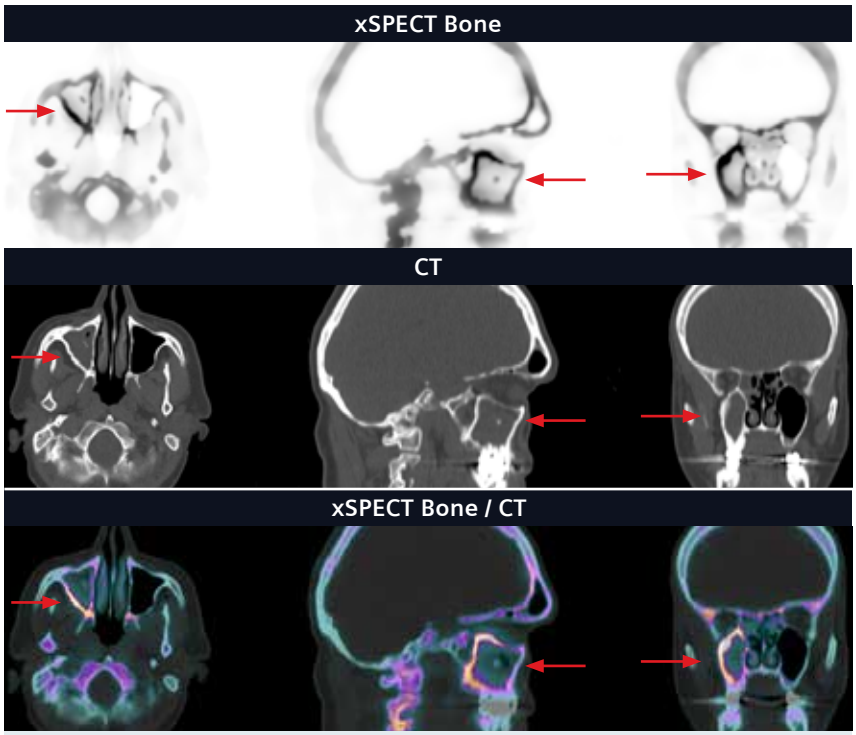
Efficiencies in the interpretation of images make xSPECT studies easier to perform, while making diagnosticians more confident in their conclusions. Underlying these clinical and operational advances are technological ones. None is more basic than Symbia Intevo's advanced detectors. Fine collimation is enhanced by their physically slim design, which enhances rotational uniformity, while preventing the kind of deflection during gantry rotation that can degrade resolution.

Support built into the rear of the patient table prevents deflection during the scan, as it extends the span of the exam to 202 cm, which is more than can be achieved using most SPECT/CT scanners. When processing data, corrective algorithms account for detector motion and gantry deflection, while figuring in the size and shape of collimator holes, as well as the distance of the patient from the detectors.

Together these technologies form the basis of what appears to be a "sea change" in nuclear medicine.



Right: Burkhard Klemenz, MD, head of the nuclear medicine department at the German Federal Armed Forces Hospital in Ulm, discusses an xSPECT case studied using Symbia Intevo (pictured in background).



xSPECT Bone demonstrates bone changes in the right maxillary sinus secondary to the aspergillosis, resulting in chronic sinusitis in the right maxilla and ethmoid bone in a 57-year-old patient. xSPECT Bone with ^{99m}Tc-DPD demonstrates tracer uptake in the skeletal borders of the cranium, mostly at the infraorbital margin and focal uptake in a calcification of 5 mm diameter within the sinus. *Data courtesy of German Federal Armed Forces Hospital, Ulm, Germany.*

* Symbia Intevo, xSPECT and xSPECT Bone 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.

The statements by Siemens' customers described herein are based on results that were achieved in the customer's unique setting. Since there is no "typical" hospital and many variables exist (e.g., hospital size, case mix, level of IT adoption) there can be no guarantee that other customers will achieve the same results.

Amyloid Plaque Imaging Comes to the UK

In 2013, a 56-year-old woman became the first clinical patient in the United Kingdom (UK) to undergo a PET scan for amyloid plaque. Siemens' PETNET Solutions delivered the radiotracer.

By **Shalmali Pal**

When imaging studies make headlines, they seldom merit international attention. So it was a bit out of the ordinary when the UK's inaugural amyloid plaque PET scan—performed at the United Kingdom's National Health Service (NHS) Charing Cross Hospital in London—not only attracted such coverage but was served up by Prime Minister (PM) David Cameron. But then again, the venue itself was unusual.

Last December, London hosted a G8 summit on dementia during which the PM announced a boost in research funding for dementia research and that the NHS would offer an imaging study that could rule out Alzheimer's disease.[1]

Shortly thereafter, Charing Cross Hospital led by Zarni Win, MRCP, FRCR, consultant PET radiologist at Charing Cross Hospital, which is part of the Imperial College Healthcare NHS Trust, completed the country's first amyloid PET scan. Imaging was performed on a Biograph™ 64 TruePoint PET•CT scanner. The ^{18}F-labeled PET radiotracer designed for amyloid plaque imaging was produced and delivered by Siemens' PETNET Solutions.

"We've got a lot of imaging studies that offer 'might be or could be' results," said Richard Perry, MD, consultant neurologist at Imperial College Healthcare NHS Trust. "This is not the case in a PET amyloid imaging scan," he said.

"The key utility [of amyloid plaque imaging] is that results typically are either positive or negative," said Perry who referred the 56-year-old for the PET scan after the patient had received conflicting clinical diagnoses.

The Advent of Amyloid Plaque Imaging

Siemens Molecular Imaging offers a comprehensive amyloid imaging solution* for use in the evaluation of patients suspected of Alzheimer's disease or other causes of cognitive decline. It is comprised of three elements:

- Siemens' PETNET Solutions, which produces and distributes the PET amyloid imaging radiotracer;
- A Biograph PET•CT scanner, which delivers the finest volumetric resolution** of 95 cubic mm; and
- *syngo*®.PET Amyloid Plaque*, software that assists in the evaluation

Beta-amyloid plaque is one of the necessary pathological features of Alzheimer's disease. Beta-amyloid plaques are deposits of a protein fragment called beta-amyloid that build up in the spaces between nerve cells (neurons) in certain areas of the brain. In a healthy brain, beta-amyloid protein fragments are broken down and removed. In a brain with Alzheimer's disease, beta-amyloid protein fragments accumulate to form hard, insoluble plaques in between neurons. Beta-amyloid accumulation builds over many years.[2] Accumulation of beta-amyloid plaques interacts with a signal pathway that causes neurofibrillary tangles, which are insoluble twisted fibers found inside the brain's cells. As increasing amounts of plaques and tangles form in particular areas of the brain, brain cells work less efficiently, eventually losing their ability to function and, ultimately, dying. Important to note, beta-amyloid plaques are seen in other neurologic conditions and older people with normal cognition. Confirmation of beta-amyloid plaques does not definitively lead to Alzheimer's disease diagnosis. It is, therefore, key to have access to innovative technologies that can help differentiate and quantify amyloid-plaque buildup in the living brain.

In June 2013, Siemens' PETNET Solutions entered into a manufacturing agreement to produce an ^{18}F-labeled radiotracer for amyloid plaque imaging in the UK. Six months later, NHS approved coverage of amyloid plaque imaging. When the first amyloid PET scan was done, Win felt more pressure than usual.

"Whenever you work with a new technology, there's always concern about obtaining a good quality scan," he explained. "We also had media and the film crews around for that first scan. So I was a bit concerned: 'What if we get a low signal, high noise scan and the image is washed out?' When the actual scan came out as very good image quality, we were very happy."

Although UK government officials look to accelerate amyloid plaque imaging, Win's group is taking a slow and steady approach, having scanned only 15 patients for amyloid plaque since their first patient. There are several reasons for the conservative approach.

First, scanning more patients will require more funding, which they are working to obtain. As of April 2014, Imperial College Healthcare NHS Trust was on track to receive funding for about 100 amyloid plaque imaging scans.

Win estimated the cost of a single amyloid plaque scan under the NHS runs between £1,300 and £1,600 (USD $2,200 to USD $2,700 or € 1,070 to € 1,310).

Second, Win and his colleagues want time to excel at the visual interpretation of the scans. They are focusing, for the time being, just on reading images.

"Of the ones we've done, 80 percent are clearly positive or negative," Perry said. "But in those instances where the results are not so clear-cut, that's where a higher level of expertise is very important. That's why I feel we're still going through their stages of gathering that clinical expertise."

Quantification using Siemens *syngo*.PET Amyloid Plaque software is designed to support the visual interpretation of these exams. But Win believes introducing quantification software too early in the learning process could lead to bias.

"I think it's much better to take the time to really learn to read the scans," he said. "Once that's been accomplished, then things like quantification software can offer more benefits."

He predicted, however, that the *syngo*.PET Amyloid Plaque quantification software could add value in reading scans from patients with more challenging presentations.

"I think [difficult cases] will always remain difficult, and thus having quantification software is like having an extra set of eyes," he said.

Following Usage Guidelines

The UK group is striving to work within the guidelines for amyloid plaque imaging set by various expert governing bodies. In 2013, the Alzheimer's Association and the Society of Nuclear Medicine and Molecular Imaging issued guidelines for amyloid imaging, covering appropriate use criteria and cutoff thresholds for a positive or negative scan.[3]

In the US, amyloid imaging is indicated in adult patients with cognitive impairment who are being evaluated for Alzheimer's disease and other causes of cognitive decline. Three UK organizations—the Royal College of Physicians, the Royal College of Radiologists, and the Administration of Radioactive Substances Advisory

"I think [difficult cases] will always remain difficult, and thus having quantification software is like having an extra set of eyes."

Zarni Win, MRCP, FRCR
Consultant PET Radiologist
Charing Cross Hospital, London, UK

Committee (ARSAC)—have narrowed the usage criteria, ruling out use of amyloid imaging in patients with suspected mild cognitive impairment (MCI). This narrower indication is fine with Win and his team.

"With Alzheimer's disease, I've found that neurologists, psychiatrists and even radiologists have heterogeneous opinions and approaches to the evaluation of the disease," he said. "And that's even more in evidence with MCI. So I think a narrow indication is the sensible way to go for now. It'll be interesting in four or five years, when we may start to see more MCI patients, how amyloid plaque imaging guidelines will look."

The group is trying to balance public expectations about the modality with what amyloid plaque imaging can actually do. Misevaluation of Alzheimer's disease is a major problem and can have devastating effects on patient and family.

"To be misevaluated with an aggressive, progressive, neurodegenerative disease that can't be stopped has a tremendous impact on their lives, those of their families and their livelihoods," Win said. "Now we've got an extra test that can reduce that trend of misevaluation."

Amyloid plaque imaging is not a screening exam, Win emphasized. Patients must be carefully assessed for dementia before being referred for an amyloid plaque scan. Once that evaluation has been done, if dementia specialists are still uncertain of the diagnosis, then an amyloid plaque scan may be in order.

"If you have a very specifically defined question that amyloyid imaging can answer, then [the results] can have a tremendous impact," Win said. "The biggest benefit of a negative scan is that it rules out Alzheimer's disease (AD). The clinician and patient can then go back to the clinic to look for other causes [behind the cognitive issues]."

While a negative amyloid scan can rule out AD, a positive one does not necessarily mean the disease is present. "The clinician may need to go back to make sure the patient was very carefully selected for the scan," Win said. "If the clinician hasn't really thought out how the information from the scan can be used, then it may not make as much of a difference in the final evaluation."

Confident Evaluations

By the time the first patient arrived for a consultation with Perry, she was nearly a year out from what ultimately proved to be an incorrect diagnosis. After experiencing some memory problems at work, she had sought help at a local clinic specializing in patients with symptoms of memory loss. A battery of cognitive tests showed respectable scores.

Yet there was some evidence of memory decline.

The initial scan showed hypometabolism in the medial temporal lobe, according to Perry. "The report read that it was consistent with Alzheimer's disease," he said. "That was a huge shock to the patient especially given her age."

The 56-year-old patient informed her employer about the tentative diagnosis, as well as the Driver and Vehicle Licensing Agency, which exerts authority over motorists in the UK. (Motorists can be fined up to £1,000 if they fail to report a medical condition that could affect their ability to operate a vehicle.)

"She became quite depressed and anxious," Perry said.

Eventually the patient traveled to London for a second opinion. What Perry saw was a patient with some symptoms of memory problems and mood disorders, but one who scored well on the memory tests. She underwent a repeat MRI and other tests. All were normal.

"So this poor lady had conflicting results: One group telling her that she had Alzheimer's disease because of the abnormal scan. But our test results were normal," Perry explained. "What she needed was clarity."

The negative results of the amyloid plaque imaging scan provided that.

"I expected the scan to be negative although one can never be 100% sure," he said. "She'd been labeled as having Alzheimer's disease without sufficient information. There were a lot of lessons to be learned from her experience."

One lesson is that a very specific subset of patients will benefit from amyloid plaque imaging. It's not a "come one, come all" screening study for cognitive issues.

Perry said he would consider amyloid imaging for patients:

- not likely to have normal age-related cognitive changes;
- with atypical presentations, such as language problems or visual problems, rather than just memory problems; and
- who may have Alzheimer's disease as well as other neurological pathologies, such as psychiatric syndromes

Clinicians must keep in mind, he said, that while the "rule out" aspect of a negative amyloid plaque imaging is a boon in the work-up of Alzheimer's disease, a positive scan is not clear-cut.

"I've had people asking whether a positive scan can be reported in a graded fashion," Perry said. "I explain that's not the purpose of this test. The point of the scan is to detect amyloid plaques."

Perry explained that some people might have amyloid plaques but exhibit no cognitive impairment. Such a scan, therefore, indicates that the patient is at increased risk for Alzheimer's disease, but there is no certainty when or even if the disease will appear. Physicians, therefore, must understand the parameters of these exams, if they are to provide the best possible management for their patients.

A Technologist's Perspective

Dele Williams, the technologist who helped perform the first amyloid plaque imaging scan at Charing Cross Hospital, said the study required no special preparation. The only difference from a typical brain PET/CT, he said, "was interest from the TV documentary film crew and magazine photographers."

Now that his institution has performed more than a half dozen amyloid plaque imaging studies, Williams has found what he called a "surprising" variability in the cognitive state of the different patients. Their ability to understand the logistics of the imaging exam, which last between 15 and 20 minutes, can impact how well the scan turns out.

"Whilst some patients appeared to show no symptoms of any neurological impairment, others were forgetful and often unaware of their surroundings and the importance of remaining still [in the scanner]," Williams explained. "These patients often needed constant reassurance and supervision during both the administration of the radiotracer and the scan to keep them from trying to get off the table."

A patient management protocol for amyloid scans at Charing Cross Hospital instructs caregivers and technologists to give patients the support they need to keep calm. The microphone built into the Biograph 64 TruePoint PET•CT has proved "invaluable" in communicating with the patient, he said.

Regarding delivery of the amyloid tracer delivered by Siemens' PETNET Solutions, Williams reported that "the tracer was delivered on time, well ahead of the injection time, which was appreciated. The tracer is also supplied in individual patient vials, as opposed to the typical multi-dose vials."

The Power of a Scan

Describing herself as "very practical," the then 56-year-old woman, now 57, realized that she was experiencing some memory issues that were beyond simple absentmindedness.

A resident of Cornwall, the patient was a home healthcare nurse. Her work consisted of weekly visits to home-bound patients. It was a routine that she had down pat.

"I used to see certain patients every day and it was always the same journey. But on occasion, I'd suddenly think 'Where have I got to go?' even though I'd been going there every day for the past week," the patient explained.

The patient decided she needed medical help after an exchange with one of her regular patients, a woman with dementia, who became confused about her location, even though she knew she was resting in bed in her apartment.

"She had all the puzzle pieces but she couldn't fit them together," she said. "I thought, 'This is me.'"

The patient summed it up in one word: Bewilderment, particularly over the most mundane aspects of life. "I could look at something obvious, like a chair, and not know what it was used for," she stated.

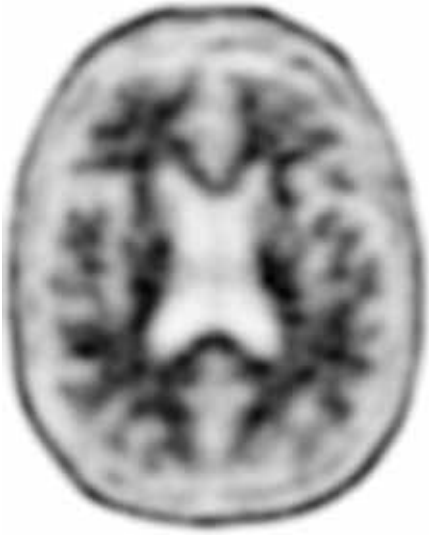
The psychiatrist with whom the patient consulted put her through a battery of clinical and imaging studies, settling on an Alzheimer's disease diagnosis. She was prescribed a low-dose of donepezil hydrochloride. The patient said the medication seemed to minimize her moments of bewilderment, but she couldn't rule out a placebo effect.

There was no ambiguity, however, about the effect the diagnosis had on her life. Not quite able to tell her family, she informed the motor vehicle department first, which requires motorists to be alerted to medical conditions that may impair their ability to drive. When she did tell her family, her husband was "absolutely devastated." The reaction of their two adult daughters was both practical—how best to manage the disease—and emotional. "One daughter said to me: 'Mum, it won't be you anymore'," the patient recalled.

At work, the 56-year-old patient initially was taken off home healthcare visits and given a desk job. But after passing an employer-ordered psychiatric assessment, she returned to her job outside the office. Yet she found it difficult to work under the increased scrutiny and, ultimately, opted for early retirement.

Yet the 56-year-old patient still wasn't sure Alzheimer's disease was the root cause of her problems. She became the first clinical NHS patient to have an amyloid PET scan in the UK. A half hour after the scan, the patient learned the answer to the clinical question she and her loved ones had been struggling with. Her problem was not Alzheimer's disease.

"If you get a negative scan, you can rule out this disease," Win said. "The negative results made a huge difference in the life of our first patient. She is young and with a family. Before the scan, the possibility of having Alzheimer's disease was taking a huge toll on everyone."



A negative amyloid imaging scan, like shown above, can help physicians rule out the possibility of Alzheimer's disease, and allow them to focus on alternate causes behind a patient's cognitive issues.

"Now we've got an extra test that can reduce that trend of misevaluation."

Zarni Win, MRCP, FRCR
Consultant PET radiologist at Charing Cross Hospital

"For [over a year], I'd been told it was Alzheimer's," she recalled. "I was sitting with my husband in the hospital cafeteria and his face…lit up like he'd won the lottery!"

In the end, the 56-year-old patient was diagnosed with MCI. She is slated to meet with Perry in June 2014 to determine what course of action, if any, will be taken to manage the mild cognitive impairment, defined as a slight but noticeable with a measurable decline in cognitive abilities. The patient said she still has moments of bewilderment, but that having the definite "no" answer to the Alzheimer's question has given her much of her life back.

"If there is one message I'd want people to understand from my experience, it's that, if you are given an Alzheimer's diagnosis—or even the possibility of an Alzheimer's diagnosis—talk to your family and make your wishes known before you lose your faculties," she said. "I think it's important to have that conversation beforehand, no matter what the diagnosis ultimately is. I believe it can save a lot of heartache."

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* *syngo*.PET Amyloid Plaque is intended for use only with approved amyloid radiopharmaceuticals in the country of use. Users should review the drug labeling for approved uses.

** Based on volumetric resolution available in competitive literature for systems greater than 70 cm bore size. Data on file.

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California PET Center Leverages Siemens Partnership To Offer Amyloid Imaging

For more than two decades, the Northern California PET Imaging Center (NCPIC) has been at the forefront of molecular imaging. The Sacramento, California, USA, center was an early adopter of PET technology, installing in 1992 one of the world's first whole-body PET scanners. Twenty-two years later, NCPIC is still leading the way in PET imaging as one of the first in the United States to offer PET amyloid imaging. Siemens has partnered with NCPIC from the beginning. Today, Siemens' PETNET Solutions provides the radiotracer to perform amyloid imaging. Likewise, it designed the PET•CT scanners that acquires the data; workstations that display the images; and the software that processes them.

By **Catherine Eby**

Amyloid protein occurs naturally in the body. It breaks down in healthy people, but accumulates in those stricken with Alzheimer's disease, combining with another protein to form neurofibrillary tangles that are associated with development of the disease. Prior to amyloid imaging with PET/CT, the only way to confirm amyloid plaque build-up was during autopsy. Now this plaque can be routinely visualized in the living brain.

The Northern California PET Imaging Center (NCPIC) has performed more than 50 amyloid imaging exams. One of the first involved a woman concerned she was developing Alzheimer's disease because of a strong family history. Her daughter was worried and frustrated by changes in her mother's behavior. A PET/CT scan, however, showed an absence of significant amyloid plaque buildup, leading physicians to look for other causes of the symptoms and explore treatment that might counter them. The negative scan also brought relief to the mother, instilled hope that an effective treatment might be found, and improved the mother's relationship with her daughter.

Sue Halliday, a clinical consultant for NCPIC, remembers the case. "The amyloid scan allowed her to be triaged to different treatment," Halliday said. "She was put on an anti-anxiety medication and everything is now fine. This is a good outcome in a situation where a negative scan really impacted the management of a patient."

Alzheimer's disease is notoriously difficult to evaluate. Research presented in 2011 at the American Academy of Neurology's 63rd Annual Meeting in Honolulu, Hawaii, USA, concluded that misevaluation is common. The study, conducted at Kuakini Health System in Honolulu, showed that autopsies of nearly half of more than 400 patients evaluated with Alzheimer's disease did not demonstrate sufficient numbers of amyloid brain lesions to support the assessment.

Errors in evaluation were especially common at the time because various dementias, including Alzheimer's disease, vascular dementia, and the early stages of Parkinson's disease have some overlapping symptoms. This overlap continues to mislead physicians. A study of the United States federal insurance program, Medicare, data presented last year at the Alzheimer's Association International Conference (AAIC) showed that 16.6 percent of more than 15,000 patients with vascular dementia had been misevaluated as having Alzheimer's disease. Of the almost 31,000 cases of Parkinson's disease reviewed in the research, 8.4 percent had been misevaluated as Alzheimer's disease.

Amyloid imaging provides additional clinical information that can support physicians in their evaluation of Alzheimer's disease. If amyloid plaque buildup is not present in a PET scan, it is unlikely that the patient is suffer-

"With amyloid imaging, now we have a way of better identifying one of the necessary pathological features of Alzheimer's."

Steve Falen, MD, PhD, Medical Director
Northern California PET Imaging Center
Sacramento, CA, USA

ing from Alzheimer's disease. Not only does such a rule-out promise relief for patients wrongly evaluated as having the disease, it allows physicians to look for other, potentially treatable causes. Doing so is medically—and fiscally—sound.

The Medicare-based research presented at last year's AAIC meeting indicated that the misevaluations of vascular dementia incurred nearly USD $12,000 in additional costs per patient in year 1 following misevaluation compared with what would have been spent, if the evaluations were correct. These were buoyed further by nearly USD $19,000 in excess costs in year 2 and another USD $21,000 in year 3, if proper evaluation required that long. Parkinson's disease patients misevaluated with Alzheimer's incurred similarly excessive and undue treatment costs of more than USD $9,000 in the first year, USD $12,000 in the second year and USD $14,000 in the third.

Ruth Tesar, CEO of the Northern California PET Imaging Center, has seen the value of amyloid imaging first hand. "We may be going down the path of thinking a patient might have Alzheimer's disease, then we do an amyloid study and it's negative," Tesar said. "That makes us look at other reasons for (the patient's symptoms)."

The impact of amyloid imaging is hard to overestimate, according to Jan Cronin, NCPIC's market development manager. It goes well beyond the patients, she said.

"Families want to know what's going on with their loved ones, and their loved ones want to know what is going to be happening to them, what road they're going to be going down and how to plan for their future," Cronin said. "If they have cognitive decline and they don't have any amyloid plaque buildup in the brain, they understand that there must be another reason for that cognitive decline."

According to Steve Falen, MD, PhD, medical director of the Northern California PET Imaging Center, amyloid imaging also has the potential to help in the development of treatments for Alzheimer's disease. "With amyloid imaging, now we have a way of better identifying one the necessary pathological features of Alzheimer's," Falen said.

Falen explains that one potential way to treat the disease could be a drug that targets the amyloid plaque, slowing or even reversing its buildup in the brain. With the ability to visualize this plaque in the brain, physicians may be able to determine which patients are potential candidates for this treatment.

"The use of PET technology with its capability of being used earlier in the disease timeline than other imaging modalities may be a valuable new tool for physicians evaluating patients with suspected Alzheimer's disease," Falen said.

A Comprehensive Amyloid Imaging Solution

NCPIC and Siemens have been working together since the imaging center opened in 1992. As a leader in molecular imaging and the provider of the only comprehensive amyloid imaging solution*, Siemens embraces the same pioneering spirit that drives NCPIC.

Siemens produces and distributes a PET amyloid imaging biomarker through its PETNET Solutions radiopharmaceutical manufacturing and distribution facilities. The dependable on-time delivery of PET radiopharmaceuticals is essential, if patients are to be scanned efficiently and effectively. Desmond Sargeant, imaging manager for NCPIC, can attest to such delivery from PETNET Solutions. "We appreciate the relationship we have with them," Sargeant said.

This relationship extends beyond radiopharmaceuticals. NCPIC purchased their Biograph™ mCT 40-slice PET•CT scanner four years ago when it was first introduced.

"Quite frankly, when we purchased it [Biograph mCT 40], we didn't really know how great this scanner would be," Tesar said. "I've been in the field for a very, very long time and when we started getting images from our Biograph mCT scanner I had never seen such a big jump in quality. It just surprised us in its excellent quality with higher sensitivity, higher resolution and improved patient throughput. The techs love this scanner. It was well worth our investment."

With the finest** volumetric resolution of 95 mm^3, Biograph mCT offers a high-resolution scan, which is important in differentiating between the tightly woven white and grey matter in the brain during an amyloid imaging scan. Amyloid plaque buildup in white matter is considered normal, while buildup in the grey matter may indicate potential neuro-degeneration.

"The scanner has a very large open bore and is a fast scanner," Cronin said. "We can accommodate patients that can't be in a scanner for very long in ten, fifteen minutes."

Capping this comprehensive solution is *syngo*®.PET Amyloid Plaque software. "With Siemens, it's one stop shopping," Sargeant said. "Siemens starts from the front-end by providing the radiopharmaceutical for amyloid imaging; we image patients on a Siemens scanner; then we use Siemens software to process the images."

The collaboration between Siemens and NCPIC in amyloid imaging extends beyond this comprehensive solution to educating the community. Both are committed to raising awareness about the forms of cognitive decline, as well as the amyloid imaging exam that can help differentiate between Alzheimer's disease and other dementia. The problem they face is enormous.

According to estimates made by the World Health Organization in 2010, more than 35.6 million people currently suffer from some type of dementia. Alzheimer's disease is the leading cause. And the number affected by Alzheimer's disease is growing.[1]

Spreading the Word

Education is critically important. Patients and physicians need to understand the value of PET/CT—how it can help in evaluating the patient and selecting the correct treatment. Demand for such knowledge is on the upswing.

"Primary care physicians want to know about it," Cronin said. "They deal with patients who come to them in early dementia and cognitive decline, so they need to know about the availability of amyloid imaging and what it has to offer."

"I've been in the field for a very, very long time and when we started getting images from our Biograph mCT scanner I had never seen such a big jump in quality."

Ruth Tesar, CEO
Northern California PET Imaging Center
Sacramento, CA, USA

"We have a very long relationship with Siemens at a very deep level... We've watched these scanners develop over the past two decades to what they are today, which is spectacular."

Bruce Finley, PET Technologist
Northern California PET Imaging Center
Sacramento, CA, USA

Biograph mCT 40-slice PET•CT scanner offers a high-resolution of 95 mm^3, which is important in differentiating between the tightly woven white and grey matter in the brain during an amyloid imaging scan.

NCPIC has put a lot of time and resources into educating the community about amyloid imaging, including pamphlets, binders, a website and meetings with physicians to explain the test and the information it can provide. They also provide resources for patients about the stages of cognitive decline and what they mean to them. Siemens aids in their outreach by providing materials to explain the value of amyloid imaging to referring physicians, as well as patients and the community.

"We use a lot of material from Siemens," Cronin said. "They have great pamphlets written in very simple terms so patients can understand. Our referring physicians really enjoy being able to have that available to give to their patients."

Cronin credits the relationship with Siemens as helping the center succeed in its mission to serve the people of Northern California. "We are very proud of our scanner, our service and our physicians for providing high-quality care. And we wouldn't be able to do it without Siemens and PETNET Solutions," she said.

A True Partner

For a relationship that spans more than 20 years, the one between NCPIC and Siemens shows no sign of slowing down. Begun with the installation of a fixed site scanner, two mobile PET•CT scanners have since joined the fold, enabling the center to provide imaging services to much of Northern California.

"We work with Siemens on many different levels right now. The scanners, the software, even the imaging stations are from Siemens," Falen said. "And, of course, we get our radiopharmaceuticals from PETNET Solutions. We feel in a way we are a part of the Siemens network because of all that we're doing together."

Bruce Finley, a PET technologist who has been with NCPIC for 16 years, couldn't agree more. "We have a very long relationship with Siemens at a very deep level," Finley said. "We work with the engineering staff, the service staff, the support staff, and the technical staff. It's wonderful being a part of that organization and seeing the talent that's there. We've watched these scanners develop over the past two decades to what they are today, which is spectacular."

References:
1. World Health Organization data, 2010.

* *syngo*.PET Amyloid Plaque is intended for use only with approved amyloid radiopharmaceuticals in the country of use. Users should review the drug labeling for approved uses.

** Based on volumetric resolution available in competitive literature for systems greater than 70 cm bore size. Data on file.

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Dutch Hospital Increases Efficiency with IQ•SPECT

Cardiology has long been a premier offering at the nuclear medicine department split between Spaarne Hospital and Kennemer Gasthuis in Hoofddorp and Haarlem, The Netherlands. In 2010, when these modern tertiary teaching hospitals were looking to replace their gamma cameras to improve on their already strong reputation, the departments decided to invest in three Symbia T SPECT•CT scanners. Equipped with IQ•SPECT technology, Symbia T helped reduce scan time by one third, increase the quality of cardiac studies and improve patient comfort.

By **Rhett Morici, Molecular Imaging Business Unit, Siemens Healthcare**

When considering the purchase of new molecular imaging systems, the nuclear medicine departments at Spaarne Hospital and Kennemer Gasthuis faced some tough challenges. Foremost, the departments where these systems would be installed had limited space. Second, its exams had to be completed within existing blocks of time. The staff were also looking for ways to improve patient comfort, as well as acquire more counts per scan to boost image quality. The solution to each was to find systems that were more efficient, in more ways than one.

"All levels of efficiency were welcome. That was the basic idea behind it," said Bart Titulaer, the nuclear medicine department's medical physicist, who was responsible for acquiring and installing their Symbia™ T systems equipped with IQ•SPECT technology.

As part of their efficiency-focused strategy, Titulaer's team chose Symbia T. "The system was an all-around good fit for our needs," Titulaer said. Limited space meant the facility needed scanners that could perform a broad range of nuclear medicine studies, while maintaining a special emphasis on cardiac procedures.

Spaarne Ziekenhuis, Hoofddorp, The Netherlands

Faster scan times and increased patient comfort were a requirement. Efficiency was all the more important considering the size of the facility.

The nuclear medicine department is split between two facilities, Kennemer Gasthuis in Haarlem and Spaarne Ziekenhuis in Hoofddorp—both of which are full-service, mid-sized hospitals with aproximately 455 beds, 120 physicians and 600 nurses. The Haarlem facility, which houses two Symbia T systems, one with IQ•SPECT, conducts approximately 4,500 to 5,000 procedures per year. About 25 percent of those procedures are cardiac.

Operational and Clinical Efficiency

Time affects all aspects of daily imaging from patient comfort to staff productivity. Before installing IQ•SPECT in March 2010, patient scans took about one minute per image, resulting in studies lasting as long as 32 minutes. Aging technology and an already low amount of injected dose (500 to 600 MBq) made completing all the assigned scans for the day difficult, according to Ton Zwijnenburg, MD, PhD, who specializes in nuclear medicine at the two departments and works daily with IQ•SPECT.

With the slow scan times of the gamma cameras then installed, Zwijnenburg noted the inconvenience for patients:

"The time we spent on cardiac studies was quite long to obtain sufficient statistics in our studies for our quality standards," he said.

Since acquiring IQ•SPECT, the nuclear medicine department completes scans 20 minutes faster—a third of the time previously needed. This has improved scheduling efficiency and patient comfort.

"We can complete a scan within eight to ten minutes. That is significantly faster than we did previously and it offers a considerably greater profit margin, compared to the old situation," Zwijnenburg said.

The improved scan time achieved with IQ•SPECT has also allowed the department to be more efficient with its schedule. According to Zwijnenburg, a typical day for both facilities before IQ•SPECT would include about four stress tests in the morning and four rest tests in the afternoon. With IQ•SPECT, the department is now looking to consolidate studies, doing in three days what previously required five days and creating space for additional studies per week.

Decreased scan times has also meant that patients have to remain still for less time. This increased patient comfort. Myocardial perfusion exams require that patients remain still for the duration of the scan to avoid motion artifacts. Patient movement can negatively impact image quality.

The faster scan times meant that Zwijnenburg has seen less patient movement and fewer motion artifacts.

"We saw clear advantages of the cardio focals and the attenuation correction [when] compared to the non-corrected and the non-cardio focal images," he said. "In a reduced amount of time, we acquire images with IQ•SPECT that are often better quality than before."

The clinical benefits did not stop there.

To achieve optimal image quality, conventional cardiac imaging requires relatively long exam time or high injected dose. Ironically, clinicians who perform IQ•SPECT exams reduce the dose and scan time, thereby minimizing patient radiation and maximizing speed. Since the standard dose in The Netherlands is already half of that typically used in the USA, Zwijnenburg explained, the improved scan times optimized the facility's injected dose.

Efficiency Learned

When Kennemer Gasthuis first began using IQ•SPECT, the staff did not immediately recognize the efficiency possible with the new technology. There was a learning curve. For the first two months, the facility performed 20 IQ•SPECT studies and duplicated each using conventional acquisition on the Symbia T scanner, as a way to be certain that they were reading the new images correctly. Then, they discussed the double studies with two doctors experienced with IQ•SPECT who were brought in by Siemens. During this process, Siemens representatives helped the department staff fine tune their acquisition protocol and process settings to achieve optimal results.

Titulaer and Zwijnenburg emphasize that the learning process was a necessary step enroute to improved operations within their department, including substantially improved image quality.

"They [nuclear medicine physicians] need to be aware that attenuation correction is much, much better with IQ•SPECT," Titulaer said. "It is important when you come from, say, a standard gamma camera, with or without attenuation correction, that you learn how to read the IQ•SPECT images. The first time you look at the IQ•SPECT image, you question whether there is an apical infarct, which typically is not the case. But that is because IQ•SPECT, in my belief, gives a better representation of the true activity distribution in the heart."

As Titualer and Zwijnenburg extol the benefits of taking the time to learn how best to interpret IQ•SPECT images, it is no coincidence that the Kennemer Gasthuis facility has recently become a Siemens IQ•SPECT fellowship site. In this role, the staff mentor outside clinicians who visit Kennemer in the reading of IQ•SPECT images.

"It is nice to do. It is good for the department, because they get more ideas about nuclear medicine from peers around the world, and it is good for physicians to discuss studies with others. We will teach fellow technicians and physicians how we perform IQ•SPECT cardiac studies, and we learn a lot as well."

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"In a reduced amount of time, we acquire images with IQ•SPECT that are often better quality than before."

Ton Zwijnenburg, MD, Nuclear Medicine Specialist
Spaarne Hosptial and Kennemer Gathuis
Hoofddorp and Harlem, The Netherlands

LewisGale Medical Center Campus in Salem, Virgina, USA

Bold Investment in Biograph TruePoint PET•CT Pays Long-Term Dividends at LewisGale Medical Center

At the depths of the recent global recession, LewisGale Medical Center replaced its mobile PET/CT service with a fixed-site scanner from Siemens. Since then, the Salem, Virginia, USA, medical center has doubled patient volume, expanded clinical offerings and reduced costs.

LewisGale Medical Center
HCA Virginia Health System

By **Matt Skoufalos**

Tight capital budgets may cause some providers to delay the purchase of new technologies, thinking they will be unable to justify the cost. But even in the toughest economic times, LewisGale Medical Center, proved that purchasing a new Siemens PET•CT was a solid investment from operational, clinical and financial perspectives.

Over the past five years, the Biograph™ TruePoint* PET•CT 16-slice scanner, installed during the worst of the global economic downturn, has added revenue, expanded the quality and number of services and provided improved care for patients at the medical center, all while helping center administrators get a better handle on costs.

Revenues have grown with a doubling of patient volume. James Crowley, who manages the molecular imaging and therapy department at LewisGale, recalls that about 50 patients were scanned per month when the medical center relied on a mobile imaging unit that regularly visited the facility five years ago. Today, the staff scans an average of 97 patients per month. Volume peaked one month at 151 patients scanned.

The molecular imaging department at LewisGale had exclusively scanned cancer patients with the mobile imaging unit. Replacing that device with a Biograph TruePoint PET•CT allowed the facility to expand its PET services to include cardiothoracic imaging. This helped transform the department into a referral center for other facilities within the four-hospital LewisGale regional health system.

"The value of a fixed PET/CT has made this unit an essential part of our business," said Mike Abbott, chief operating officer for LewisGale Medical Center. "Our smaller hospitals simply don't have the volume for a fixed PET scanner. Within our system, Biograph TruePoint PET•CT is a valuable tool that we have 24/7."

Out with the Mobile

Replacing mobile imaging with the fixed PET/CT ironed out a variety of challenges. Previously, noise and light intrusion in the van made the mobile scanner a less-than-ideal tool for physicians looking to meet the growing demand for neurological studies at the medical center, Crowley said.

Consistency was another problem. When PET/CT scans were performed using the mobile service, different scanners would be sent to the site on different days. Consequently, the staff was not able to determine whether changes seen in follow-up studies were due to changes in the patient or variability in the equipment used to scan them.

"Once you have a cancer diagnosis, you know that patient will have to be imaged again," said Jackson W. Kiser, MD, president of Radiology Associates of Roanoke, which provides radiological services at LewisGale. "But with multiple studies potentially being performed on multiple scanners, producing comparable images was a challenge."

The sensitivity of the crystals is different from one system to another, just as the electronics used to acquire the data varies. "We weren't really sure if we were collecting data for the follow-up scan in the same way that we did the for baseline data," he said.

Also of concern, the PET/CT van was not ideal for critically ill patients. Kiser recalled how the first cardiac viability study his department performed in the mobile unit was on a diabetic patient who had been on an insulin drip in the ICU.

"We had to take the patient offsite from where most of the patient care services were," he said. "If his blood sugar would have bottomed out, if we'd had to resuscitate him, it would have been challenging."

"Our smaller hospitals simply don't have the volume for a fixed PET scanner. Within our system, Biograph TruePoint PET•CT is a valuable tool that we have 24/7."

Mike Abbott, Chief Operating Officer
LewisGale Medical Center, Salem, VA, USA

"With our cardiac PET scans, for example, you get better image quality with less radiation, and that's a win-win for everybody."

Jackson W. Kiser, MD
President, Radiology Associates of Roanoke
Roanoke, VA, USA

The Catalyst to Act

The factor that spurred LewisGale to invest in a fixed scanner was the installation of a cyclotron in nearby Roanoke, Virginia, USA. Kiser recalls how new possibilities immediately opened up for LewisGale following installation of the Siemens PET•CT. Costs became easier to control, he said, just as access to different isotopes allowed a broader range of studies.

The scanner, with its 227-kg /500-pound patient capacity, paid dividends in the cardiac imaging of obese and overweight patients, Kiser said. PET•CT helped to detect early a lesion in one patient who might not have been able to fit in the mobile scanners that used to visit LewisGale.

The bore on Biograph TruePoint easily accommodates obese patients, Kiser said, and the shorter scan times lessen discomfort for patients with claustrophobia. "These patients get a bit antsy in there," he said. "With Biograph TruePoint, you can reduce your bed times and still get a diagnostic study; you have high enough sensitivity."

The added weight capacity of the table offers "almost no deflection," which helps ensure the quality of the image captured during the study, he said.

"It's also more powerful," he said. "With our cardiac PET scans, for example, you get better image quality with less radiation, and that's a win-win for everybody."

Expanding Clinical Reach

Oncology is the forte of PET/CT. But, with the right equipment, other applications are possible with increased efficiencies. The Biograph TruePoint PET•CT scanner allowed radiologists at LewisGale to to complete an entire workflow in as little as an hour, Crowley said.

Moreover, with the addition of medical air, suction and oxygen connections to the fixed room that houses the Biograph TruePoint PET•CT scanner, critically ill patients can benefit from advanced imaging, while receiving the support they need and saving the department time and money.

Early Payback

The PET•CT scanner has allowed radiologists at LewisGale to participate in clinical research trials, which Crowley said have conferred added value to the facility.

Complementing the Biograph TruePoint PET•CT is another Siemens technology, *syngo*®.via, a software solution that automates the acquisition and processing of imaging data. "We were easily accepted into clinical trials because we're able to get the acquired PET images simply through the *syngo* software suite," Crowley said.

Participating in clinical trials also revealed the downstream benefits of Biograph TruePoint as a multi-faceted staff education tool. With greater use of the scanner in varied applications, such as cardiac perfusion imaging, Kiser said the technologists gained a wider range of skills, while developing a closer relationship with physicians.

"We're constantly talking; they're telling me what's going on with the scanner and I'm telling them what's going on with the patient," Kiser said. "They are getting an education on cardiac physiology that they never would have gotten in the cath lab or an ICU."

Boosting Productivity

For Kiser, the reliability of Biograph TruePoint has been a boon, maximizing the availability of PET/CT and patient access to PET/CT. "I can probably count the number of times we've had failures on one hand, and that's over a four- or five-year period," he said.

Above: (Left to right) James Crowley, Jackson W. Kiser, MD, and Mike Abbott.

LewisGale based its decision to acquire the Siemens PET•CT partly on its performance record at another site. Reliability was one factor. Image quality was another.

"I'd had experience with Siemens at a former hospital, and I knew the crystal technology to be number one," Kiser said. "That's the standard of comparison. It's why practitioners want PET scanners with detectors made from Siemens' LSO (lutetium oxyorthosilicate) crystal. If you want the best scanner, the best image quality, you have to go with Siemens."

"We wanted Siemens image quality [and] scan time," Crowley said. "We wanted Biograph TruePoint. The system sold itself."

"We wanted Siemens image quality [and] scan time... We wanted Biograph TruePoint. The system sold itself."

James Crowley, Manager
Molecular Imaging and Therapy Department, LewisGale Medical Center
Salem, VA, USA

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* Biograph TruePoint is not available in the EU or any country requiring CE marked products.

Case 1

Delineation of Femoral Lytic Lesions with xSPECT Bone in a Patient with Multiple Myeloma

By **Partha Ghosh, MD, Molecular Imaging Business Unit, Siemens Healthcare**

Data courtesy of University of Erlangen, Erlangen, Germany

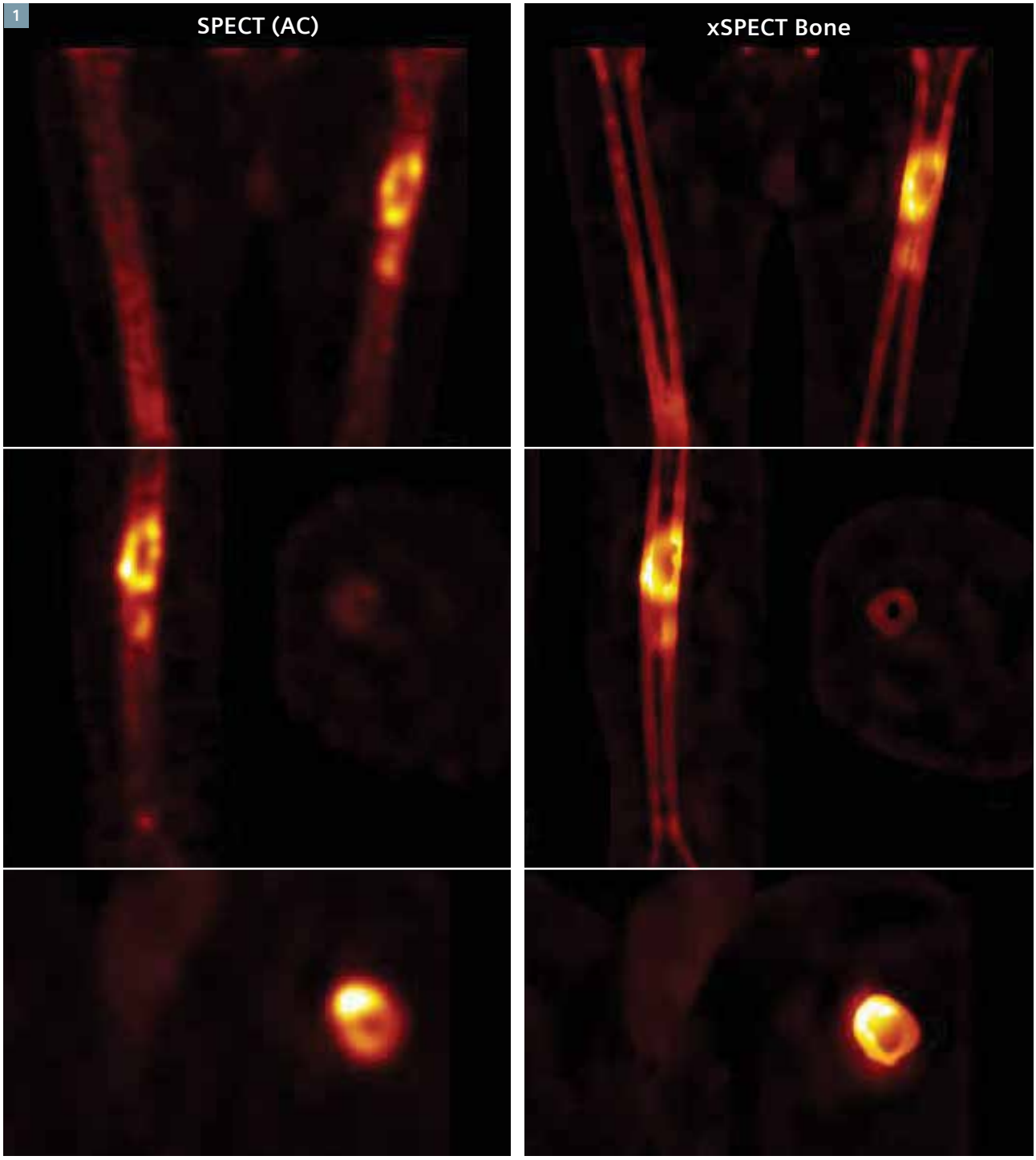
History

A 75-year-old man with a history of multiple myeloma presented with bilateral thigh pain. Patient was referred for a ^{99m}Tc DPD bone xSPECT/CT study. Conventional 3D iterative SPECT with attenuation correction (AC) and xSPECT Bone* imaging were both performed. A thin-slice diagnostic CT of the femur was performed as an integrated procedure.

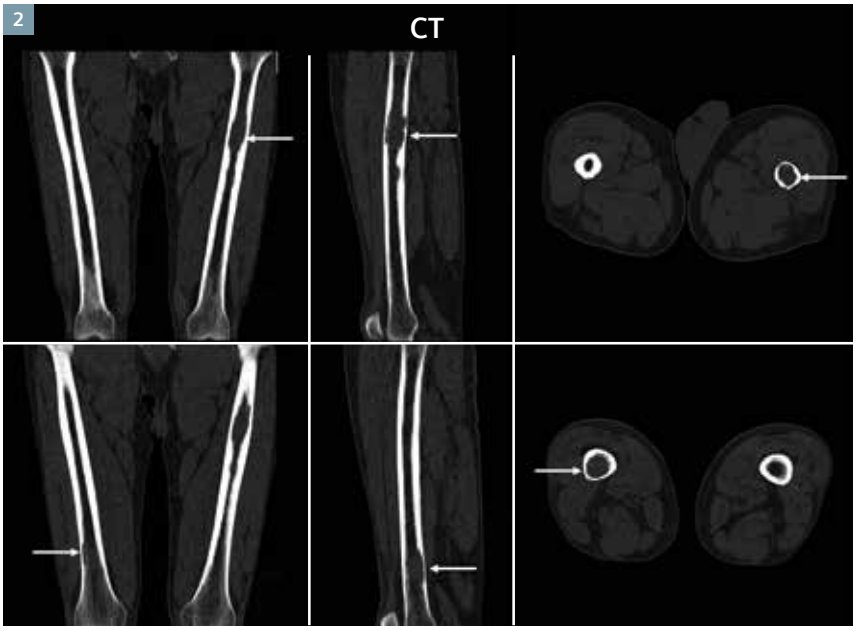
Diagnosis

xSPECT Bone showed a large lytic lesion in the upper half of the left femoral shaft and a smaller lesion just below the larger lesion. The central photopenic area with peripheral hypermetabolism is typical of a lytic lesion with peripheral bone erosion. Another similar lesion was also visualized in the lower third of the right femoral shaft. Compared to 3D iterative reconstruction, xSPECT Bone shows sharper delineation of the hypermetabolic edges of the lytic bone lesion, as well as improved delineation of the normal cortical bone of the femoral shaft and marrow cavity. Transverse reconstruction in the xSPECT* study shows improved delineation of the hypermetabolic medial margin of the lesion involving the upper part of the left femoral shaft.

CT images show lesions in the upper part of the left femoral shaft and lower third of the left femoral shaft, both of which show erosion of the inner cortical table with absence of bony expansion and without irregularities of the outer cortical surface or periosteum. No soft tissue involvement or swelling is visualized. The inner cortical table erosion without any osteoblastic activity, calcification or sclerosis within the marrow suggests a marrow lesion with infiltration into and eroding the inner cortical bone. This is typical of multiple myeloma. CT also shows a small secondary lesion just below the large lesion in the left femur.

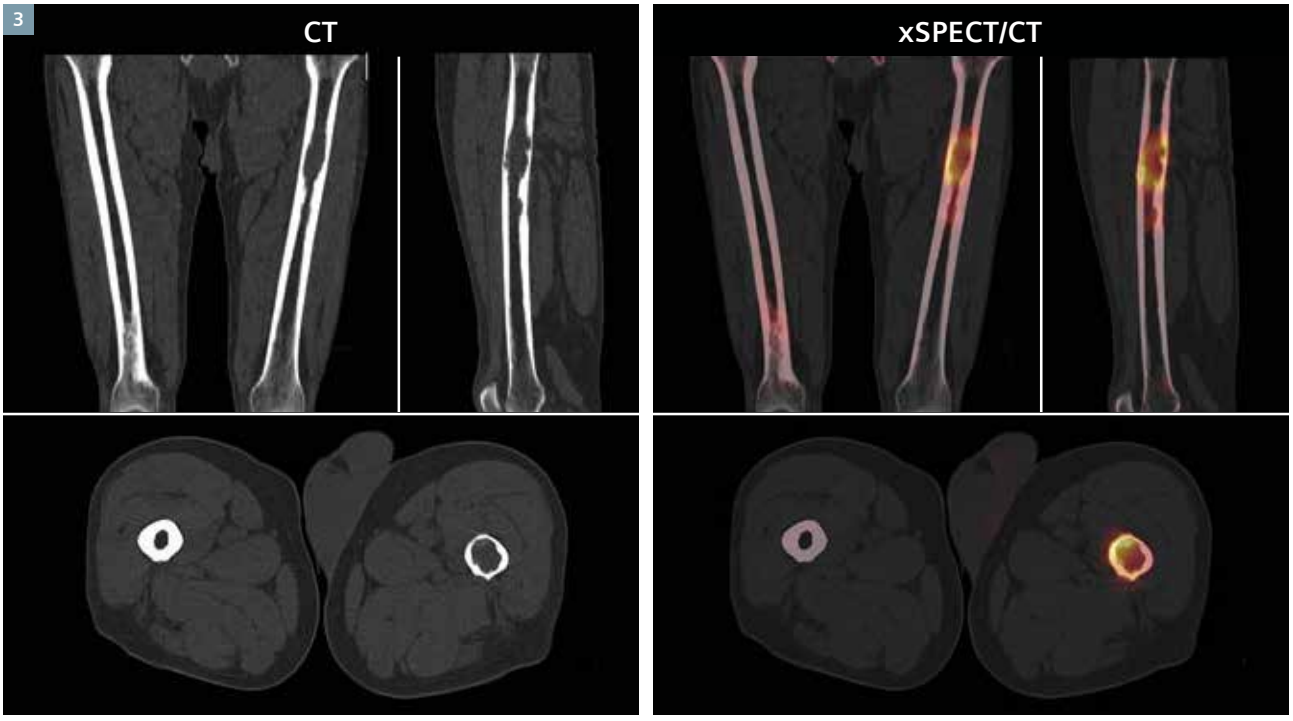


1 Comparison of SPECT (AC) and xSPECT Bone shows lytic lesion in the shaft of the left femur.

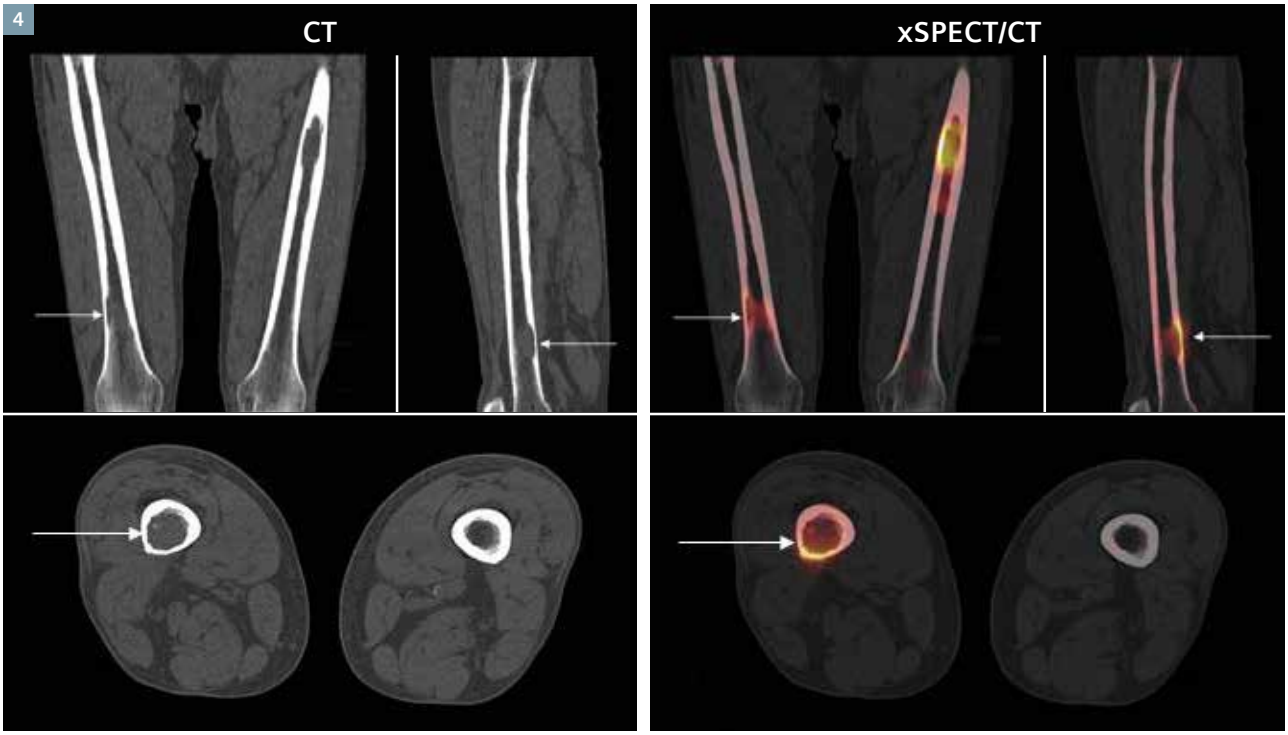


Fusion of CT and xSPECT Bone images show exact coregistration of the hypermetabolic peripheral margin of the myeloma lesions arising from the marrow to the erosion of the inner cortical table typical of the myeloma lesions. The sharp definition of the hypermetabolic rim of the lesions by xSPECT Bone helps its exact coregistration with the erosion. Focal hyperintensities in regions of the hypermetabolic peripheral rim suggest cortical zones with significantly more active erosion, which may be at risk of fracture.

2 CT shows erosion of the inner table of the cortex of the femoral shaft on both sides (*arrows*).



3 CT and fusion of CT and xSPECT Bone shows exact coregistration of the hypermetabolic edge of the lytic lesion in the left femoral shaft to the erosion of the inner table of cortex.



4 Fusion images show coregistration of peripheral hypermetabolic rim of the lesion in the lower part of the femoral right shaft, with the erosion in the inner cortical table.

Discussion

Since myeloma and plasmacytomas arise from the plasma cells of bone marrow and do not show new bone formation, bone scanning has not been widely recommended for multiple myeloma work-ups. X-ray, CT and MRI are the major modalities currently used. However, some cases may be associated with reactive bone changes. For example, this study shows an erosion of the inner table of the femoral shaft's cortex. This is due to myeloma, which causes reactive hypermetabolism as defined on xSPECT Bone. Skeletal scintigraphy plays a role in identification of such reactive changes. In patients presenting with bone pain in which skeletal scintigraphy is performed, such lesions may be unearthed.

Value of xSPECT Bone Imaging

Characterizing the reactive nature of the hypermetabolism that was seen on the rim of the lytic femoral shaft lesions, secondary to bony erosion, was made possible by the exact co-registration of the erosion in the inner cortical table with the hypermetabolic rim, which was sharply defined by xSPECT Bone. The focal areas of hyperintensity within the hypermetabolic lesional margin, defined sharply by xSPECT Bone, defined the cortical zones with exaggerated erosion that have potential for fracture.

Examination Protocol

Scanner	Symbia Intevo™* 6
Injected dose	825 MBq (22 mCi) ^{99m}Tc DPD
Scan delay	3 hours post injection
Parameters	32 frames, 25 sec/frame, 3D iterative SPECT (AC) and xSPECT Bone reconstruction
CT	130 kV, 10 eff mAs, 3 mm slice thickness

* xSPECT Bone, xSPECT and Symbia Intevo 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.

PLM Reference Number: FAU FS23

Case 2

Improved Characterization of Small Solitary Lung Nodule Using HD•Chest and FlowMotion in a Patient with Rectal Carcinoma

By **Partha Ghosh, MD, Molecular Imaging Business Unit, Siemens Healthcare**

Data courtesy of Royal Brisbane Hospital, Brisbane, Australia

History

A 61-year-old male patient with a history of rectal carcinoma treated with recto-sigmoid resection and partial hepatectomy for solitary liver metastases underwent Fludeoxyglucose F 18 (^{18}F FDG)* PET/CT for a follow-up.

The PET/CT study was performed on Biograph mCT Flow™**. Following non-contrast whole-body CT, the PET acquisition was performed with variable table speed. The liver and upper abdomen were acquired through integrated respiratory gating, with faster acquisition for the extremities in order to optimize acquisition time.

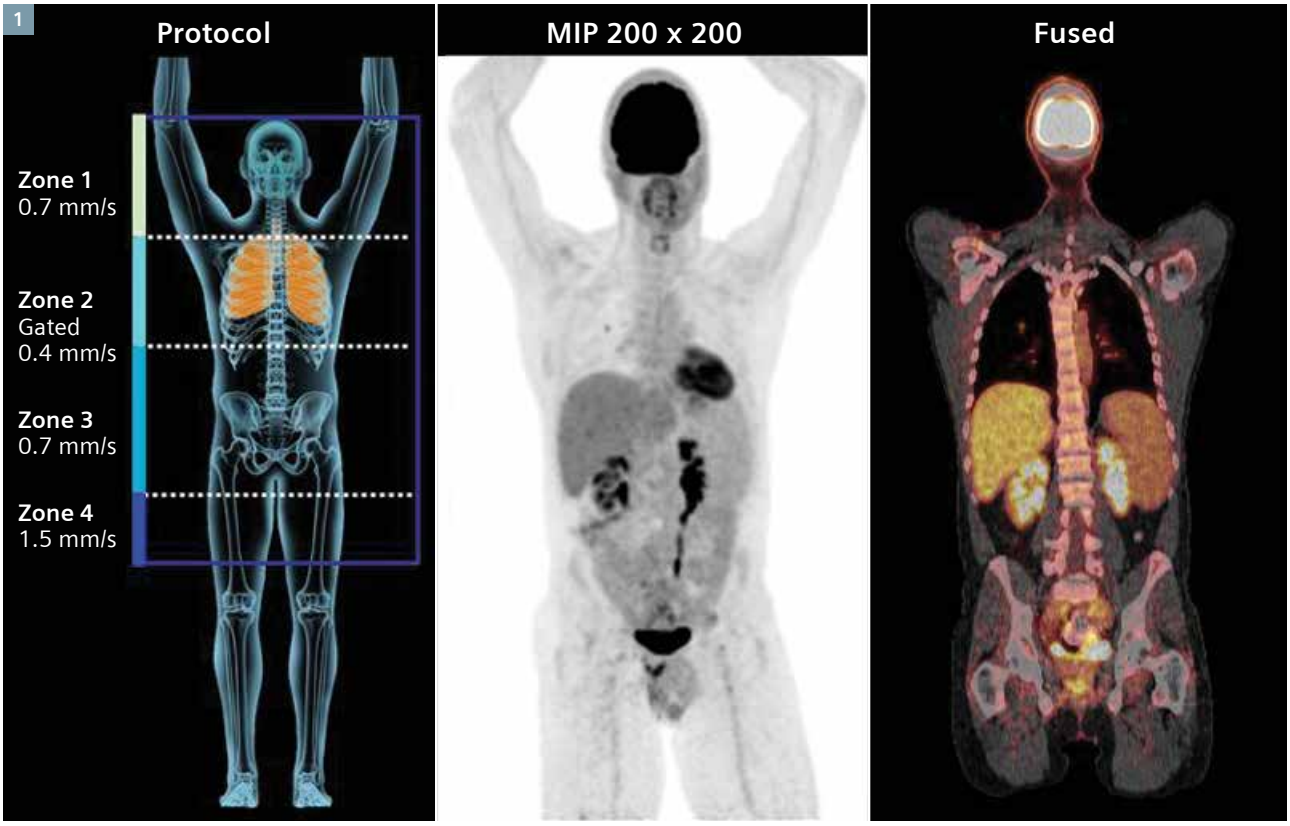
The whole-body PET study was reconstructed as a non-gated 200x200 matrix reconstruction. However, the gated data from the thorax and upper abdomen were reconstructed as HD•Chest with 33% duty cycle in order to obtain relatively motion-free images of the lung for improved evaluation of lung lesions.

Diagnosis

Coronal MIP and thin MIP images of the whole-body PET study shows a solitary focal hypermetabolic nodular lesion in the lung, which is suspicious for malignancy with an SUV_{max} of 2.9 in the non-gated study. The surgical resection bed in the anterior part of the left lobe of the liver shows normal tracer uptake. Both the renal pelvis and left upper ureter show tracer retention. Mild ^{18}F FDG uptake in bilateral inguinal nodes is likely to be reactive.

The HD•Chest reconstruction of the respiratory-gated data of the lung, which is now part of the single scan protocol due to the use of FlowMotion™**, demonstrates sharper delineation of the hypermetabolic lung nodule with higher lesion conspicuity and increased target to background as compared to non-gated acquisition.

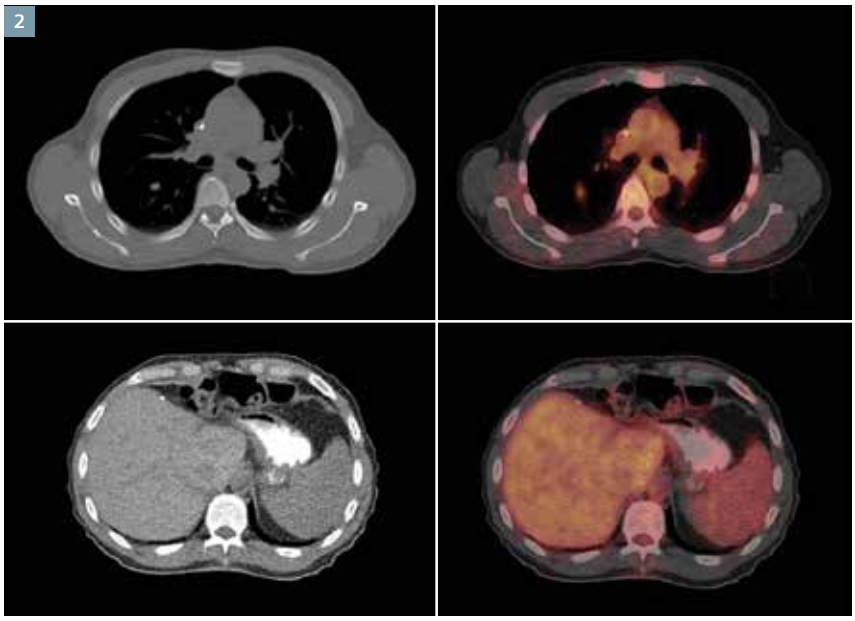
Quantitative comparison between non-gated reconstruction and HD•Chest shows substantially higher SUV_{max} with HD•Chest compared to that obtained from the non-gated reconstruction. SUV_{max} increased from 2.97 to 3.65 with HD•Chest, an increase of 23%. This can be attributed to the lack of peripheral blurring and smaller lesion dimension achieved with HD•Chest by eliminating the respiratory motion artifacts. The SUV_{max} level is consistent with a diagnosis of malignancy in the pulmonary nodule, possibly secondary to lung metastases from rectal carcinoma.



1 Whole-body PET images acquired with FlowMotion show a solitary lung nodule.

Comment

This clinical example illustrates the improved visualization and higher quantitative accuracy for small lung nodules that are achieved through amplitude-based, optimized respiratory-gating (HD•Chest), which eliminates respiratory motion-related peripheral blurring and loss of lesion conspicuity. The 23% higher SUV_{max} obtained with HD•Chest—secondary to elimination of respiratory motion-related partial volume effects and blurring—strongly supports the diagnosis of malignancy in the lung nodule. Although the SUV_{max} of 2.97 obtained from the non-gated study suggests malignancy, the increased SUV_{max} following elimination of respiratory motion-related effects imparts



2 CT and fused PET/CT images show a solitary hypermetabolic lung nodule and normal tracer uptake in the resection bed in the anterior part of the left lobe of the liver.

significant additional diagnostic confidence and also confirms the absence of other lung lesions. CT shows the lung nodule to be 8 mm in diameter. The sharp delineation of such a small nodule with HD•Chest reflects the improved lesion conspicuity, target-to-background ratio and higher quantitative accuracy obtained through the elimination of respiratory motion-related blurring and partial volume effects with HD•Chest.

Although respiratory gating helps eliminate respiratory motion and is able to sharply define the lesion in individually gated frames, the relatively lower count statistics and higher background noise in the individual frames may hinder visualization of very small lesions or lesions with low uptake. HD•Chest uses amplitude-based gating, which uses a portion of the total gated list-mode data with the least motion based on amplitude histogram. This provides relatively motion-free images with higher count statistics for higher image quality and improved small lesion conspicuity. FlowMotion acquisition enables respiratory gating within extremely flexible ranges, which helps generate motion-managed HD•Chest reconstructions precisely from the regions of interest without undue time penalty.

Value of FlowMotion Technology

Accurate SUV quantification is key to management decision-making in lung nodules. SUV_{max} higher than 2.5 has been shown to have a higher probability of malignancy. Since SUV in lung nodules may be affected by partial volume effects, due to respiratory motion in non-gated PET, motion management in PET acquisition, like HD•Chest, may improve quantification due to elimination of respiratory motion effects. This is particularly important for small nodules with lower levels of hypermetabolism as seen in early lesions. Detection of small nodules with low uptake may also be enhanced by HD•Chest since

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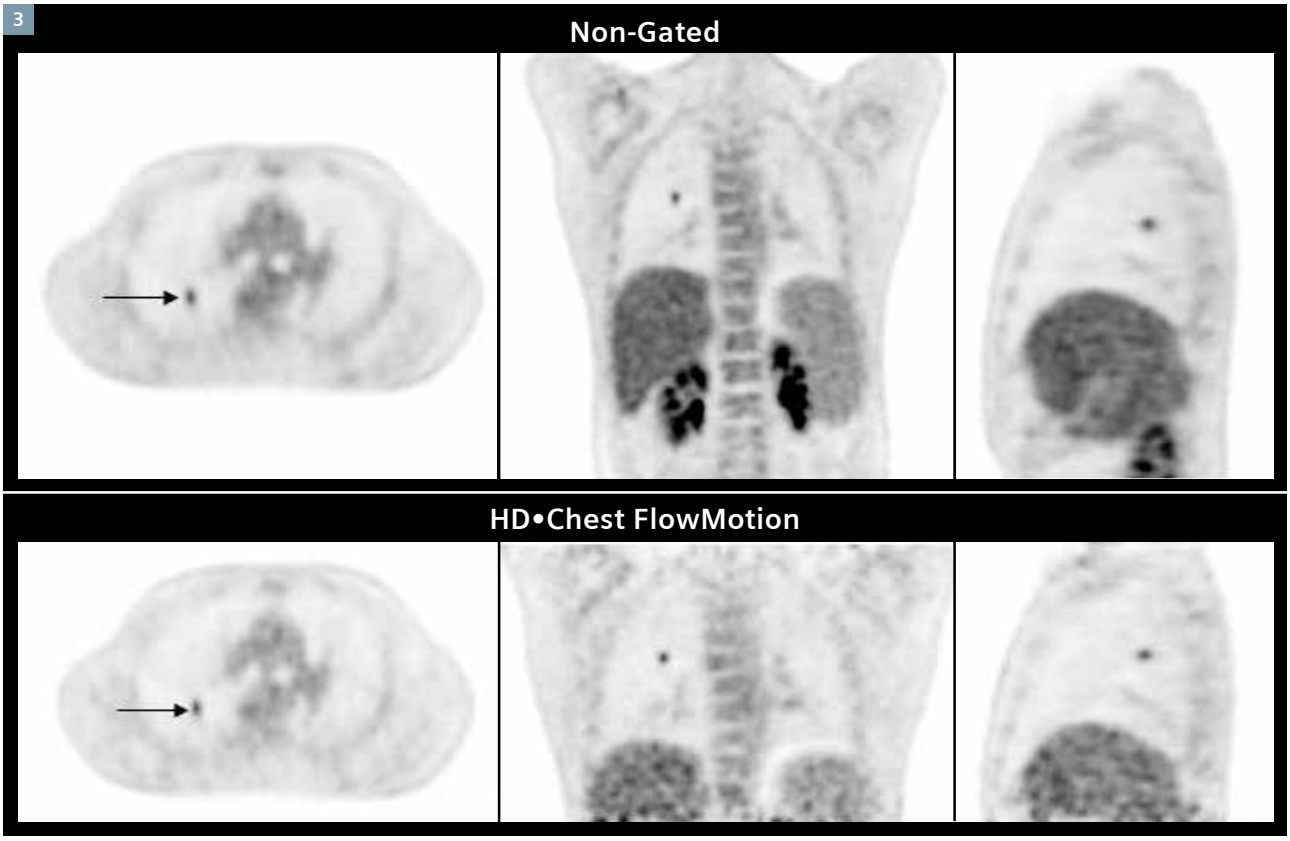
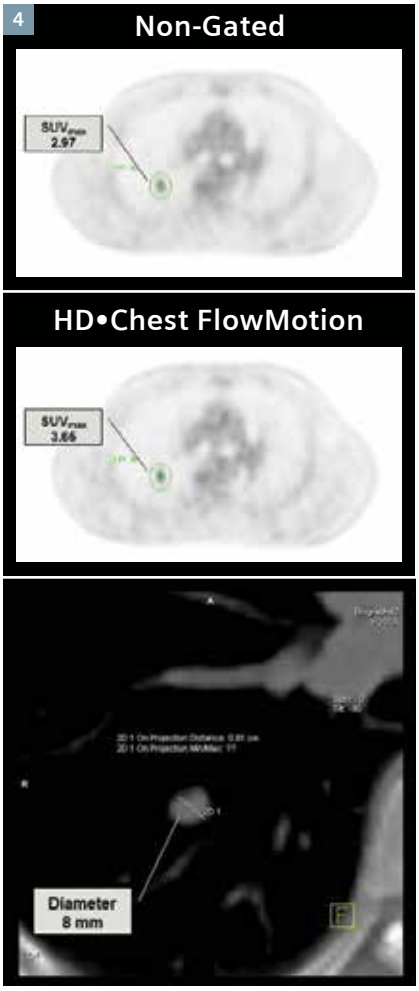


3 Comparison of thoracic non-gated PET and HD•Chest reconstructions of the thorax showing sharper delineation of hypermetabolic solitary lung nodule with HD•Chest *(arrow)*.

lesion conspicuity is improved by eliminating respiratory motion-related blurring. Integration of HD•Chest with FlowMotion acquisition offers great flexibility of the area to be covered and opens the possibility of seamless routine use of this technique, with potential improvement in lesion detectability and informed therapy decision. Thus, FlowMotion enables gated acquisition in narrow or wide ranges not limited by bed positions in order to perform acquisition tailored to the patient's clinical requirements.



4 CT shows a solitary lung nodule with a diameter of 8 mm. HD•Chest shows higher SUV_{max} of 3.65 of the lung nodule compared to SUV_{max} of 2.97 obtained from non-gated PET acquisition of the lung.

* The full prescribing information for the Fludeoxyglucose F 18 injection can be found on pages 78-80.

** Biograph mCT Flow and FlowMotion 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.

The statements by Siemens' customers described herein are based on results that were achieved in the customer's unique setting. Since there is no "typical" hospital and many variables exist (e.g., hospital size, case mix, level of IT adoption) there can be no guarantee that other customers will achieve the same results.

Examination Protocol

Scanner	Biograph mCT Flow
Injected dose	334 MBq ^{18}F FDG
Scan delay	1 hour post injection
FlowMotion Acquisition	Variable table speed (*Figure 1*) ultraHD•PET with integrated respiratory gating for thorax and upper abdomen
CT	100 kV, 45 eff mAs, 5 mm slice thickness

PLM Reference Number: P213_44

Indications

Fludeoxyglucose F 18 Injection is indicated for positron emission tomography (PET) imaging in the following settings:

- **Oncology:** For assessment of abnormal glucose metabolism to assist in the evaluation of malignancy in patients with known or suspected abnormalities found by other testing modalities, or in patients with an existing diagnosis of cancer.
- **Cardiology:** For the identification of left ventricular myocardium with residual glucose metabolism and reversible loss of systolic function in patients with coronary artery disease and left ventricular dysfunction, when used together with myocardial perfusion imaging.
- **Neurology:** For the identification of regions of abnormal glucose metabolism associated with foci of epileptic seizures.

Important Safety Information

- **Radiation Risks:** Radiation-emitting products, including Fludeoxyglucose F 18 Injection, may increase the risk for cancer, especially in pediatric patients. Use the smallest dose necessary for imaging and ensure safe handling to protect the patient and healthcare worker.
- **Blood Glucose Abnormalities:** In the oncology and neurology setting, suboptimal imaging may occur in patients with inadequately regulated blood glucose levels. In these patients, consider medical therapy and laboratory testing to assure at least two days of normoglycemia prior to Fludeoxyglucose F 18 Injection administration.
- **Adverse Reactions:** Hypersensitivity reactions with pruritus, edema and rash have been reported; have emergency resuscitation equipment and personnel immediately available.

Case 3

^{18}F FDG* PET•CT Staging in a Case of Lymphoma Presenting as a Chest Wall Tumor

By E. Nitzsche, MD, PhD, Professor, Department of Nuclear Medicine, Kantonsspital Aarau, Aarau, Switzerland

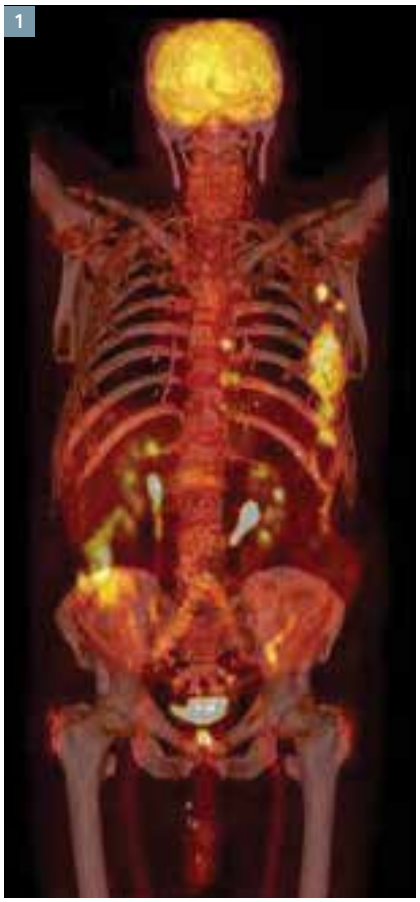
Data courtesy of Kantonsspital Aarau, Aarau, Switzerland

History

An 86-year-old man presented with ill-defined swelling in the left lateral chest wall, close to the anterior axillary fold, with local pain and tenderness. Histopathological evaluation of the biopsy from the swelling suggested large B cell lymphoma. The patient was referred for a Fludeoxyglucose F 18 (^{18}F FDG) PET•CT study for primary staging.

Diagnosis

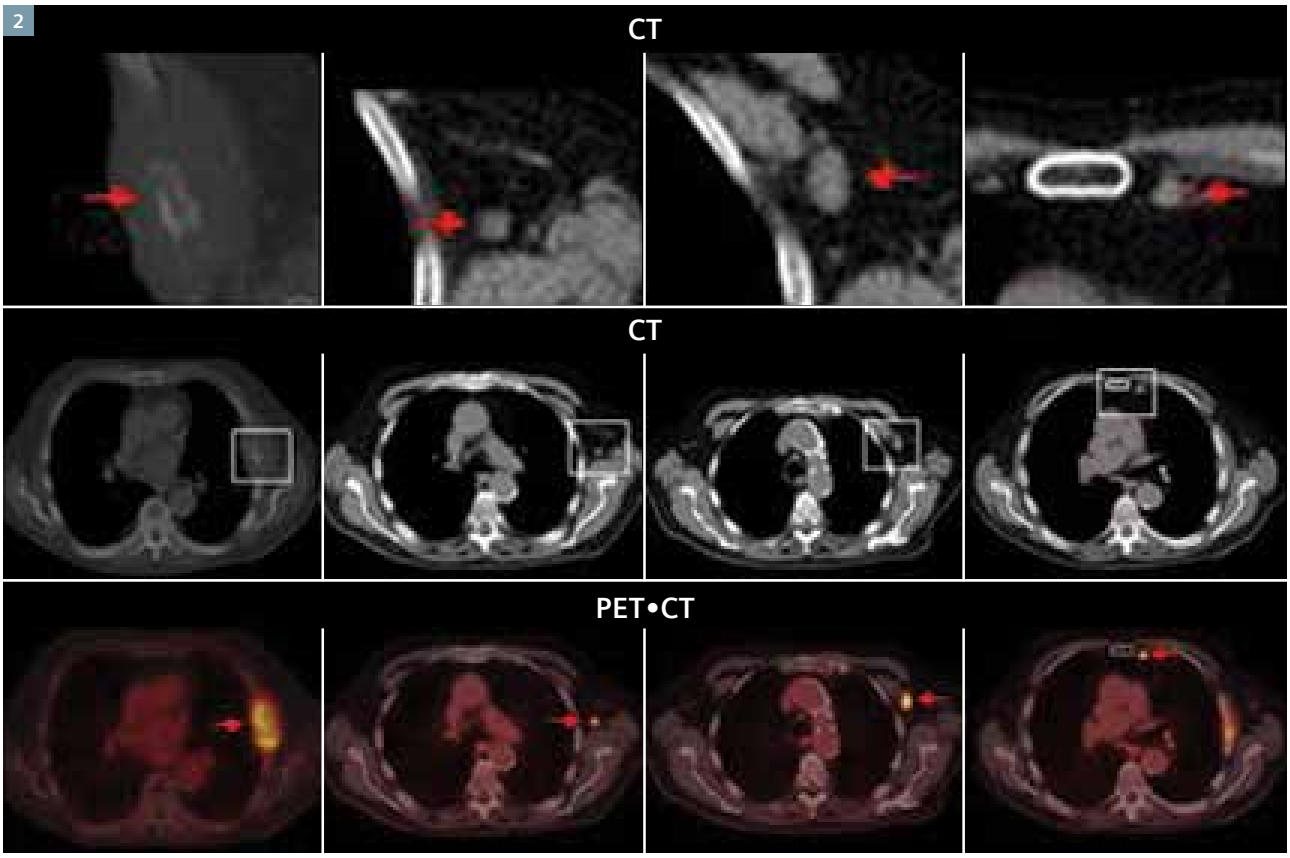
^{18}F FDG PET•CT showed a hypermetabolic chest wall lesion with associated destruction of the left fifth rib, laterally. The mass was adjacent to and indented the pleura, but there was no associated effusion. Several hypermetabolic axillary lymph node masses were also visualized. One of the axillary nodes was normal in size on CT, but the others were enlarged. PET•CT also showed a hypermetabolic left internal mammary node with borderline enlargement on CT. No other hypermetabolic lesion was visualized. Liver, spleen and marrow did not show lymphomatous involvement.



1 ^{18}F FDG PET and volume-rendered-fused PET•CT images show hypermetabolic chest wall mass with axillary and mediastinal metastases.

Comments

Lymphoma presenting as a chest wall tumor is rare and only sporadic cases are available. In a series of four cases, Witte et al[1] demonstrated that Hodgkin's and large B cell lymphoma were associated with chest wall involvement. Several cases were associated with bone destruction, either manubrium sterni or ribs. The treatment was primarily chemotherapy associated with chest wall irradiation. There was no prior case of PET•CT imaging in the lymphoma presenting with chest wall tumors that could be identified. However, in a series of three cases of lymphoma with associated pyothorax, in which PET•CT imaging was used[2], ^{18}F FDG PET showed a very high SUV_{max} in the involved areas.



2 CT and fused PET•CT transverse slices show chest wall tumor and axillary and internal mammary lymph nodal lesions.

In this rare case of lymphoma presenting as a primary chest wall tumor, ^{18}F FDG PET•CT defined the extent of chest wall involvement, the presence of small lymph node involvement in axillary and internal mammary nodes, and clearly established the absence of associated pleural or lung infection or pyothorax.

Value of Technology

High lesion contrast from HD•PET reconstruction on a Biograph™ mCT PET•CT is instrumental in sharp visualization of small hypermetabolic internal mammary and axillary lymph nodes, which are normal by CT criteria.

Examination Protocol

Scanner	Biograph mCT with TrueV and HD•PET
Injected dose	305 MBq ^{18}F FDG mCi
Protocol	2.5 min/bed low-dose CT

* Indications and important safety information on Fludeoxyglucose F 18 injection can be found on pages 53 and 73. The full prescribing information can be found on pages 78-80.

References:
1. Witte et al. GMS Thoracic Surgical Science 2006, Vol. 3.
2. Abe et al. Oncol Lett. 2010 Sep;1(5): 833-836.

Case 4

Improved Visualization of Small Liver Metastases Using HD•Chest and FlowMotion

By **Partha Ghosh, MD, Molecular Imaging Business Unit, Siemens Healthcare**

Data courtesy of Royal Brisbane Hospital, Brisbane, Australia

History

An 81-year-old male patient with a history of colorectal carcinoma treated with partial colectomy presented with elevated serum carcinoembryonic antigen (CEA). In view of the suspicion of metastases, the patient was referred for a PET•CT scan.

PET•CT studies were performed on a Biograph mCT Flow™* scanner. After the non-contrast, whole-body CT, a whole-body PET acquisition was initiated using variable table speed. The liver and upper abdomen were acquired with integrated respiratory gating. Faster acquisition was used for the extremities, in order to optimize acquisition time.

The whole-body PET study was reconstructed as a non-gated, 200x200 matrix reconstruction. However, the region of the liver and upper abdomen was reconstructed with a higher matrix (400x400) as a non-gated study. The gated data for the same region was also reconstructed as HD•Chest with 50% duty cycle in order to obtain relatively motion-free images of the liver for improved evaluation of liver metastases. FlowMotion™ acquisition enabled routine use of HD•Chest as a part of seamless routine acquisition with high flexibility of the range of the region of respiratory gated acquisition.

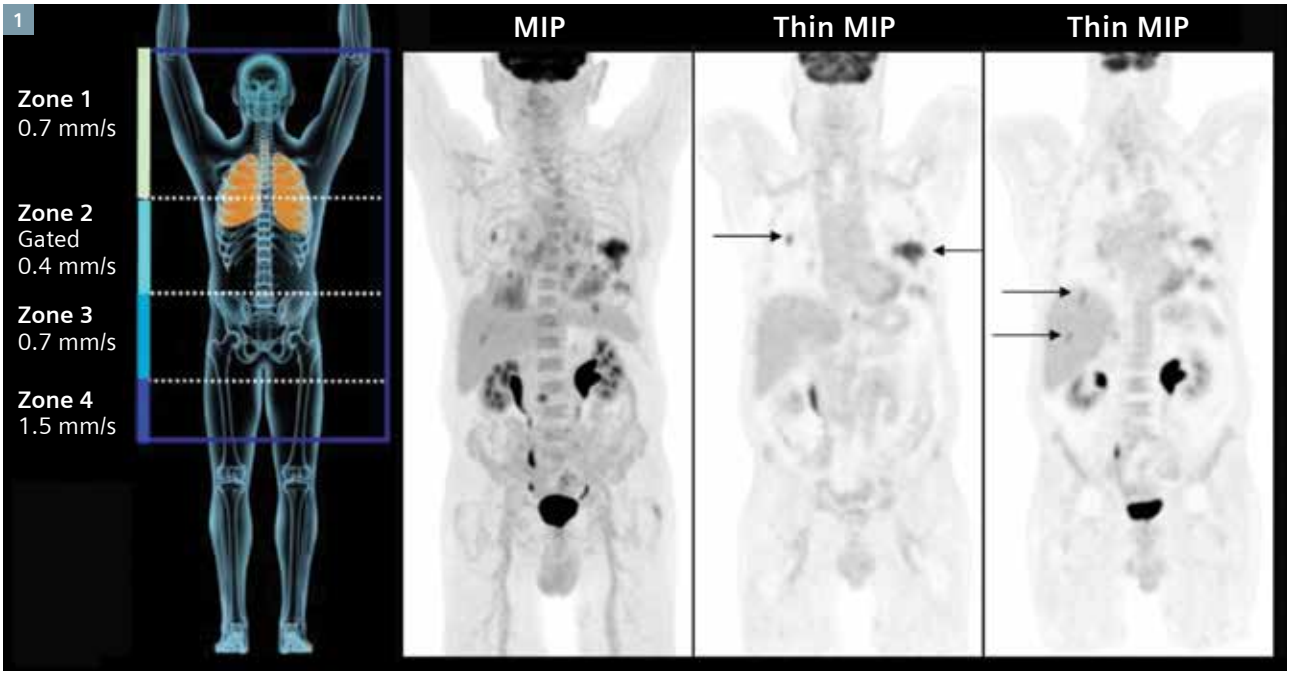
Diagnosis

Coronal maximum intensity projection (MIP) and thin-MIP images of the whole-body PET study show two focal hypermetabolic lesions in the liver, which are suggestive of liver metastases. Glucose-avid region in the left lung and another small focal region in right lung are probably related to inflammation. Left renal pelvis shows tracer retention. Note the linear uptake and blurring of the margins of the small liver lesions, which are related to respiratory motion during acquisition since the whole-body study is reconstructed as a non-gated acquisition.

CT and fused PET•CT images of the thorax show honeycombing of the left lung and right lung base, which corresponds to high tracer uptake and suggests extensive bilateral inflammatory lesions, probably resolving pneumonitis.

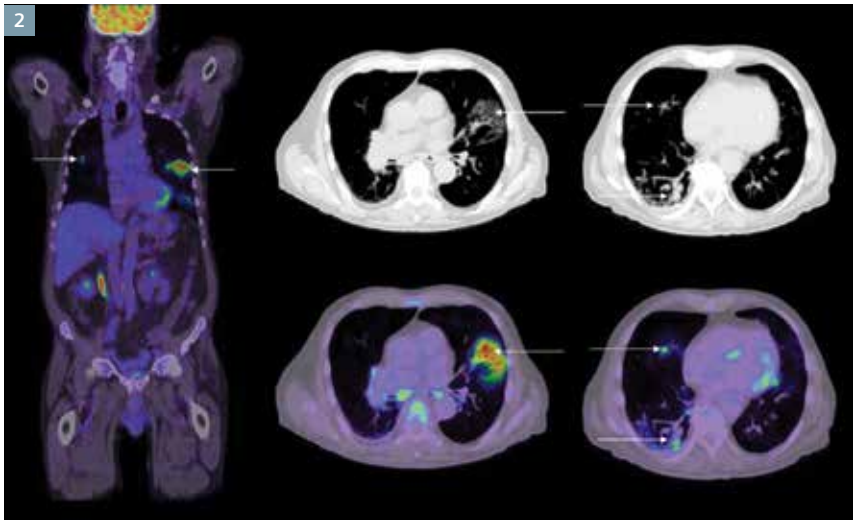
The high-resolution, non-gated reconstruction of the respiratory gated acquisition of the upper abdomen shows the liver metastases as small elongated focal hypermetabolic areas. The elongated nature of the uptake and blurring of the edges secondary to respiratory motion are especially prominent in the liver lesion near the dome of the diaphragm.

The HD•Chest reconstruction of the respiratory gated data of the liver and upper abdomen demonstrates improved delineation of both the liver metastases with higher lesion conspicuity, increased target to background with improved visibility and sharper definition of the edges, as compared to non-gated acquisition. This is especially conspicuous in the lesion near the dome of the diaphragm.



1 Whole-body PET images acquired with FlowMotion show lung and liver lesions.

Quantitative comparison between non-gated reconstruction and HD•Chest shows a substantially higher SUV_{max} with HD•Chest compared to that obtained from the non-gated reconstruction. SUV_{max} went from 3.92 to 4.8 with HD•Chest, an increase of 22%, which can be attributed to the lack of peripheral blurring and smaller lesion dimension achieved with HD•Chest by eliminating the respiratory motion effects. FlowMotion technology enables respiratory gated acquisition in flexible ranges as was utilized in this patient who required gating for the liver but not the lung in view of the predominance of liver metastases in colorectal carcinoma.



2 CT and fused PET•CT images suggest the lung lesions to be of inflammatory origin.

3 200x200 matrix reconstruction of non-gated PET acquisition of liver and upper abdomen shows two liver lesions with blurring due to respiratory motion.

Comments

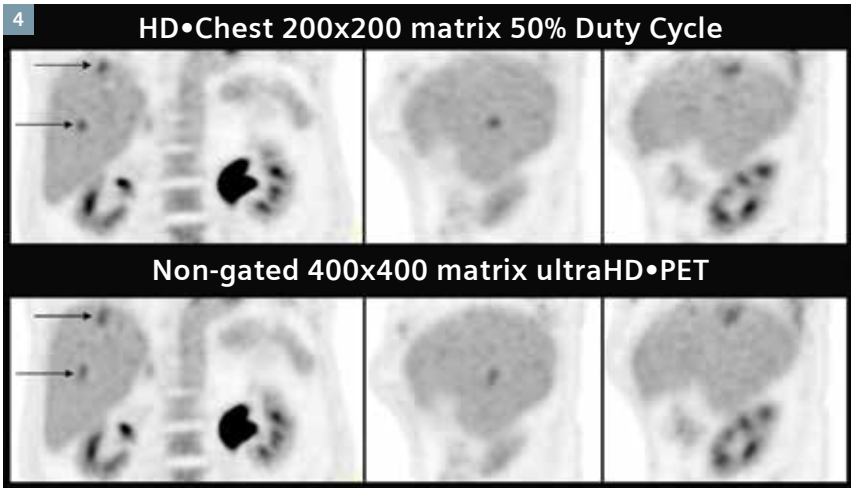
This clinical example illustrates the significant distortion of small liver lesions with peripheral blurring and loss of conspicuity secondary to respiratory motion when PET is acquired without respiratory gating. This may lead to lower detectability of small liver metastases with PET/CT.

Although respiratory gating helps eliminate respiratory motion and is able to sharply define the lesion in individual gated frames, the relatively lower count statistics and higher background noise in the individual frames may hinder visualization of very small lesions or lesions with low uptake.

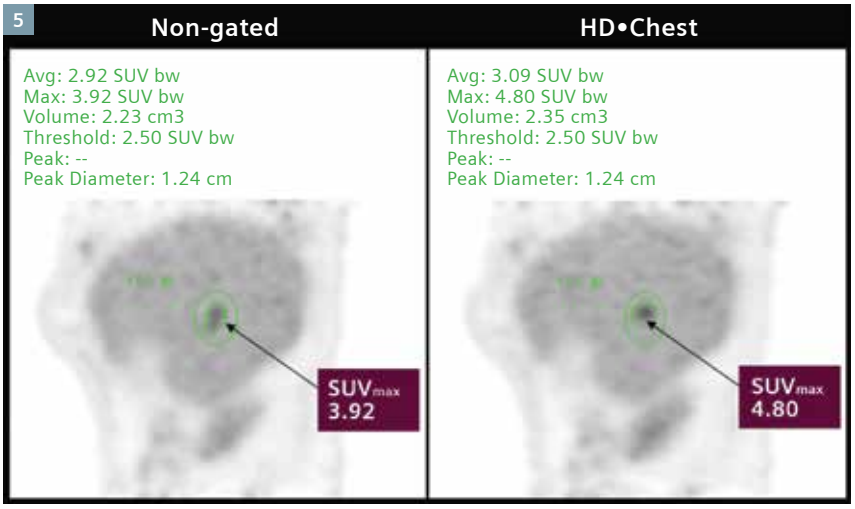
HD•Chest uses amplitude-based gating, which utilizes the portion of the total gated list mode data that has the least motion based on amplitude histogram and provides relatively motion-free images with higher count statistics for improved image quality and small lesion conspicuity.

HD•Chest is an attractive tool for improved delineation of small liver lesions, since it provides relatively motion-free images with sufficient image quality and count density without significant increase in scan time. HD•Chest, when integrated into FlowMotion acquisition, can be used with extreme flexibility, thereby enabling precise definition of the region to be acquired with respiratory gating.

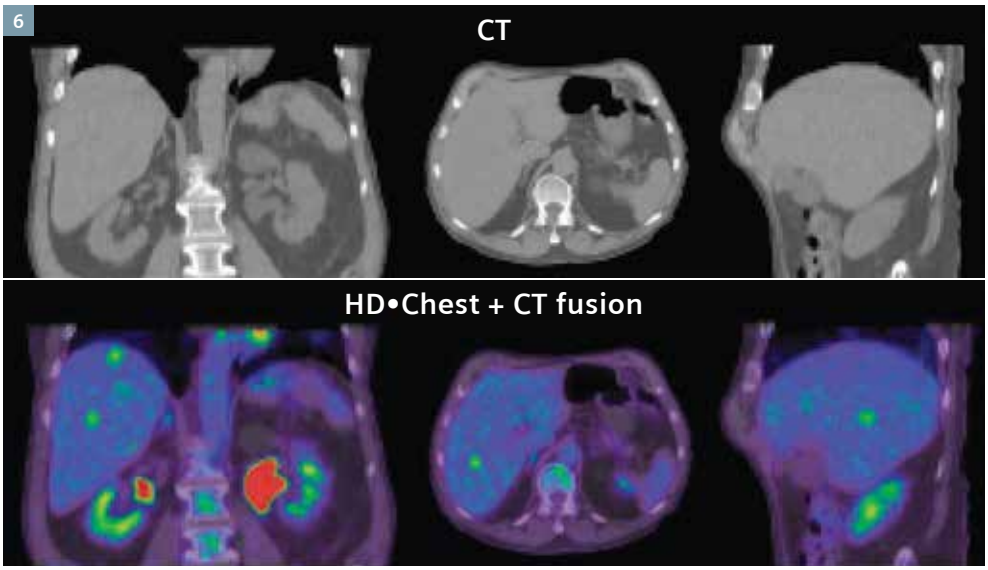
In a recent study comparing non-gated PET and HD•Chest in 31 patients with liver metastases,[1] out of a total of 82 hepatic and 25 perihepatic lesions, 13 new lesions were identified by HD•Chest as compared to standard PET. In this study, five-minute optimal gating (HD•Chest) acquisition demonstrated improved image quality and 66% higher target to background ratio and 24% higher SUV_{max} for metastatic lesions as compared to non-gated PET acquired at 2.5 minutes per bed. In a patient with a single lesion seen on standard PET, the use of HD•Chest identified two liver metastases, which significantly changed patient management from surgical removal of solitary metastases to radiofrequency ablation of two metastatic lesions. In another patient, HD•Chest helped the physician identify a lesion in the pancreas that had been previously identified as a peritoneal metastases by non-gated PET.



4 Comparison of non-gated and HD•Chest reconstructions of the liver and upper abdomen shows improved definition of liver lesions when using HD•Chest.



5 Comparison of SUV_{max} of liver lesion shows significantly higher SUV_{max} with HD•Chest than in the non-gated acquisition.



6 Non-contrast CT and fusion of CT and HD•Chest reconstruction shows sharp boundaries of small liver metastases that are not well visualized on non-contrast CT, thereby highlighting the value of PET and elimination of respiratory motion for delineation of such small lesions with minimal morphological changes.

Value of FlowMotion Technology

In view of the therapy options, such as surgical removal of solitary liver metastases, cryotherapy, radiofrequency ablation of individual lesions or chemotherapy in extensive metastases, proper detection of early liver metastases or exclusion of liver lesions assumes a key importance in the therapy decision. Thus, integrated techniques like HD•Chest, which improve the diagnostic confidence and detectability of small liver, lung or upper abdominal lesions without undue time burden, are of value in PET/CT scanning.

Continuous bed motion and anatomy-based planning with FlowMotion opens the possibility of seamless, routine use of HD•Chest with the opportunity for improvement in lesion detectability and more informed therapy decisions.

Examination Protocol

Scanner	Biograph mCT Flow
Injected dose	334 MBq ^{18}F FDG
Scan delay	1 hour post injection
Protocol	FlowMotion acquisition, variable table speed. *(Figure 1)* ultraHD•PET with integrated respiratory gating for upper abdomen
CT	120 kV, 56 eff mAs, 3 mm slice thickness

* Biograph mCT Flow is not commercially available in all countries. Due to regulatory reasons, its future availability cannot be guaranteed. Please contact your local Siemens organization for further details.

The statements by Siemens customers described herein are based on results that were achieved in the customer's unique setting. Since there is no "typical" hospital and many variable exist (e.g., hospital size, case mix, level of IT adoption) there can be no guarantee that other customers will achieve the same results.

References:
1. Van Der Gucht, et al. (2013). European Journal of Radiology, Nov. 2013 online, article in press.

Case 5

Dynamic ^{82}Rb PET•CT Estimation of Myocardial Blood Flow as an Indicator of Post Angioplasty Reperfusion in Ischemic Viable Myocardium

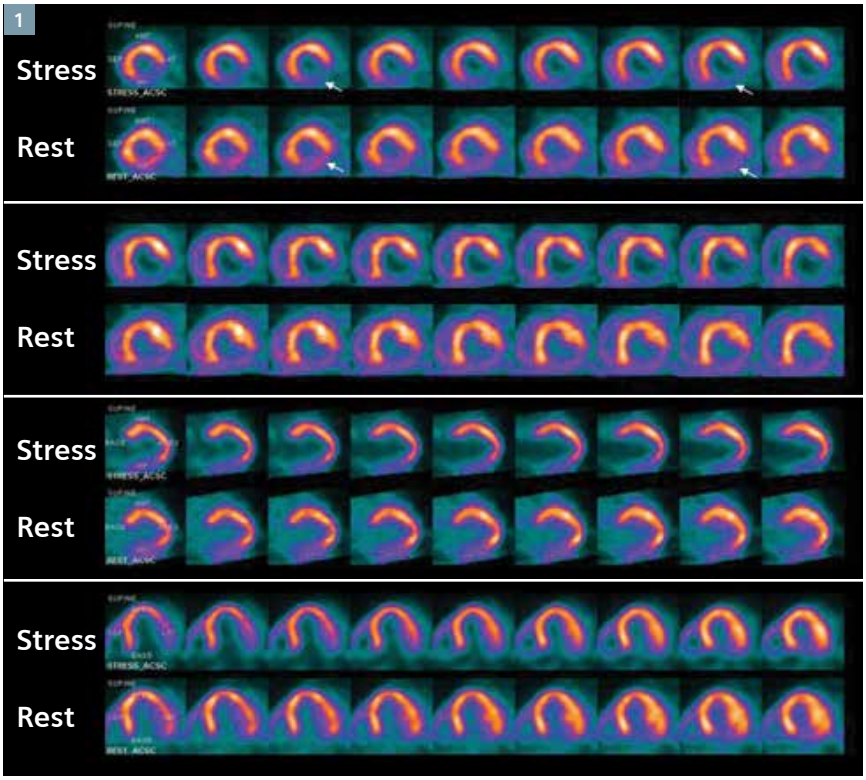
By **Dr. Parthiban Arumugam, MD, Manchester Royal Infirmary, Manchester, United Kingdom**

Data courtesy of Manchester Royal Infirmary, Manchester, United Kingdom

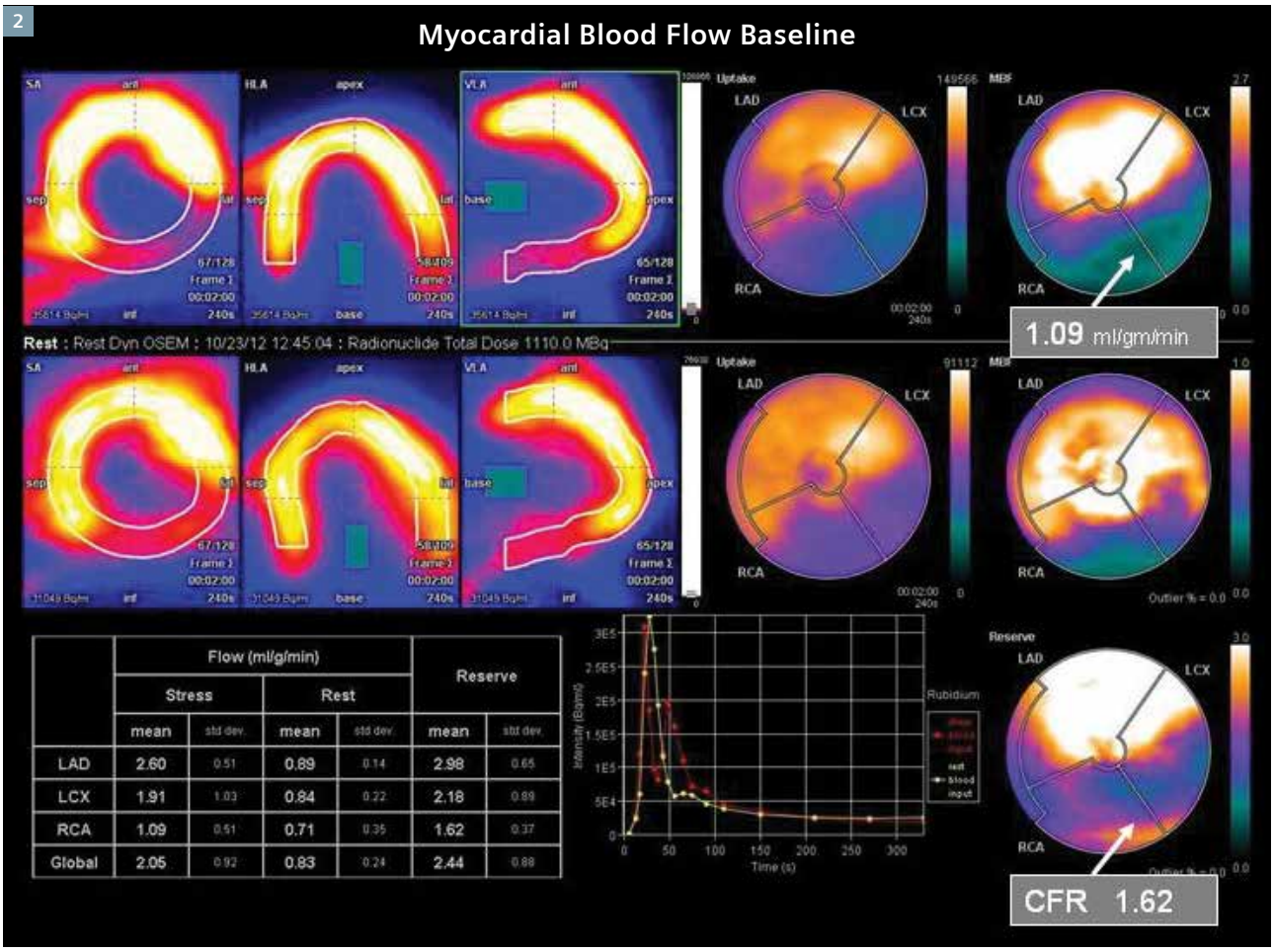
History

A 64-year-old male patient with intermittent angina presented for a PET myocardial perfusion study. A dynamic ^{82}Rb PET•CT study was performed at rest and during Adenosine stress. The study was performed on a Biograph™ TruePoint 64, and the data were evaluated using *syngo*®.PET Myocardial Blood Flow (MBF) software package for an estimation of myocardial blood flow.

The PET myocardial perfusion study demonstrated severe stress-inducible reduction in perfusion in the inferolateral myocardium *(arrows)*, with partial reversibility visualized in the resting images *(Figure 1)*. The anterior wall, septum and most of the lateral wall show normal perfusion. The left ventricle (LV) appears dilated in



1 Stress/rest ^{82}Rb myocardial perfusion PET study.



	Flow (ml/g/min)				Reserve	
	Stress		Rest			
	mean	std dev.	mean	std dev.	mean	std dev.
LAD	2.60	0.51	0.89	0.14	2.98	0.65
LCX	1.91	1.03	0.84	0.22	2.18	0.89
RCA	1.09	0.51	0.71	0.35	1.62	0.37
Global	2.05	0.92	0.83	0.24	2.44	0.88

2 Myocardial blood flow and coronary flow reserve estimation using *syngo*.PET MBF software shows low-stress absolute flow rates and coronary flow reserve in the inferolateral wall.

the post-stress images, reflecting the severity of ischemia. The persistence of the inferolateral hypo perfusion in the rest-study, with minor reversibility, reflects the severity of the right coronary artery (RCA) stenosis with gross resting hypo perfusion.

MBF was low in the inferolateral myocardium during peak stress (1.09 ml/gm/min in the inferolateral segment *(arrows, Figure 2)* compared to 2.6 ml/gm/min in the anterior wall, which is within normal limits). Also, resting blood flow in the inferolateral myocardium is significantly lower than that of the anterior wall. The myocardial flow reserve is 1.62 in the inferolateral segment, with the accepted normal value being more than twice the resting flow.

The patient underwent coronary angiography, which demonstrated tight RCA stenosis and occlusion of the distal circumflex artery. The perfusion pattern correlates well with the angiographic appearance.

The patient underwent successful angioplasty of the RCA stenosis. A follow-up ^{82}Rb myocardial perfusion PET was performed after one year due to recurrence of symptoms. Stress/rest ^{82}Rb PET•CT was performed.

Diagnosis

Compared to the initial images, the post-angioplasty perfusion study, performed one year later, also shows a partial improvement in perfusion to the inferolateral segments at peak stress. Perfusion at rest is, however, significantly improved compared to the initial study, suggesting significant improvement in resting perfusion in the inferolateral myocardium.

Stress MBF in the inferolateral myocardium was 2.22 ml/gm/min, while the anterior wall was 2.91 ml/gm/min. Stress MBF in the inferolateral myocardium was significantly higher

in the post-angioplasty study, compared to the initial study (1.09 ml/gm/min). Although, visually, there appears to be a reversible perfusion defect in the inferolateral myocardium in the post-angioplasty situation, the normal stress MBF is possibly a reflection of successful revascularization following angioplasty. The resting MBF in inferolateral myocardium was comparable to the initial study. The myocardial flow reserve in the inferolateral segments (3.8) was significantly increased, which is higher than in the normally perfused segments (anterior wall coronary flow reserve 2.51). In comparison, the coronary flow reserve (CFR) in inferolateral myocardium for the initial study was only 1.62.

Comments

Because of the persistent relative stress hypoperfusion in the post-angioplasty study, the increase in CFR and stress MBF in the inferolateral myocardium is significant. Resting perfusion is not significantly different in pre- and post-angioplasty states. The asymmetric increase in CFR, compared to the visual stress perfusion pattern in the inferolateral myocardium following angioplasty, may reflect the absolute increase in blood flow in the right coronary and the myocardial small vessels post angioplasty, although the peak stress flow relative to the normal myocardium was lower leading to the visualization of hypo perfusion in the short axis slices. The significant increase in inferolateral myocardial CFR may be an early sign of successful reperfusion following angioplasty, even when myocardial perfusion in the ischemic area was below that of the normally perfused LV segments.

Gradual recovery of CFR in ischemic segments post angioplasty is demonstrated by PET. Neumann et al[1] demonstrated that, in patients with acute myocardial infarction (MI) with successful recanalization of the occluded artery, CFR of the infarct region improves in most patients within one hour, and further improves within two weeks despite the persistence of a perfusion defect. Stewart et al[2], in a series of 21 patients with acute MI, demonstrated gradual and continuous improvement in vasodilator response and coronary flow reserve in infarct related myocardial regions following angioplasty using serial ^{13}N NH3 PET studies.

The interesting aspect of this case is the high CFR in the inferolateral myocardium in a study performed one year following angioplasty. Since the RCA had a tight stenosis, recovery of myocardial perfusion in the affected vessel may be slow and resting perfusion may remain low for an extended period of time, as shown in this case. However, significant increase in vasodilator response, and in stress MBF, reflects the microcirculatory reactivity to stress, and the patency and vasodilatory capacity of the supplying vessel post angioplasty.

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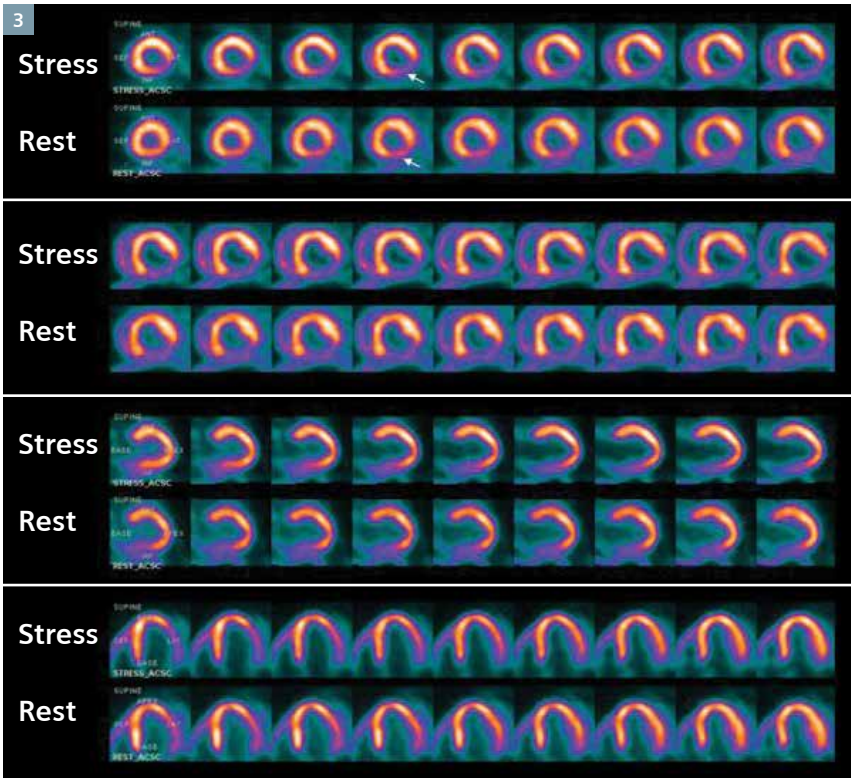


3 ^{82}Rb PET•CT myocardial perfusion study shows a significant perfusion defect in the inferolateral myocardium with evidence of reversibility in the rest images.

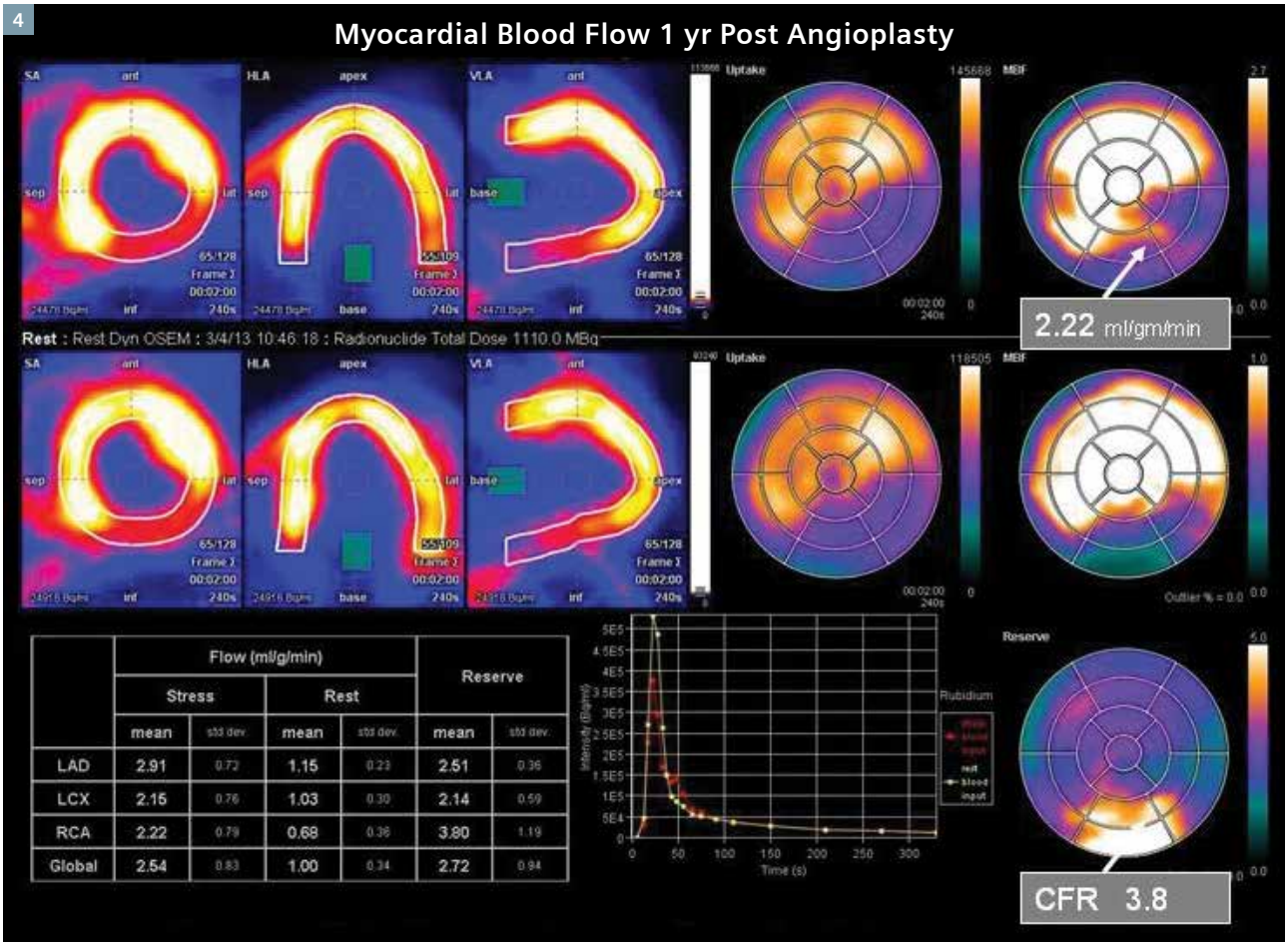
Value of Technology

Myocardial blood flow measurements using ^{82}Rb dynamic PET perfusion studies are helpful for quantitative assessments of coronary interventions, especially stents. MBF measurements with *syngo*.PET MBF software enable routine usage of such quantitative measurements due to the automated nature of the software and its ease of use.

Examination Protocol

Scanner	Biograph TruePoint 64
Injected dose	^{82}Rb 40 mCi stress and 40 mCi rest injection
Acquisition	Dynamic list mode, CT low dose for CT attenuation correction

References:
1. Am Coll Cardiol. 1997 Nov 1;30(5):1270-6.
2. J Nucl Med. 1997 May;38(5):770-7.



4 Myocardial blood flow evaluation using *syngo*.PET MBF software shows normal blood flow values in inferolateral myocardium at peak stress with high CFR.

Case 6

Paraspinal Sentinel Node Identified in a Patient with Melanoma using SPECT•CT

By Michael S. Hofman, MBBS, FRACP, FANNMS, Molecular Imaging Center for Cancer Imaging, Peter MacCallum Cancer Center, Melbourne, Australia

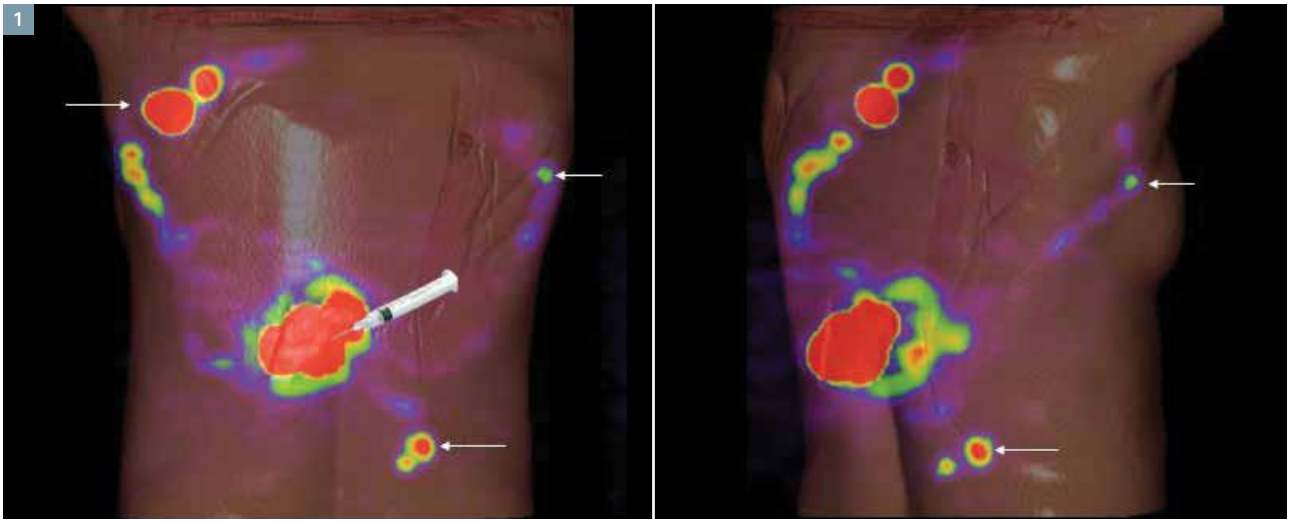
Data courtesy of Peter MacCallum Cancer Center, Melbourne, Australia

History

A patient with melanoma was referred for a SPECT•CT lymphoscintigraphy to localize the sentinel lymph nodes for draining. Following peritumoral injection of ^{99m}Tc Nanocolloid, initial dynamic planar images were acquired. A SPECT•CT with non-contrast diagnostic CT was subsequent performed on a Symbia™ T6.

Diagnosis

In this patient, three pathways of lymphatic drainage and three consequent sentinel nodes are well visualized. Without SPECT•CT, the inferior contralateral pathway would be difficult to define and possibly overlooked. The fused SPECT•CT images *(Figure 2)* clearly demonstrate an additional sentinel node posterior to the right para-spinal muscle (red circle on the CT image), which is located below subcutaneous fat, dorsal to the muscle. This node is easily accessible surgically. In addition, a secondary tier node has localized to the retroperitoneal space just below the posterior abdominal wall (white circle on CT and white arrow on fused SPECT•CT image). This illustrates an intra-abdominal retroperitoneal progression of the lymphatic drainage route. In this type of case, an excisional biopsy of the paraspinal subcutaneous node should be considered, as it may add further prognostic information for this patient.



1 3D volume surface rendering of SPECT•CT lymphoscintigraphy shows tracer retention at the site injection adjacent in to the melanoma in the mid-back at the mid-level (injection syringe) along with lymphatic and tracer drainage to the sentinel nodes in the left posterior scapular region and right axilla bilateral axilla *(arrows)*. Additional nodal pathway drains inferiorly across midline *(arrow)*.

Comments

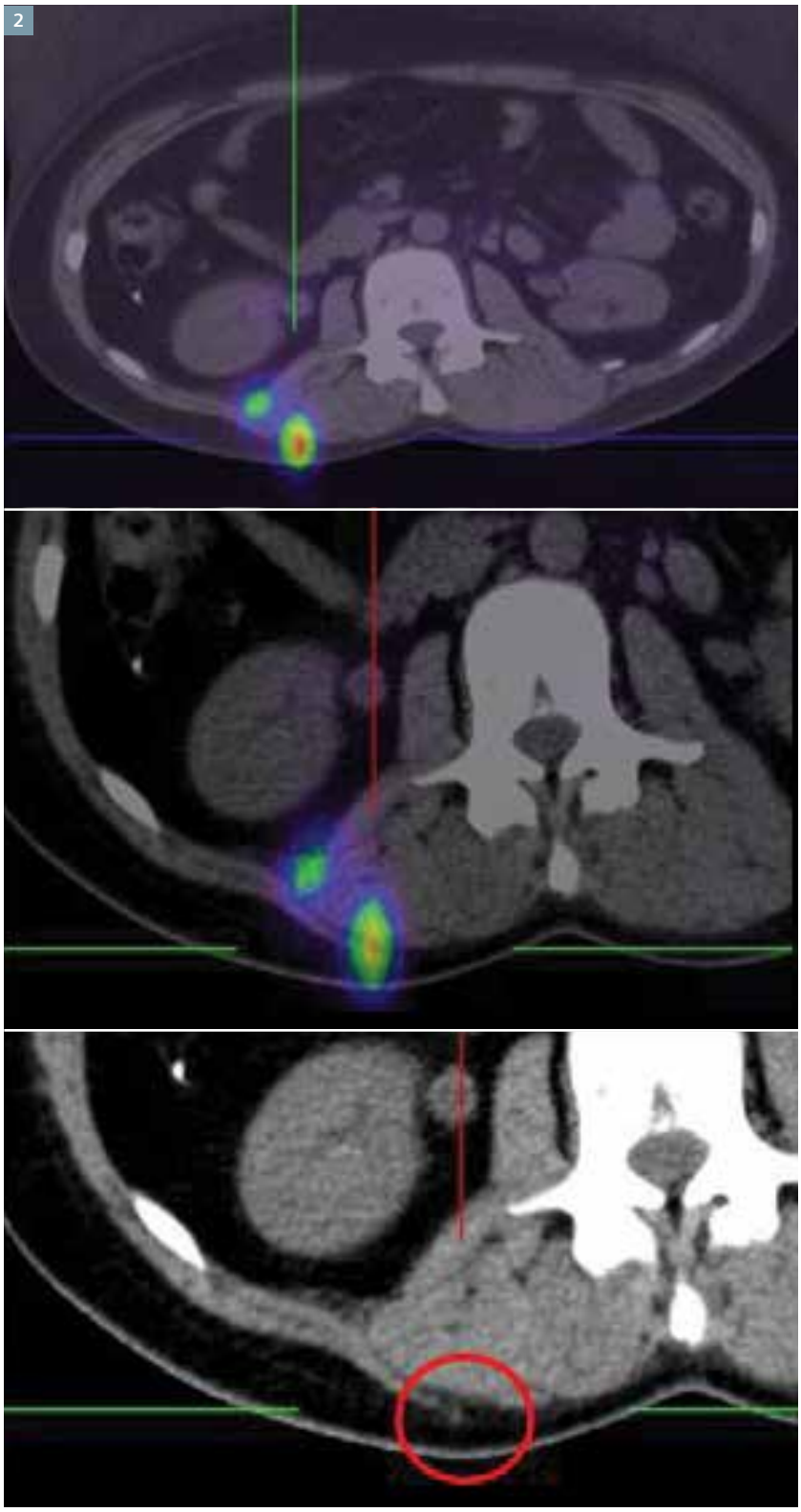
Precise localization of atypically positioned sentinel nodes provides new insights into pathways of lymphatic drainage. Ordinarily, a subsequent presentation with a retroperitoneal nodal metastasis in such a patient would be considered representative of a hematogenenous metastasis. However, it is clear from the SPECT•CT images that, in this patient, it actually represents a loco-regional drainage pathway. In such an event, the differentiation of a loco-regional from hematogeneous metastasis may have significant prognostic ramifications for the patient, and it could alter the treatment approach.

Value of Technology

The precise sentinel node localization seen in this case is possible only because of the integrated high-quality CT performance of the SPECT•CT; also, because of the precise alignment of the SPECT and CT table positions—along with the absence of table deflection that is irrespective of the patient weight—precise co-registration is possible. The surface and volume-fused SPECT•CT images add further dimension and confidence for localization by the surgeon. These technological features translate into more precise localization of aberrant lymphatic pathways and, consequently, positively impact patient management.

Examination Protocol

Scanner	Symbia T6
Injected dose	30 MBq ^{99m}Tc Nanocolloid peritumoral injection
Protocol	Initial dynamic planar acquisition
SPECT	32 frames 40 sec/frame
CT	130 kV 70mAs



2 Volume-rendered-fused SPECT•CT image from a different orientation shows the relationship of the paraspinal subcutaneous sentinel node with the smaller retroperitoneal node.

Case 7

Detection of Primary Pancreatic Carcinoma by ^{18}F FDG* PET•CT

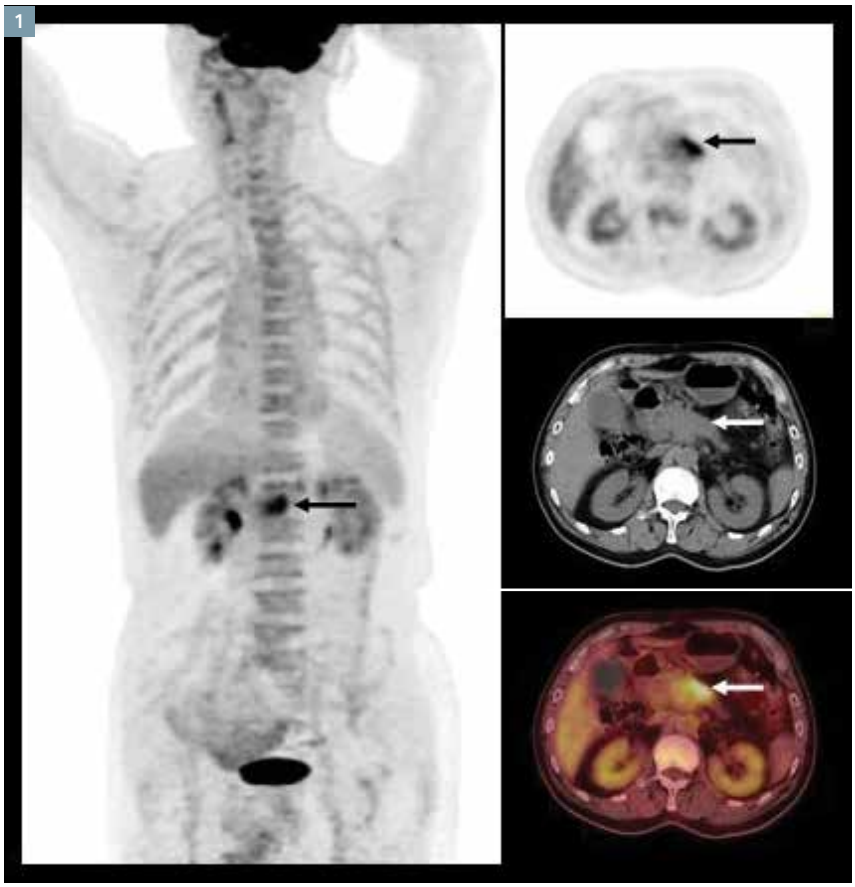
By **Partha Ghosh, MD, Molecular Imaging Business Unit, Siemens Healthcare**

Data courtesy of Beijing Hospital, Beijing, China

History

A 76-year-old male presented with repeated bouts of vomiting and occasional abdominal pain. Initial investigation demonstrated elevated serum CA19-9. The initial clinical diagnosis was pancreatitis. Consequently, the patient was treated conservatively. Although there was significant symptomatic improvement with a conservative therapy, serum CA19-9 elevated persistently. Because of this, a contrast CT of the abdomen was performed. The CT demonstrated widening in the body and tail of the pancreas. Suspecting a pancreatic mass, possibly malignant, the patient underwent Fludeoxyglucose F 18 (^{18}F FDG) PET•CT to evaluate for a focal pancreatic lesion.

^{18}F FDG PET•CT was performed on a Biograph™ mCT, 60 minutes following an IV injection of 10 mCi of ^{18}F FDG.



1 MIP and transverse sections through the pancreas of the PET•CT study shows hypermetabolic pancreatic lesion.

Diagnosis

The PET maximum intensity projection (MIP) image shows a hypermetabolic pancreatic lesion *(arrow, Figure 1)* without additional peripancreatic or distal focal hypermetabolic metastases. The increased marrow uptake might relate to previous therapy or reactive marrow hyperplasia. Axial PET, CT and fused PET•CT images at the level of the pancreas show a hypermetabolic lesion involving the body and tail (SUV_{max} 6.3, SUV_{peak} 4.98), corresponding exactly to the widened body and tail of the pancreas, which appeared to be the site of the primary pancreatic carcinoma. The absence of lymph nodal metastases and the absence of biliary obstruction are positive prognostic indicators.

Comments

In view of the delineation of the primary pancreatic tumor as well as the absence of metastases on the PET and CT, surgery was advised, although stereotactic radiotherapy was another therapeutic possibility. ^{18}F FDG PET•CT has demonstrated high accuracy for staging locally advanced pancreatic carcinoma both for delineation of primary tumor as well as loco-regional metastases. In a series of 71 patients, Topkan et al[1] demonstrated that PET•CT had identified metastases not detected in conventional imaging in 26.8% cases. Median overall survival in patients without metastases on PET•CT was significantly higher (11.4 months) compared to the patient group with PET positive metastases (6.2 months).

The intensity of uptake in the primary tumor with ^{18}F FDG PET•CT is of prognostic significance in pancreatic carcinoma. SUV_{max} higher than 10 in the pre-radiation PET•CT is associated with a lower median survival (9.8 months) compared to 15.3 months in a group with SUV_{max} less than 5.[2] In this particular case, the primary tumor SUV_{max} (6.3) suggests a better prognosis.

Patients with chronic pancreatitis are often at risk of developing pancreatic carcinoma and ^{18}F FDG PET•CT has been shown to be effective in identifying pancreatic malignancies in these patients.[3] However, coexistence of acute pancreatitis and pancreatic carcinoma is uncommon, as in this case. Tumor induced obstruction to the pancreatic duct may be a possible etiology. Although ^{18}F FDG uptake may be diffusely increased in acute pancreatitis, the focal increase in uptake in the pancreatic tail with high SUV_{max} was typical of malignancy.

Value of Technology

The lesion contrast possible on Biograph mCT with time of flight and point spread function combination (ultraHD•PET) improves delineation of the lesion margin, especially in pancreatic lesions that are associated with, to some degree, respiratory motion. Higher lesion contrast and target-to-background increase visibility of pancreatic lesions, which compensate for edge blurring due to respiratory motion. Improved lesion margin delineation may help surgical margin planning or stereotactic radiation target delineation.

Examination Protocol

Scanner	Biograph mCT
Injected dose	10 mCi ^{18}F FDG
Scan delay	1 hour post injection
CT	120 kV, 139 eff mAs, 3 mm slice thickness
PET	2 min/bed ultraHD•PET 6 beds

* Indications and important safety information on Fludeoxyglucose F 18 injection can be found on pages 53 and 73. The full prescribing information can be found on pages 78-80.

References:
1. Cancer Imaging. 2013 Oct 4; 13(3): 423-8.
2. Schellenberg et al. Int J Radiat Oncol Biol Phys. 2010 Aug 1; 77(5): 1420-5.
3. van Kouwen. EJNM. 2005; 32: 399-404.

The View Ahead for Molecular Imaging

Siemens' Pictures of the Future project forecasts expanding role for Molecular Imaging

By John Hayes

Looking more than a decade into the future, Siemens experts, in collaboration with opinion leaders around the world, predict an increasingly varied, important and prosperous role for molecular imaging (MI) in medicine.

In the years to come, MI, at least in some circumstances, will be used to guide biopsies; genetic profiling will identify patients at risk for certain cancers that can be evaluated with in vitro diagnostics and molecular imaging; and new biotracers will allow better targeting of pathologies, just as they will be combined with therapeutic doses to treat patients.

These possibilities and more were uncovered as part of a project initiated by Siemens Molecular Imaging Pictures of the Future project. The initiative began with Siemens experts analyzing hundreds of trends in medicine. They selected those most likely to have significant impact on MI, developed hypotheses as to what those impacts might be and then field tested their predictions through interviews with MI leaders in North America, Europe, Brazil, China and India.

"It's exciting how many opportunities are out there for MI," said Ward Digby, PhD, Pictures of the Future core team member and director of product portfolio management for Siemens Molecular Imaging. "From the beginning, Siemens has been an innovation pioneer in the fields of SPECT and PET. As we look further out, it's motivating to explore the variety of new areas where we can help shape MI's role in patient management."

With a time frame from now to 2030, Siemens' Pictures of the Future offers new insights into how emerging developments could realistically shape the role of MI moving forward. The study identified six core scenarios:

1. Leveraging its ability to analyze the biological characteristics of pathology, MI will allow practitioners to take an earlier role in detection, diagnosis and therapy. The use of theranostics—the combination of diagnostics and therapy—will spread, providing advances enabled by gains in tracer specificity and quantification.
2. MI technology will focus on changing patient management by maintaining high image quality (sensitivity and specificity) through equipment advances, while looking for innovative ways to reduce costs. The combination of lower costs and novel scanner technology will help expand the market for MI.
3. Throughout the projected period, the volume and types of tracers available for routine SPECT and PET exams will grow in response to increasing clinical demand for new indications that impact patient care.
4. MI will become more closely bound to radiation and radioisotope therapies in oncology, as the threads between detection, diagnosis and therapy become tightly intertwined.
5. New software will significantly impact business models, ushering in new approaches and enhancing practices by creating new opportunities in patient care.
6. Payers will increasingly demand evidence that MI scans are capable of changing patient management; likewise, the availability of new therapies will become increasingly important to address the diagnosis made from the scan.

For an in-depth look into each of the scenarios identified by Pictures of the Future, *Imaging Life* is producing a series of online articles beginning in October. For further insight into scenario one, visit **siemens.com/imaginglife**.

New resources now available on MIU 360:

Biograph mCT Flow:
- Updated Clinical Image Gallery: FlowMotion™
- Tips & Tricks: Setting Scan Range on the New Biograph mCT Flow™*
- Case Study: FlowMotion ^{18}F FDG** PET•CT Evaluation of Chemoradiation Response in a Case of Lung Carcinoma
- University of Michigan Case Study: Thyroid Cancer

U.S. Radiology Benefit Manager (RBM) Resource:
- Reimbursement marketing kit containing referring physician letter template and FAQ flyer on US PET Medicare reimbursement

Symbia Intevo*:
- Updated Clinical Image Gallery: xSPECT*
- Article: xSPECT—A New Benchmark in Image Quality and Quantification
- Case Study: xSPECT Imaging in a Patient with Diffuse Skeletal Metastases

Growth Resources:
- White paper: ^{18}F FDG PET/CT and Breast Cancer: Understanding Where PET/CT is Appropriate in the Diagnosis and Treatment of Breast Cancer

MI World Summit:
- Article: Highlights from the Molecular Imaging World Summit 2014
- Video: Scientific talks from clinicians and researchers on PET/CT and SPECT/CT

Visit: **www.siemens.com/miu360**

Explore MIU 360 and Surround Yourself with Resources to Grow Your Practice

MI University 360 (MIU 360) is Siemens Molecular Imaging's customer portal. Increase referrals by helping educate referring physicians with clinical case studies, marketing toolkits and reference materials. Optimize scanning workflow with tips and tricks, scanning protocols and clinical examples. Whether you are a practice administrator or an imaging physician, MIU 360 is an excellent resource to grow your practice.

Case Study Spotlight

Biograph mCT Flow

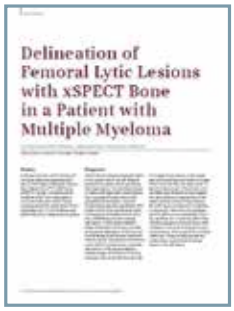
Detection of Brain Metastases in a Patient with Breast Carcinoma with ^{18}F FDG PET•CT using Hi-Rez Reconstruction and FlowMotion Technology


Detection of Brain Metastases in a Patient with Breast Carcinoma with ^{18}F FDG* PET•CT using Hi-Rez Reconstruction and FlowMotion Technology

Patient with operated breast carcinoma underwent ^{18}F FDG PET•CT with FlowMotion™ technology. Sharper lesion delineation using higher matrix reconstruction, enabled by high count statistics obtained through slow table-speed acquisition, demonstrated hypermetabolic basal ganglial metastases.

Symbia Intevo

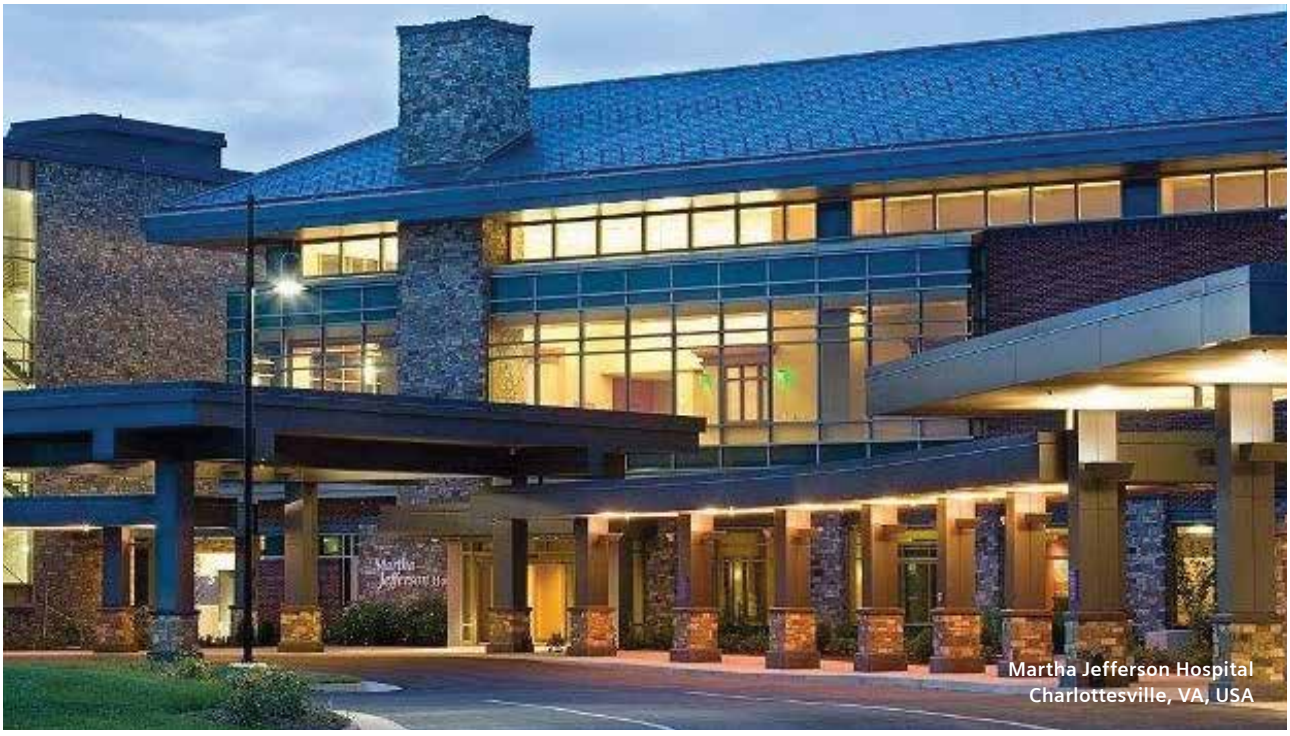
Delineation of Femoral Lytic Lesions with xSPECT Bone in a Patient with Multiple Myeloma


Delineation of Femoral Lytic Lesions with xSPECT Bone in a Patient with Multiple Myeloma

A patient with myeloma involving the shafts of both femurs was evaluated with xSPECT Bone, which demonstrated sharp delineation of cortical hypermetabolism localized to the margins of the lytic lesions, thus showing the reactive nature of the uptake secondary to cortical erosion.

* Biograph mCT Flow, Symbia Intevo, xSPECT and xSPECT Bone 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.

**Indications and important safety information on Fludeoxyglucose F 18 Injection can be found on page 53 and 73. The full prescribing information can be found on pages 78-80.



Martha Jefferson Hospital
Charlottesville, VA, USA

A Tale of Two Practices: PETNET Boosts Growth at In- and Outpatient Facilities

By Jonathan Batchelor

Formulating an effective business strategy can be a formidable task for many imaging practices. Understanding this challenge, Siemens' PETNET Solutions, in addition to providing access to a wide portfolio of PET radiopharmaceuticals, offers a wealth of expertise and tools to assist imaging practices in marketing their PET services to referring physicians.

PETNET Solutions' partnership with Martha Jefferson Hospital, a 176-bed nonprofit facility that is a part of the Sentara Healthcare system, is helping the community hospital located in Charlottesville, VA, USA, to increase patient access to PET imaging services. Across the country, PETNET Solutions and Imaging Healthcare Specialists work closely together to strategically position their ten diagnostic imaging centers in the San Diego County area in California.

The PET services offered by these two providers rely on PETNET Solutions for their PET radiotracers. But PETNET Solutions' assistance in strategic planning and outreach programs also helps them build their practices, forging a win-win situation based on growing demand for PET imaging.

Expert and personalized attention is the key to success, according to Liz Colvin, supervisor of nuclear medicine and PET/CT at Martha Jefferson Hospital. "Our PETNET Solutions' representative is incredibly helpful," Colvin said. "He has a clinical background, which really allows him to speak to what we do on a daily basis. He's a great resource who's always available via email or phone."

Sarah Woroniecki, marketing director at Imaging Healthcare Specialists, lauds the support of PETNET Solutions to boost Imaging Healthcare Specialists' efforts in reaching out to referring physicians. "PETNET Solutions has been a great partner and resource for helping us to educate the referring community," Woroniecki said. "They have provided our team with knowledge and content for several educational events for the referring community."

Nurturing an understanding of what PET can do clinically is essential to improving healthcare, as well as to

growing the practices of imaging centers. This is true for established PET radiopharmaceuticals, such as fludeoxyglucose F 18 (^{18}F FDG)*, as well as for ones that are less widely used.

Martha Jefferson Reaches Out

Founded in 1903 by eight local physicians, Martha Jefferson Hospital employs a staff of 1,600. It has 365 affiliated physicians. The institution is part of Sentara Healthcare, a not-for-profit health care organization serving southeastern and central Virginia and northeastern North Carolina. Headquartered in Norfolk, VA, USA, it provides services to more than two million residents in the surrounding region.

Martha Jefferson Hospital has been a partner with Siemens' PETNET Solutions since 2012. The PETNET Solutions pharmacy is only a few blocks from the hospital.

Colvin has been with the hospital for 30 years. In addition to being a nuclear medicine technologist and supervisor, she is involved in regulatory affairs and quality management.

"We do about 40 PET/CT studies a month," Colvin said.

The hospital uses a mobile scanner to perform PET/CT, but the goal is to install one on the hospital grounds.

About 90 percent of the PET/CT exams performed at the facility utilize ^{18}F FDG. These are primarily oncology studies. The remainder involve cardiac and brain-perfusion imaging, as well as some sodium fluoride F 18 (^{18}F NaF)** scanning.

"We're also actively exploring amyloid PET/CT imaging," Colvin said. "We're completing the continuing education work on that in preparation for taking on our first case."

Mike Yeatts, who works with Colvin, is the medical imaging liaison for the hospital. His job, he explained, is to create and foster partnerships with referring practices.

"I try to make the process as seamless as possible for both the providers and the patients," he said. Yeatts has been with Martha Jefferson Hospital for just over two years; he holds an MBA and brings a background in the pharmaceutical industry to his position.

Colvin said that when they informed PETNET Solutions of their decision to offer ^{18}F NaF imaging, the first question from their PETNET Solutions representative was, "How can I help?" Martha Jefferson Hospital immediately replied.

"Mike and I selected the providers who use this service and our PETNET Solutions representative came along with us to assist in our educational outreach to the community," Colvin said. "This initiative has been really effective at informing our providers of what we offer and how we can help them with their PET/CT imaging needs."

Just what is that need? By 2030, it is forecasted that more than one billion people worldwide will be age 65 or older[1] and more than 50 percent of the population will be obese.[2] The incidence of cancer, heart disease and dementia would likely increase, as well as PET/CT's role in the detection of disease and monitoring of treatment.

Similar increases are forecasted for the USA. "Within our service area, we understand our referral base," Yeatts said. "Our PETNET Solutions representative and I touch base about which providers would benefit from one of our PET/CT services, such as ^{18}F NaF imaging. We'll sit down together, and he'll offer assistance in putting a game plan together for reaching out to those physicians. It allows us to be progressive in the service we offer, which benefits the patient experience."

Although Martha Jefferson Hospital has had ^{18}F NaF imaging available for the past two years, Yeatts and the PETNET Solutions team still perform outreach efforts and follow up with the provider base.

"This allows us to keep in touch so we can receive feedback on how to best meet the needs of our patients. It also gives us an idea of what they're doing in their practices, which helps us see if we can be of further service to them in their imaging needs," Yeatts said. "Having a resource like PETNET Solutions has definitely helped this process."

Colvin agreed that getting out of the hospital and into physician offices with educational outreach has helped more patients have access to PET/CT studies, potentially impacting their outcome. The program is designed as an educational forum.

"Education has been really well received, and we have seen many patients receiving PET/CT scans," Yeatts said.

Educational outreach needs to be conducted on an ongoing basis, he advises. This was illustrated by the growth of ^{18}F NaF imaging. Demand initially rose for this scan and then leveled off. "It started picking up again after we did some further outreach," Yeatts said. "So, it's easy to see the impact these efforts have on growth for patient access to PET/CT studies."

Colvin also noted that the Martha Jefferson Hospital physician community does not consider outreach efforts to be intrusive. On the contrary, physicians appreciate them.

"Most of the patients they're sending to us are pretty sick," she said. "And PET/CT is really an awesome imaging exam from a clinical perspective. Our job is to deliver good imaging and accurate reports along with appropriate clinical use, and that's really helpful to our patients and our physicians."

Siemens' PETNET Solutions has also helped the hospital expand its ^{18}F NaF imaging line. Not surprisingly, the expansion came at the suggestion of the PETNET Solutions representative, who noted to Colvin and her colleagues that the radiotracer has several cancer indications. One of these is breast cancer, which may require bone scanning—an application well suited to the use of this PET radiopharmaceutical. Another is multiple myeloma, which is difficult to diagnose with other imaging modalities, but less so with PET.

"We want to offer state-of-the-art imaging services and capabilities. Our partnership with PETNET Solutions has allowed us to achieve these goals. It's truly been a partnership that promotes patient care first."

"We want to offer state-of-the-art imaging services and capabilities. Our partnership with PETNET Solutions has allowed us to achieve these goals."

Liz Colvin, Supervisor of Nuclear Medicine and PET/CT, Martha Jefferson Hospital in Charlottesville, VA, USA

Photo (left to right): Karrie Chaney, Iva Bare, Danielle Snapp, Liz Colvin, and Mike Yeatts of Martha Jefferson Hospital.

Imaging Healthcare Specialists Prepares for Growth

Imaging Healthcare Specialists is very different from Martha Jefferson Hospital. The outpatient imaging service operates from multiple locations. Imaging Healthcare Specialists provides interventional radiology, X-ray, dual-energy X-ray absorptiometry (DEXA), women's imaging, CT, MRI and nuclear medicine, including PET/CT.

Their service area represents more than three million people in Southern California. Overall, they see a diverse patient population with a wide mix of payers (both public and private), according to Imaging Healthcare Specialists' marketing director, Sarah Woroniecki.

Woroniecki has a diverse background, with a mix of both clinical and business that provides a unique perspective on PET Imaging. She began her career as a nuclear medicine technologist and naturally evolved into a marketing role.

Imaging Healthcare Specialists operates two PET/CT scanners at fixed sites. A majority of the PET scans they perform are on cancer patients, involving mostly ^{18}F FDG and, to a lesser extent, ^{18}F NaF. However, brain scans are becoming more prevalent in recent years.

"We're focusing on growing our PET brain imaging services with both the amyloid imaging tracer and ^{18}F FDG," she said. "We're also keeping an eye out for greater adoption of ^{18}F NaF bone imaging by more private payers, so we can expand that part of our service line."

According to Woroniecki, Imaging Healthcare Specialists has been partnering with Siemens' PETNET Solutions for the supply of PET radiopharmaceuticals since about 2007. It has also been using PETNET Solutions expertise to build demand for its services.

Imaging Healthcare Specialists recently hosted an educational event for referring physicians whose patients may benefit from amyloid imaging. "One of our radiologists discussed the importance of including PET/CT imaging in the evaluation of dementias, including Alzheimer's disease. The physicians in attendance were engaged and quite interested in the topic," Woroniecki said. "In the past, we have offered educational seminars on ^{18}F NaF PET/CT imaging."

It's not just at the group level that PETNET Solutions helps its partners with PET marketing. The PETNET Solutions representative has helped with one-on-one educational meetings.

"I'll ascertain the interest on the part of the referrer and will set up a meeting," Woroniecki said. "Then our PETNET Solutions representative will join me. There's usually a pretty big interest in these sessions from our referrers."

Imaging Healthcare Specialists is the leading provider of outpatient imaging services in San Diego county, and they serve almost every physician practicing in the area.

Siemens' PETNET Solutions has also helped train Imaging Healthcare Specialist staff in marketing. One in particular stands out, PETNET Solutions' "Taking It To The Streets" program.

"With this, PETNET Solutions came in and trained our marketing personnel on how to market to and educate our community about PET services," she said.

In addition to such on-site training, Siemens' PETNET Solutions offers a comprehensive suite of tools available online to its partners. Imaging Healthcare Specialists staff gain access to these tools through the online portal, Molecular Imaging LifeNet (www.mi-lifenet.com).

"There are lots of material for patients, technologists and referrers," she said. "That's been a great help."

Also online is information about studies that describe the uses of PET for different cancer indications, as well as a CPT code guide for PET/CT. The Imaging Healthcare Specialists staff have distributed these materials, where needed in their referring community. PETNET Solutions also provides Imaging Healthcare Specialists with a Quarterly Market Snapshot that Woroniecki has found particularly useful.

"The PETNET Quarterly Market Snapshot helps us see our share of the PET/

CT market in our community," she said. It's a great tool in that it gives us an idea of where we are growing and what we need to focus on for more growth. It also allows us to keep track of the referring community and to identify any trends that may be occurring within it."

Woroniecki added that in addition to providing a quick look back over the past quarter's PET/CT service, the tool is being used to create an action plan for PET growth in both the near- and long-term.

Imaging Healthcare Specialists has also begun PET/CT educational outreach to nurse practitioners and physician assistants, many of whom work in physician offices.

"We've hosted educational sessions for these groups and have helped inform them on what PET/CT scans they can order, why they would order them, and how they would go about ordering them," she said. "We've been able to provide our radiologists for question and answer sessions with them. We've received really positive feedback from that community for these events."

Siemens' PETNET Solutions has also assisted Imaging Healthcare Specialists with its in-house PET/CT training, she said. "We've had several events where PETNET Solutions has done continuing education with our nuclear medicine technologists, which provides them with CEU credits."

The marketing, training and education assistance provided by Siemens' PETNET Solutions has been a boon to PET/CT utilization at Imaging Healthcare Specialists.

"I believe our partnership with PETNET Solutions has definitely helped our PET growth," Woroniecki said. "Imaging Healthcare Specialists has come to be seen by our referring community as the definitive source for both our PET education and for getting answers to PET questions."

Keeping her referring community informed on the latest advances in PET imaging, and how Imaging Healthcare Specialists can fulfill those clinical requirements, has expanded the practice, Woroniecki noted.

"Our referrers have been very positive about our PET information and education efforts," she said. "PET can be challenging to understand, as it doesn't follow the same rules as conventional anatomic imaging modalities. As such, our referring community has welcomed our outreach. It helps them know what indications are best suited to PET and it gives them the tools to order those studies."

References:

1. Why Aging Population Matters – Global Perspective National Institute of Aging/National Institute of Health. Publication No. 07-6134. March 2007.
2. Obesity and Severe Obesity Forecasts Through 2030. Am J Prev Med. 2012 Jun; 42(6): 563-70.

* The full prescribing information for the Fludeoxyglucose F 18 injection can be found on pages 78-80.

** The full prescribing information for Sodium Fluoride F 18 injection can be found on pages 81-82.

The statements by Siemens customers described herein are based on results that were achieved in the customer's unique setting. Since there is no "typical" hospital and many variable exist (e.g., hospital size, case mix, level of IT adoption) there can be no guarantee that other customers will achieve the same results.

Indications

Fludeoxyglucose F 18 Injection is indicated for positron emission tomography (PET) imaging in the following settings:

- **Oncology:** For assessment of abnormal glucose metabolism to assist in the evaluation of malignancy in patients with known or suspected abnormalities found by other testing modalities, or in patients with an existing diagnosis of cancer.
- **Cardiology:** For the identification of left ventricular myocardium with residual glucose metabolism and reversible loss of systolic function in patients with coronary artery disease and left ventricular dysfunction, when used together with myocardial perfusion imaging.
- **Neurology:** For the identification of regions of abnormal glucose metabolism associated with foci of epileptic seizures.

Important Safety Information

- **Radiation Risks:** Radiation-emitting products, including Fludeoxyglucose F 18 Injection, may increase the risk for cancer, especially in pediatric patients. Use the smallest dose necessary for imaging and ensure safe handling to protect the patient and healthcare worker.
- **Blood Glucose Abnormalities:** In the oncology and neurology setting, suboptimal imaging may occur in patients with inadequately regulated blood glucose levels. In these patients, consider medical therapy and laboratory testing to assure at least two days of normoglycemia prior to Fludeoxyglucose F 18 Injection administration.
- **Adverse Reactions:** Hypersensitivity reactions with pruritus, edema and rash have been reported; have emergency resuscitation equipment and personnel immediately available.

Sodium Fluoride F 18 Injection: For Intravenous Use

Indications and Usage:
Sodium Fluoride F 18 Injection is a radioactive diagnostic agent for positron emission tomography (PET) indicated for imaging of bone to define areas of altered osteogenic activity.

Important Safety Information:

- **Allergic Reactions:** As with any injectable drug product, allergic reactions and anaphylaxis may occur. Emergency resuscitation equipment and personnel should be immediately available.
- **Cancer Risk:** Sodium Fluoride F 18 Injection may increase the risk of cancer. Use the smallest dose necessary for imaging and ensure safe handling to protect the patient and health care worker.
- **Adverse Reactions:** No adverse reactions have been reported for Sodium Fluoride F 18 Injection based on a review of the published literature, publicly available reference sources, and adverse drug reaction reporting system.

Q&A: IQ•SPECT Doubles Throughput at Busy Cardiovascular Hospital in Brazil

In 2011, the nuclear medicine lab at Pró-Cardíaco decided to upgrade to a Symbia T2 SPECT•CT system with IQ•SPECT. Now, 18 months later, the staff is leading the way as a fellowship site for IQ•SPECT. Dr. Cláudio Tinoco Mesquita provided insights into the lab's decision to acquire the system and how they have leveraged the technology to improve their productivity and patient care.

By **Catherine Eby**

Why did Pró-Cardíaco decide to invest in a Symbia T2 scanner?

Tinoco Mesquita: We chose the Symbia™ T2 SPECT•CT system because our mission is to assist in highly complex cases that are referred to our hospital. In addition to nuclear cardiology exams with attenuation correction, we perform white blood cell scintigraphy for the localization of infections, ^{123}I-MIBG whole-body scans to search for pheochromocytomas, ^{99m}Tc-octreotide scans for the evaluation of neuroendocrine tumors, ^{99m}Tc-sestamibi scans for hyperparathyroidism and ictal brain SPECT for epileptical-focused localization, as well as other complex exams that depend on the full potential of nuclear medicine and CT. The quality of the hybrid images we would be able to obtain with a Symbia T2 SPECT•CT with IQ•SPECT was the pivotal factor in our decision to acquire the system.

Why did you upgrade to IQ•SPECT?

Tinoco Mesquita: We do not have a lot of space in our institution. It was not possible to operate two SPECT systems, and we needed the ability to perform more exams. So, we decided to upgrade to a technology that could increase our productivity without losing image quality.

What IQ•SPECT feature is most important for your practice?

Tinoco Mesquita: For us, the most important aspect of IQ•SPECT is the very fast acquisition time. We reduced our acquisition time from over 20 minutes (15 minutes supine plus five minutes prone) to just five minutes (four minutes for the SPECT plus one minute for the low-dose CT). Additionally, our accuracy increased by having attenuation-corrected images.

Did IQ•SPECT help you to improve throughput? How many cardiac examinations are you able to do now versus prior to acquiring IQ•SPECT?

Tinoco Mesquita: IQ•SPECT greatly improved our throughput—we doubled the number of cardiac scans from 11-12 per day to 22-24 scans per day. In peak periods, we have performed up to 32 scans in a 12-hour working day. Within the first 18 months, we have scanned over 2,000 patients using IQ•SPECT.

How has IQ•SPECT impacted staff scheduling?

Tinoco Mesquita: Because we have more patients and a shorter acquisition time, our nuclear technologists are very busy all day long.

Pró-Cardíaco Hospital

Pró-Cardíaco Hospital is a 100-bed tertiary cardiovascular hospital in Rio de Janeiro, Brazil, which specializes in unique heart procedures, such as heart transplantation, left-ventricular device implantation and transcatheter aortic valve implantation.

The nuclear medicine lab has been in operation for more than 10 years and includes four nuclear medicine physicians, a medical physicist, a biologist, nuclear medicine technologists, nurses and cardiologists. Additionally, as a teaching hospital, the staff includes nuclear medicine, intensive care medicine and cardiology residents.

> *"The quality of the hybrid images we would be able to obtain with a Symbia T2 SPECT•CT with IQ•SPECT was the pivotal factor in our decision to acquire the system."*
>
> **Cláudio Tinoco Mesquita,** MD
> Pró-Cardíaco Hospital, Rio de Janeiro, Brazil

In your opinion, what is the clinical value of IQ•SPECT?

Tinoco Mesquita: The advantages we have realized with IQ•SPECT include reduced acquisition time, 25 percent less dose than our previous scans; and when we scan stress-only images, we can reduce dose by up to 65 percent with better image quality, increased counts and attenuation-corrected images.

Did you need training to use this improved method of acquiring cardiac images? How long did it take for you and your staff to become confident when reading the images?

Tinoco Mesquita: Naturally, we needed some training. At first, we performed scans both with the LEHR collimator and with the **SMART**ZOOM collimators to compare images and create our new mental map of cardiac images with IQ•SPECT. After a few exams, we also exchanged experience with a more advanced user, Dr. Bouchard from Canada. After a few weeks, we became confident enough to only use IQ•SPECT and since then we have performed more than 2,000 scans.

Our staff has completely adapted to IQ•SPECT, but initially it was important for them to gain experience with the technology as the approach is unique. If you are not familiar with using attenuation-corrected myocardial SPECT, you have to adapt to specific image signatures. This was a fairly easy process though, and now, when we see images performed without IQ•SPECT, we have to adjust how we read the images.

What are the key things to keep in mind when transitioning from other image reconstruction methods, for example, filtered-back projection, to IQ•SPECT imaging?

Tinoco Mesquita: You have to understand and identify some changes in the IQ•SPECT images that differentiate them from filtered-back projection images. Some physicians call them image signatures. The most common is the apical thinning that is attributed to attenuation correction. Another important image signature is the better homogeneous distribution of the counts compared to previous image reconstruction methods that have increased lateral wall counts. You have to configure these changes to create a new map for reading the exam. Some physicians can do this very quickly, while for others it can take a bit longer.

Can you share examples of the clinical value that IQ•SPECT has brought to your practice?

Tinoco Mesquita: Because we do a lot of emergency cases, sometimes you have two or three new patients on the schedule. With a fast system, like Symbia T2 with IQ•SPECT, it helps you keep up with demand and avoid chaos. Another important aspect is the CT images. Sometimes you can find another cause for the patient symptoms by just reviewing these low-dose CT images. We have discovered some lung tumors and pleural effusions that were previously unnoticed.

What does it mean to be a Siemens fellowship site, and why did you decide to have your facility designated as one?

Tinoco Mesquita: We decided to share our experience with other groups because we believe that it can be very helpful in their transition to IQ•SPECT. As we are a teaching hospital, we are very adept at helping people learn and experience new technologies.

What guidance would you provide to someone who has just upgraded to IQ•SPECT to help ensure a smooth transition?

Tinoco Mesquita: You must have a goal, for example, to increase the quality and number of exams. Learn how to use the technology. Compare cases. Compare images. Exchange experiences. Create a new mental map of the exam. You have to move yourself from a stationary point to a new point.

If you could summarize IQ•SPECT in one sentence, what would it be?

Tinoco Mesquita: Fast and good.

Is there anything else you would like to add about your experience with IQ•SPECT?

Tinoco Mesquita: Lead your team. Be the change. Move everyone with you. It is the only way for a smooth transition to a new technology such as IQ•SPECT. If you do that, you will see amazing results.

The statements by Siemens' customers described herein are based on results that were achieved in the customer's unique setting. Since there is no "typical" hospital and many variables exist (e.g., hospital size, case mix, level of IT adoption) there can be no guarantee that other customers will achieve the same results.

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Clinical Images: Cover—P166_34, P158_32, S135_23; Pg. 13—P166_34; Pg. 14—S115_21; Pg. 15—S122_23; Pg. 16—P158_32

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Fludeoxyglucose F 18 Injection safely and effectively. See full prescribing information for Fludeoxyglucose F 18 Injection.

Fludeoxyglucose F 18 Injection, USP

For intravenous use

Initial U.S. Approval: 2005

RECENT MAJOR CHANGES

Warnings and Precautions (5.1, 5.2) 7/2010

Adverse Reactions (6) 7/2010

INDICATIONS AND USAGE

Fludeoxyglucose F18 Injection is indicated for positron emission tomography (PET) imaging in the following settings:

- Oncology: For assessment of abnormal glucose metabolism to assist in the evaluation of malignancy in patients with known or suspected abnormalities found by other testing modalities, or in patients with an existing diagnosis of cancer.
- Cardiology: For the identification of left ventricular myocardium with residual glucose metabolism and reversible loss of systolic function in patients with coronary artery disease and left ventricular dysfunction, when used together with myocardial perfusion imaging.
- Neurology: For the identification of regions of abnormal glucose metabolism associated with foci of epileptic seizures (1).

DOSAGE AND ADMINISTRATION

Fludeoxyglucose F 18 Injection emits radiation. Use procedures to minimize radiation exposure. Screen for blood glucose abnormalities.

- In the oncology and neurology settings, instruct patients to fast for 4 to 6 hours prior to the drug's injection. Consider medical therapy and laboratory testing to assure at least two days of normoglycemia prior to the drug's administration (5.2).
- In the cardiology setting, administration of glucose-containing food or liquids (e.g., 50 to 75 grams) prior to the drug's injection facilitates localization of cardiac ischemia (2.3).

Aseptically withdraw Fludeoxyglucose F 18 Injection from its container and administer by intravenous injection (2).

The recommended dose:

- for adults is 5 to 10 mCi (185 to 370 MBq), in all indicated clinical settings (2.1).
- for pediatric patients is 2.6 mCi in the neurology setting (2.2).

Initiate imaging within 40 minutes following drug injection; acquire static emission images 30 to 100 minutes from time of injection (2).

DOSAGE FORMS AND STRENGTHS

Multi-dose 30mL and 50mL glass vial containing 0.74 to 7.40 GBq/mL (20 to 200 mCi/mL) Fludeoxyglucose F 18 Injection and 4.5mg of sodium chloride with 0.1 to 0.5% w/w ethanol as a stabilizer (approximately 15 to 50 mL volume) for intravenous administration (3).

CONTRAINDICATIONS

None

WARNINGS AND PRECAUTIONS

- Radiation risks: use smallest dose necessary for imaging (5.1).
- Blood glucose adnormalities: may cause suboptimal imaging (5.2).

ADVERSE REACTIONS

Hypersensitivity reactions have occurred; have emergency resuscitation equipment and personnel immediately available (6).

To report SUSPECTED ADVERSE REACTIONS, contact PETNET Solutions, Inc. at 877-473-8638 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

Pregnancy Category C: No human or animal data. Consider alternative diagnostics; use only if clearly needed (8.1).

- Nursing mothers: Use alternatives to breast feeding (e.g., stored breast milk or infant formula) for at least 10 half-lives of radioactive decay, if Fludeoxyglucose F 18 Injection is administered to a woman who is breast-feeding (8.3).
- Pediatric Use: Safety and effectiveness in pediatric patients have not been established in the oncology and cardiology settings (8.4).

See 17 for PATIENT COUNSELING INFORMATION

Revised: 1/2011

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Fludeoxyglucose F 18 Injection is indicated for positron emission tomography (PET) imaging in the following settings:

1.1 Oncology

For assessment of abnormal glucose metabolism to assist in the evaluation of malignancy in patients with known or suspected abnormalities found by other testing modalities, or in patients with an existing diagnosis of cancer.

1.2 Cardiology

For the identification of left ventricular myocardium with residual glucose metabolism and reversible loss of systolic function in patients with coronary artery disease and left ventricular dysfunction, when used together with myocardial perfusion imaging.

1.3 Neurology

For the identification of regions of abnormal glucose metabolism associated with foci of epileptic seizures.

2 DOSAGE AND ADMINISTRATION

Fludeoxyglucose F 18 Injection emits radiation. Use procedures to minimize radiation exposure. Calculate the final dose from the end of synthesis (EOS) time using proper radioactive decay factors. Assay the final dose in a properly calibrated dose calibrator before administration to the patient [see Description (11.2)].

2.1 Recommended Dose for Adults

Within the oncology, cardiology and neurology settings, the recommended dose for adults is 5 to 10 mCi (185 to 370 MBq) as an intravenous injection.

2.2 Recommended Dose for Pediatric Patients

Within the neurology setting, the recommended dose for pediatric patients is 2.6 mCi, as an intravenous injection. The optimal dose adjustment on the basis of body size or weight has not been determined [see Use in Special Populations (8.4)].

2.3 Patient Preparation

- To minimize the radiation absorbed dose to the bladder, encourage adequate hydration. Encourage the patient to drink water or other fluids (as tolerated) in the 4 hours before their PET study.
- Encourage the patient to void as soon as the imaging study is completed and as often as possible thereafter for at least one hour.
- Screen patients for clinically significant blood glucose abnormalities by obtaining a history and/or laboratory tests [see Warnings and Precautions (5.2)]. Prior to Fludeoxyglucose F 18 PET imaging in the oncology and neurology settings, instruct patient to fast for 4 to 6 hours prior to the drug's injection.
- In the cardiology setting, administration of glucose-containing food or liquids (e.g., 50 to 75 grams) prior to Fludeoxyglucose F18 Injection facilitates localization of cardiac ischemia

2.4 Radiation Dosimetry

The estimated human absorbed radiation doses (rem/mCi) to a newborn (3.4 kg), 1-year old (9.8 kg), 5-year old (19 kg), 10-year old (32 kg), 15-year old (57 kg), and adult (70 kg) from intravenous administration of Fludeoxyglucose F 18 Injection are shown in Table 1. These estimates were calculated based on human[2] data and using the data published by the International Commission on Radiological Protection[4] for Fludeoxyglucose ^{18} F. The dosimetry data show that there are slight variations in absorbed radiation dose for various organs in each of the age groups. These dissimilarities in absorbed radiation dose are due to developmental age variations (e.g., organ size, location, and overall metabolic rate for each age group). The identified critical organs (in descending order) across all age groups evaluated are the urinary bladder, heart, pancreas, spleen, and lungs.

Table 1. Estimated Absorbed Radiation Doses (rem/mCi) After Intravenous Administration of Fludeoxyglucose F-18 Injection[a]

Organ	Newborn (3.4 kg)	1-year old (9.8 kg)	5-year old (19 kg)	10-year old (32 kg)	15-year old (57 kg)	Adult (70 kg)
Bladder wallb	4.3	1.7	0.93	0.60	0.40	0.32
Heart wall	2.4	1.2	0.70	0.44	0.29	0.22
Pancreas	2.2	0.68	0.33	0.25	0.13	0.096
Spleen	2.2	0.84	0.46	0.29	0.19	0.14
Lungs	0.96	0.38	0.20	0.13	0.092	0.064
Kidneys	0.81	0.34	0.19	0.13	0.089	0.074
Ovaries	0.80	0.8	0.19	0.11	0.058	0.053
Uterus	0.79	0.35	0.19	0.12	0.076	0.062
LLI wall *	0.69	0.28	0.15	0.097	0.060	0.051
Liver	0.69	0.31	0.17	0.11	0.076	0.058
Gallbladder wall	0.69	0.26	0.14	0.093	0.059	0.049
Small intestine	0.68	0.29	0.15	0.096	0.060	0.047
ULI wall **	0.67	0.27	0.15	0.090	0.057	0.046
Stomach wall	0.65	0.27	0.14	0.089	0.057	0.047
Adrenals	0.65	0.28	0.15	0.095	0.061	0.048
Testes	0.64	0.27	0.14	0.085	0.052	0.041
Red marrow	0.62	0.26	0.14	0.089	0.057	0.047
Thymus	0.61	0.26	0.14	0.086	0.056	0.044
Thyroid	0.61	0.26	0.13	0.080	0.049	0.039
Muscle	0.58	0.25	0.13	0.078	0.049	0.039
Bone surface	0.57	0.24	0.12	0.079	0.052	0.041
Breast	0.54	0.22	0.11	0.068	0.043	0.034
Skin	0.49	0.20	0.10	0.060	0.037	0.030
Brain	0.29	0.13	0.09	0.078	0.072	0.070
Other tissues	0.59	0.25	0.13	0.083	0.052	0.042

[a] MIRDOSE 2 software was used to calculate the radiation absorbed dose. Assumptions on the biodistribution based on data from Gallagher et al.1 and Jones et al.2

[b] The dynamic bladder model with a uniform voiding frequency of 1.5 hours was used. *LLI = lower large intestine; **ULI = upper large intestine

2.5 Radiation Safety – Drug Handling

- Use waterproof gloves, effective radiation shielding, and appropriate safety measures when handling Fludeoxyglucose F 18 Injection to avoid unnecessary radiation exposure to the patient, occupational workers, clinical personnel and other persons.
- Radiopharmaceuticals should be used by or under the control of physicians who are qualified by specific training and experience in the safe use and handling of radionuclides, and whose experience and training have been approved by the appropriate governmental agency authorized to license the use of radionuclides.
- Calculate the final dose from the end of synthesis (EOS) time using proper radioactive decay factors. Assay the final dose in a properly calibrated dose calibrator before administration to the patient [see Description (11.2)].
- The dose of Fludeoxyglucose F 18 used in a given patient should be minimized consistent with the objectives of the procedure, and the nature of the radiation detection devices employed.

2.6 Drug Preparation and Administration

- Calculate the necessary volume to administer based on calibration time and dose.
- Aseptically withdraw Fludeoxyglucose F 18 Injection from its container.
- Inspect Fludeoxyglucose F 18 Injection visually for particulate matter and discoloration before administration, whenever solution and container permit.
- Do not administer the drug if it contains particulate matter or discoloration; dispose of these unacceptable or unused preparations in a safe manner, in compliance with applicable regulations.
- Use Fludeoxyglucose F 18 Injection within 12 hours from the EOS.

2.7 Imaging Guidelines

- Initiate imaging within 40 minutes following Fludeoxyglucose F 18 Injection administration.
- Acquire static emission images 30 to 100 minutes from the time of injection.

3 DOSAGE FORMS AND STRENGTHS

Multiple-dose 30 mL and 50 mL glass vial containing 0.74 to 7.40 GBq/mL (20 to 200 mCi/mL) of Fludeoxyglucose F 18 Injection and 4.5 mg of sodium chloride with 0.1 to 0.5% w/w ethanol as a stabilizer (approximately 15 to 50 mL volume) for intravenous administration.

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Radiation Risks

Radiation-emitting products, including Fludeoxyglucose F 18 Injection, may increase the risk for cancer, especially in pediatric patients. Use the smallest dose necessary for imaging and ensure safe handling to protect the patient and health care worker [see Dosage and Administration (2.5)].

5.2 Blood Glucose Abnormalities

In the oncology and neurology setting, suboptimal imaging may occur in patients with inadequately regulated blood glucose levels. In these patients, consider medical therapy and laboratory testing to assure at least two days of normoglycemia prior to Fludeoxyglucose F 18 Injection administration.

6 ADVERSE REACTIONS

Hypersensitivity reactions with pruritus, edema and rash have been reported in the post-marketing setting. Have emergency resuscitation equipment and personnel immediately available.

7 DRUG INTERACTIONS

The possibility of interactions of Fludeoxyglucose F 18 Injection with other drugs taken by patients undergoing PET imaging has not been studied.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Animal reproduction studies have not been conducted with Fludeoxyglucose F 18 Injection. It is also not known whether Fludeoxyglucose F 18 Injection can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Consider alternative diagnostic tests in a pregnant woman; administer Fludeoxyglucose F 18 Injection only if clearly needed.

8.3 Nursing Mothers

It is not known whether Fludeoxyglucose F 18 Injection is excreted in human milk. Consider alternative diagnostic tests in women who are breast-feeding. Use alternatives to breast feeding (e.g., stored breast milk or infant formula) for at least 10 half-lives of radioactive decay, if Fludeoxyglucose F 18 Injection is administered to a woman who is breast-feeding.

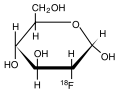
8.4 Pediatric Use

The safety and effectiveness of Fludeoxyglucose F 18 Injection in pediatric patients with epilepsy is established on the basis of studies in adult and pediatric patients. In pediatric patients with epilepsy, the recommended dose is 2.6 mCi. The optimal dose adjustment on the basis of body size or weight has not been determined. In the oncology or cardiology settings, the safety and effectiveness of Fludeoxyglucose F 18 Injection have not been established in pediatric patients.

11 DESCRIPTION

11.1 Chemical Characteristics

Fludeoxyglucose F 18 Injection is a positron emitting radiopharmaceutical that is used for diagnostic purposes in conjunction with positron emission tomography (PET) imaging. The active ingredient 2-deoxy-2-[^{18}F]fluoro-D-glucose has the molecular formula of $C_6H_{11}{}^{18}FO_5$ with a molecular weight of 181.26, and has the following chemical structure:



Fludeoxyglucose F 18 Injection is provided as a ready to use sterile, pyrogen free, clear, colorless solution. Each mL contains between 0.740 to 7.40GBq (20.0 to 200 mCi) of 2-deoxy-2-[^{18}F]fluoro-D-glucose at the EOS, 4.5 mg of sodium chloride and 0.1 to 0.5% w/w ethanol as a stabilizer. The pH of the solution is between 4.5 and 7.5. The solution is packaged in a multiple-dose glass vial and does not contain any preservative.

11.2 Physical Characteristics

Fluorine F 18 decays by emitting positron to Oxygen O 16 (stable) and has a physical half-life of 109.7 minutes. The principal photons useful for imaging are the dual 511 keV gamma photons, that are produced and emitted simultaneously in opposite direction when the positron interacts with an electron (Table 2).

Table 2. Pricipal Radiation Emission Data for Fluorine F18

Radiation/Emission	% Per Disintegration	Mean Energy
Positron (b+)	96.73	249.8 keV
Gamma (±)*	193.46	511.0 keV

*Produced by positron annihilation

From: Kocher, D.C. Radioactive Decay Tables DOE/TIC-I 1026, 89 (1981)

The specific gamma ray constant (point source air kerma coefficient) for fluorine F 18 is 5.7 R/hr/mCi (1.35 x 10-6 Gy/hr/kBq) at 1 cm. The half-value layer (HVL) for the 511 keV photons is 4 mm lead (Pb). The range of attenuation coefficients for this radionuclide as a function of lead shield thickness is shown in Table 3. For example, the interposition of an 8 mm thickness of Pb, with a coefficient of attenuation of 0.25, will decrease the external radiation by 75%.

Table 3. Radiation Attenuation of 511 keV Photons by lead (Pb) shielding

Shield thickness (Pb) mm	Coefficient of attenuation
0	0.00
4	0.50
8	0.25
13	0.10
26	0.01
39	0.001
52	0.0001

For use in correcting for physical decay of this radionuclide, the fractions remaining at selected intervals after calibration are shown in Table 4.

Table 4. Physical Decay Chart for Fluorine F18

Minutes	Fraction Remaining
0*	1.000
15	0.909
30	0.826
60	0.683
110	0.500
220	0.250

*calibration time

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Fludeoxyglucose F 18 is a glucose analog that concentrates in cells that rely upon glucose as an energy source, or in cells whose dependence on glucose increases under pathophysiological conditions. Fludeoxyglucose F 18 is transported through the cell membrane by facilitative glucose transporter proteins and is phosphorylated within the cell to [^{18}F] FDG-6-phosphate by the enzyme hexokinase. Once phosphorylated it cannot exit until it is dephosphorylated by glucose-6-phosphatase. Therefore, within a given tissue or pathophysiological process, the retention and clearance of Fludeoxyglucose F 18 reflect a balance involving glucose transporter, hexokinase and glucose-6-phosphatase activities. When allowance is made for the kinetic differences between glucose and Fludeoxyglucose F 18 transport and phosphorylation (expressed as the ‚lumped constant" ratio), Fludeoxyglucose F 18 is used to assess glucose metabolism.

In comparison to background activity of the specific organ or tissue type, regions of decreased or absent uptake of Fludeoxyglucose F 18 reflect the decrease or absence of glucose metabolism. Regions of increased uptake of Fludeoxyglucose F 18 reflect greater than normal rates of glucose metabolism.

12.2 Pharmacodynamics

Fludeoxyglucose F 18 Injection is rapidly distributed to all organs of the body after intravenous administration. After background clearance of Fludeoxyglucose F 18 Injection, optimal PET imaging is generally achieved between 30 to 40 minutes after administration.

In cancer, the cells are generally characterized by enhanced glucose metabolism partially due to (1) an increase in activity of glucose transporters, (2) an increased rate of phosphorylation activity, (3) a reduction of phosphatase activity or, (4) a dynamic alteration in the balance among all these processes. However, glucose metabolism of cancer as reflected by Fludeoxyglucose F 18 accumulation shows considerable variability. Depending on tumor type, stage, and location, Fludeoxyglucose F 18 accumulation may be increased, normal, or decreased. Also, inflammatory cells can have the same variability of uptake of Fludeoxyglucose F 18.

In the heart, under normal aerobic conditions, the myocardium meets the bulk of its energy requirements by oxidizing free fatty acids. Most of the exogenous glucose taken up by the myocyte is converted into glycogen. However, under ischemic conditions, the oxidation of free fatty acids decreases, exogenous glucose becomes the preferred myocardial sub strate, glycolysis is stimulated, and glucose taken up by the myocyte is metabolized immediately instead of being converted into glycogen. Under these condi

tions, phosphorylated Fludeoxyglucose F 18 accumulates in the myocyte and can be detected with PET imaging.

In the brain, cells normally rely on aerobic metabolism. In epilepsy, the glucose metabolism varies. Generally, during a seizure, glucose metabolism increases. Interictally, the seizure focus tends to be hypometabolic.

12.3 Pharmacokinetics

Distribution: In four healthy male volunteers, receiving an intravenous administration of 30 seconds in duration, the arterial blood level profile for Fludeoxyglucose F 18 decayed triexponentially. The effective half-life ranges of the three phases were 0.2 to 0.3 minutes, 10 to 13 minutes with a mean and standard deviation (STD) of 11.6 (±) 1.1 min, and 80 to 95 minutes with a mean and STD of 88 (±) 4 min.

Plasma protein binding of Fludeoxyglucose F 18 has not been studied.

Metabolism: Fludeoxyglucose F 18 is transported into cells and phosphorylated to [^{18}F]-FDG-6- phosphate at a rate proportional to the rate of glucose utilization within that tissue. [F18]-FDG-6-phosphate presumably is metabolized to 2-deoxy-2-[F18]fluoro-6-phospho-D-mannose([F 18]FDM-6-phosphate).

Fludeoxyglucose F 18 Injection may contain several impurities (e.g., 2-deoxy-2-chloro-D-glucose (ClDG)). Biodistribution and metabolism of ClDG are presumed to be similar to Fludeoxyglucose F 18 and would be expected to result in intracellular formation of 2-deoxy-2-chloro-6-phospho-D-glucose (ClDG-6-phosphate) and 2-deoxy-2-chloro-6-phospho-D-mannose (ClDM-6-phosphate). The phosphorylated deoxyglucose compounds are dephosphorylated and the resulting compounds (FDG, FDM, ClDG, and ClDM) presumably leave cells by passive diffusion. Fludeoxyglucose F 18 and related compounds are cleared from non-cardiac tissues within 3 to 24 hours after administration. Clearance from the cardiac tissue may require more than 96 hours. Fludeoxyglucose F 18 that is not involved in glucose metabolism in any tissue is then excreted in the urine.

Elimination: Fludeoxyglucose F 18 is cleared from most tissues within 24 hours and can be eliminated from the body unchanged in the urine. Three elimination phases have been identified in the reviewed literature. Within 33 minutes, a mean of 3.9% of the administrated radioactive dose was measured in the urine. The amount of radiation exposure of the urinary bladder at two hours post-administration suggests that 20.6% (mean) of the radioactive dose was present in the bladder.

Special Populations:

The pharmacokinetics of Fludeoxyglucose F 18 Injection have not been studied in renally-impaired, hepatically impaired or pediatric patients. Fludeoxyglucose F 18 is eliminated through the renal system. Avoid excessive radiation exposure to this organ system and adjacent tissues.

The effects of fasting, varying blood sugar levels, conditions of glucose intolerance, and diabetes mellitus on Fludeoxyglucose F 18 distribution in humans have not been ascertained [see Warnings and Precautions (5.2)].

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Animal studies have not been performed to evaluate the Fludeoxyglucose F 18 Injection carcinogenic potential, mutagenic potential or effects on fertility.

14 CLINICAL STUDIES

14.1 Oncology

The efficacy of Fludeoxyglucose F 18 Injection in positron emission tomography cancer imaging was demonstrated in 16 independent studies. These studies prospectively evaluated the use of Fludeoxyglucose F 18 in patients with suspected or known malignancies, including non-small cell lung cancer, colo-rectal, pancreatic, breast, thyroid, melanoma, Hodgkin's and non-Hodgkin's lymphoma, and various types of metastatic cancers to lung, liver, bone, and axillary nodes. All these studies had at least 50 patients and used pathology as a standard of truth. The Fludeoxyglucose F 18 Injection doses in the studies ranged from 200 MBq to 740 MBq with a median and mean dose of 370 MBq.

In the studies, the diagnostic performance of Fludeoxyglucose F 18 Injection varied with the type of cancer, size of cancer, and other clinical conditions. False negative and false positive scans were observed. Negative Fludeoxyglucose F 18 Injection PET scans do not exclude the diagnosis of cancer. Positive Fludeoxyglucose F 18 Injection PET scans can not replace pathology to establish a diagnosis of cancer. Non-malignant conditions such as fungal infections, inflammatory processes and benign tumors have patterns of increased glucose metabolism that may give rise to false-positive scans. The efficacy of Fludeoxyglucose F 18 Injection PET imaging in cancer screening was not studied.

14.2 Cardiology

The efficacy of Fludeoxyglucose F 18 Injection for cardiac use was demonstrated in ten independent, prospective studies of patients with coronary artery disease and chronic left ventricular systolic dysfunction who were scheduled to undergo coronary revascularization. Before revascularization, patients underwent PET imaging with Fludeoxyglucose F 18 Injection (74 to 370 MBq, 2 to 10 mCi) and perfusion imaging with other diagnostic radiopharmaceuticals. Doses of Fludeoxyglucose F 18 Injection ranged from 74 to 370 MBq (2 to 10 mCi). Segmental, left ventricular, wall-motion assessments of asynergic areas made before revascularization were compared in a blinded manner to assessments made after successful revascularization to identify myocardial segments with functional recovery.

Left ventricular myocardial segments were predicted to have reversible loss of systolic function if they showed Fludeoxyglucose F 18 accumulation and reduced perfusion (i.e., flow-metabolism mismatch). Conversely, myocardial segments were predicted to have irreversible loss of systolic function if they showed reductions in both Fludeoxyglucose F 18 accumulation and perfusion (i.e., matched defects).

Findings of flow-metabolism mismatch in a myocardial segment may suggest that successful revascularization will restore myocardial function in that segment. However, false-positive tests occur regularly, and the decision to have a patient undergo revascularization should not be based on PET findings alone. Similarly, findings of a matched defect in a myocardial segment may suggest that myocardial function will not recover in that segment, even if it is successfully revascularized. However, false-negative tests occur regularly, and the decision to recommend against coronary revascularization, or to recommend a cardiac transplant, should not be based on PET findings alone. The reversibility of segmental dysfunction as predicted with Fludeoxyglucose F 18 PET imaging depends on successful coronary revascularization. Therefore, in patients with a low likelihood of successful revascularization, the diagnostic usefulness of PET imaging with Fludeoxyglucose F 18 Injection is more limited.

14.3 Neurology

In a prospective, open label trial, Fludeoxyglucose F 18 Injection was evaluated in 86 patients with epilepsy. Each patient received a dose of Fludeoxyglucose F 18 Injection in the range of 185 to 370 MBq (5 to 10 mCi). The mean age was 16.4 years (range: 4 months to 58 years; of these, 42 patients were less than 12 years and 16 patients were less than 2 years old). Patients had a known diagnosis of complex partial epilepsy and were under evaluation for surgical treatment of their seizure disorder. Seizure foci had been previously identified on ictal EEGs and sphenoidal EEGs. Fludeoxyglucose F 18 Injection PET imaging confirmed previous diagnostic findings in 16% (14/87) of the patients; in 34% (30/87) of the patients, Fludeoxyglucose F 18 Injection PET images provided new findings. In 32% (27/87), imaging with Fludeoxyglucose F 18 Injection was inconclusive. The impact of these imaging findings on clinical outcomes is not known.

Several other studies comparing imaging with Fludeoxyglucose F 18 Injection results to subsphenoidal EEG, MRI and/or surgical findings supported the concept that the degree of hypometabolism corresponds to areas of confirmed epileptogenic foci. The safety and effectiveness of Fludeoxyglucose F 18 Injection to distinguish idiopathic epileptogenic foci from tumors or other brain lesions that may cause seizures have not been established.

15 REFERENCES

1. Gallagher B.M., Ansari A., Atkins H., Casella V., Christman D.R., Fowler J.S., Ido T., MacGregor R.R., Som P., Wan C.N., Wolf A.P., Kuhl D.E., and Reivich M. "Radiopharmaceuticals XXVII. 18F-labeled 2-deoxy-2-fluoro-d-glucose as a radiopharmaceutical for measuring regional myocardial glucose metabolism in vivo: tissue distribution and imaging studies in animals," J Nucl Med, 1977; 18, 990-6.
2. Jones S.C., Alavi, A., Christman D., Montanez, I., Wolf, A.P., and Reivich M. "The radiation dosimetry of 2 [F-18] fluoro-2-deoxy-D-glucose in man," J Nucl Med, 1982; 23, 613-617.
3. Kocher, D.C. "Radioactive Decay Tables: A handbook of decay data for application to radiation dosimetry and radiological assessments," 1981, DOE/TIC-I 1026, 89.
4. ICRP Publication 53, Volume 18, No. l-4,1987, pages 75-76.

16 HOW SUPPLIED/STORAGE AND DRUG HANDLING

Fludeoxyglucose F 18 Injection is supplied in a multi-dose, capped 30 mL and 50 mL glass vial containing between 0.740 to 7.40 GBq/mL (20 to 200 mCi/mL), of no carrier added 2-deoxy-2-[F 18] fluoro-D-glucose, at end of synthesis, in approximately 15 to 50 mL. The contents of each vial are sterile, pyrogen-free and preservative-free.

NDC 40028-511-30; 40028-511-50

Receipt, transfer, handling, possession, or use of this product is subject to the radioactive material regulations and licensing requirements of the U.S. Nuclear Regulatory Commission, Agreement States or Licensing States as appropriate.

Store the Fludeoxyglucose F 18 Injection vial upright in a lead shielded container at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

Store and dispose of Fludeoxyglucose F 18 Injection in accordance with the regulations and a general license, or its equivalent, of an Agreement State or a Licensing State.

The expiration date and time are provided on the container label. Use Fludeoxyglucose F 18 Injection within 12 hours from the EOS time.

17 PATIENT COUNSELING INFORMATION

Instruct patients in procedures that increase renal clearance of radioactivity. Encourage patients to:

- drink water or other fluids (as tolerated) in the 4 hours before their PET study.
- void as soon as the imaging study is completed and as often as possible thereafter for at least one hour.

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PETNET Solutions

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HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Sodium Fluoride F 18 Injection safely and effectively. See full prescribing information for Sodium Fluoride F 18 Injection.

SODIUM FLUORIDE F 18 INJECTION

For Intravenous Use

Initial U.S. Approval: January 2011

INDICATIONS AND USAGE

Sodium Fluoride F 18 Injection is a radioactive diagnostic agent for positron emission tomography (PET) indicated for imaging of bone to define areas of altered osteogenic activity (1).

DOSAGE AND ADMINISTRATION

- Sodium Fluoride F18 Injection emits radiation and must be handled with appropriate safety measures (2.1).
- Administer 300-450 MBq (8–12 mCi) as an intravenous injection in adults (2.4).
- Administer approximately 2.1 MBq/kg in children with a minimum of 19 MBq (0.5 mCi) and a maximum of 148 MBq (4 mCi) as an intravenous injection (2.5).
- Imaging can begin 1–2 hours after administration; optimally at one hour post administration (2.7).
- Encourage patients to void immediately prior to imaging the lumbar spine and bony pelvis (2.7).

DOSAGE FORMS AND STRENGTHS

Multiple-dose vial containing 370–7,400 MBq/mL (10–200 mCi/mL) of no-carrier-added sodium fluoride F18 at the end of synthesis (EOS) reference time in aqueous 0.9% sodium chloride solution (3). Sodium Fluoride F18 Injection is a clear, colorless, sterile, pyrogen-free and preservative-free solution for intravenous administration.

CONTRAINDICATIONS

None (4).

WARNINGS AND PRECAUTIONS

- Allergic Reactions: As with any injectable drug product, allergic reactions and anaphylaxis may occur. Emergency resuscitation equipment and personnel should be immediately available (5.1).
- Cancer Risk: Sodium Fluoride F 18 Injection may increase the risk of cancer. Use the smallest dose necessary for imaging and ensure safe handling to protect the patient and health care worker (5.2).

ADVERSE REACTIONS

No adverse reactions have been reported for Sodium Fluoride F 18 Injection based on a review of the published literature, publicly available reference sources, and adverse drug reaction reporting systems (6).

To report SUSPECTED ADVERSE REACTIONS, contact NCI/DCTD/CIP at 1-301-496-9531 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

- Pregnancy: No human or animal data. Any radiopharmaceutical, including Sodium Fluoride F18 injection, may cause fetal harm. Use only if clearly needed (8.1)
- Nursing: A decision should be made whether to interrupt nursing after Sodium Fluoride F 18 Injection administration or not to administer Sodium Fluoride F 18 Injection taking into consideration the importance of the drug to the mother. (8.3)
- Pediatrics: Children are more sensitive to radiation and may be at higher risk of cancer from Sodium Fluoride F18 injection (8.4).

See 17 for PATIENT COUNSELING INFORMATION

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Sodium Fluoride F 18 Injection is indicated for diagnostic positron emission tomography (PET) imaging of bone to define areas of altered osteogenic activity.

2 DOSAGE AND ADMINISTRATION

2.1 Radiation Safety - Drug Handling

- Wear waterproof gloves and effective shielding when handling Sodium Fluoride F 18 Injection. Use appropriate safety measures, including shielding, consistent with proper patient management to avoid unnecessary radiation exposure to the patient, occupational workers, clinical personnel, and other persons.
- Radiopharmaceuticals should be used by or under the control of physicians who are qualified by specific training and experience in the safe use and handling of radionuclides, and whose experience and training have been approved by the appropriate governmental agency authorized to license the use of radionuclides.
- Use aseptic technique to maintain sterility during all operations involved in the manipulation and administration of Sodium Fluoride F 18 Injection.
- The dose of Sodium Fluoride F 18 Injection should be minimized consistent with the objectives of the procedure, and the nature of the radiation detection devices employed.
- The final dose for the patient should be calculated using proper decay factors from the time of End of Synthesis (EOS), and measured by a suitable radioactivity calibration system before administration [see Description (11.2)].

2.2 Radiation Safety - Patient Preparation

- To minimize the radiation-absorbed dose to the bladder, encourage adequate hydration. Encourage the patient to ingest at least 500 mL of fluid immediately prior and subsequent to the administration of Sodium Fluoride F 18 Injection.
- Encourage the patient to void one-half hour after administration of Sodium Fluoride F 18 Injection and as frequently thereafter as possible for the next 12 hours.

2.3 Drug Preparation and Administration

- Calculate the necessary volume to administer based on calibration time and dose.
- Inspect Sodium Fluoride F 18 Injection visually for particulate matter and discoloration before administration, whenever solution and container permit.
- Do not administer Sodium Fluoride F 18 Injection containing particulate matter or discoloration; dispose of these unacceptable or unused preparations in a safe manner, in compliance with applicable regulations.
- Aseptically withdraw Sodium Fluoride F 18 Injection from its container.

2.4 Recommended Dose for Adults

- Administer 300–450 MBq (8–12 mCi) as an intravenous injection.

2.5 Recommended Dose for Pediatric Patients

In reported clinical experience in approximately 100 children, weight based doses (2.1 MBq/kg) ranging from 19 MBq–148 MBq (0.5 mCi–4 mCi) were used.

2.6 Radiation Dosimetry

The age/weight- based estimated absorbed radiation doses (mGy/MBq) from intravenous injection of Sodium Fluoride F 18 Injection are shown in Table 1. These estimates were calculated based on human data and using the data published by the Nuclear Regulatory Commission [1] and the International Commission on Radiological Protection for Sodium Fluoride Injection [2]. The bone, bone marrow and urinary bladder are considered target and critical organs.

Table 1. Estimated Absorbed Radiation Doses After Intravenous Administration of Sodium Fluoride F 18 Injection

Organ	Estimated Radiation Dose mGy/MBq				
	Adult 70 kg [1]	15 year 56.8 kg [2]	10 year 33.2 kg [2]	5 year 19.8 kg [2]	1 year 9.7 kg [2]
Adrenals	0.0062	0.012	0.018	0.028	0.052
Brain	0.0056	N/A	N/A	N/A	N/A
Bone surfaces	0.060	0.050	0.079	0.13	0.30
GI Breasts	0.0028	0.0061	0.0097	0.015	0.030
Gallbladder wall	0.0044	N/A	N/A	N/A	N/A
Stomach wall	0.0038	0.008	0.013	0.019	0.036
Small intestine	0.0066	0.012	0.018	0.028	0.052
Upper large intestine wall	0.0058	0.010	0.016	0.026	0.046
Lower large intestine wall	0.012	0.016	0.025	0.037	0.063
Heart wall	0.0039	N/A	N/A	N/A	N/A
Kidneys	0.019	0.025	0.036	0.053	0.097
Liver	0.0040	0.0084	0.013	0.021	0.039
Lungs	0.0041	0.0084	0.013	0.020	0.039
Muscle	0.0060	N/A	N/A	N/A	N/A
Ovaries	0.011	0.016	0.023	0.036	0.063
Pancreas	0.0048	0.0096	0.015	0.023	0.044
Red marrow	0.028	0.053	0.088	0.18	0.38
Skin	0.0040	N/A	N/A	N/A	N/A
Spleen	0.0042	0.0088	0.014	0.021	0.041
Testes	0.0078	0.013	0.021	0.033	0.062
Thymus	0.0035	N/A	N/A	N/A	N/A
Thyroid	0.0044	0.0084	0.013	0.020	0.036
Urinary bladder wall	0.25	0.27	0.4	0.61	1.1
Uterus	0.019	0.023	0.037	0.057	0.099
Other tissue	N/A	0.010	0.015	0.024	0.044
Effective Dose Equivalent mSv/MBq	0.027	0.034	0.052	0.086	0.17

[1] Data from Nuclear Regulatory Commission Report, Radiation Dose Estimates for Radiopharmaceuticals, NUREG/CR-6345, page 10, 1996.

[2] Data from ICRP publication 53, Radiation Dose to Patients from Radiopharmaceuticals , Ann ICRP, Volume 18, pages 15 and 74, 1987

2.7 Imaging Guidelines

- Imaging of Sodium Fluoride F 18 Injection can begin 1–2 hours after administration; optimally at 1 hour post administration.
- Encourage the patient to void immediately prior to imaging the fluoride F18 radioactivity in the lumbar spine or bony pelvis.

3 DOSAGE FORMS AND STRENGTHS

Multiple-dose vial containing 370–7.400 MBq/mL (10–200 mCi/mL) at EOS reference time of no-carrier-added sodium fluoride F18 in aqueous 0.9% sodium chloride solution. Sodium Fluoride F 18 Injection is a clear, colorless, sterile, pyrogen-free and preservative-free solution for intravenous administration.

4 CONTRAINDICATIONS
None.

5 WARNINGS AND PRECAUTIONS

5.1 Allergic Reactions
As with any injectable drug product, allergic reactions and anaphylaxis may occur. Emergency resuscitation equipment and personnel should be immediately available.

5.2 Radiation Risks
Sodium Fluoride F 18 Injection may increase the risk of cancer. Carcinogenic and mutagenic studies with Sodium Fluoride F18 injection have not been performed. Use the smallest dose necessary for imaging and ensure safe handling to protect the patient and health care worker [see Dosage and Administration (2.1)].

6 ADVERSE REACTIONS
No adverse reactions have been reported for Sodium Fluoride F 18 Injection based on a review of the published literature, publicly available reference sources, and adverse drug reaction reporting systems. However, the completeness of these sources is not known.

7 DRUG INTERACTIONS
The possibility of interactions of Sodium Fluoride F 18 Injection with other drugs taken by patients undergoing PET imaging has not been studied.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy Pregnancy Category C
Any radiopharmaceutical including Sodium Fluoride F 18 Injection has a potential to cause fetal harm. The likelihood of fetal harm depends on the stage of fetal development, and the radionuclide dose. Animal reproductive and developmental toxicity studies have not been conducted with Sodium Fluoride F 18 Injection. Prior to the administration of Sodium Fluoride F 18 Injection to women of childbearing potential, assess for presence of pregnancy. Sodium Fluoride F 18 Injection should be given to a pregnant woman only if clearly needed.

8.3 Nursing Mothers
It is not known whether Sodium Fluoride F 18 Injection is excreted into human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to interrupt nursing after administration of Sodium Fluoride F 18 Injection or not to administer Sodium Fluoride F 18 Injection, taking into account the importance of the drug to the mother. The body of scientific information related to radioactivity decay, drug tissue distribution and drug elimination shows that less than 0.01% of the radioactivity administered remains in the body after 24 hours (10 half-lives). To minimize the risks to a nursing infant, interrupt nursing for at least 24 hours.

8.4 Pediatric Use
In reported clinical experience in approximately 100 children, weight based doses (2.1 MBq/kg) ranging from 19 MBq–148 MBq (0.5 mCi - 4 mCi) were used. Sodium Fluoride F18 was shown to localize to areas of bone turnover including rapidly growing epiphyses in developing long bones. Children are more sensitive to radiation and may be at higher risk of cancer from Sodium Fluoride F18 injection.

11 DESCRIPTION

11.1 Chemical Characteristics
Sodium Fluoride F 18 Injection is a positron emitting radiopharmaceutical, containing nocarrier-added, radioactive fluoride F18 that is used for diagnostic purposes in conjunction with PET imaging. It is administered by intravenous injection. The active ingredient, sodium fluoride F18, has the molecular formula Na[18F] with a molecular weight of 40.99, and has the following chemical structure:

Na + ^{18}F

Sodium Fluoride F 18 Injection is provided as a ready-to-use, isotonic, sterile, pyrogen-free, preservative-free, clear and colorless solution. Each mL of the solution contains between 370 MBq to 7,400 MBq (10 mCi to 200 mCi) sodium fluoride F18, at the EOS reference time, in 0.9% aqueous sodium chloride. The pH of the solution is between 4.5 and 8. The solution is presented in 30 mL multiple- dose glass vials with variable total volume and total radioactivity in each vial.

11.2 Physical Characteristics
Fluoride F18 decays by positron (ß+) emission and has a half-life of 109.7 minutes. Ninety seven percent of the decay results in emission of a positron with a maximum energy of 633 keV and 3% of the decay results in electron capture with subsequent emission of characteristic X-rays of oxygen. The principal photons useful for diagnostic imaging are the 511 keV gamma photons, resulting from the interaction of the emitted positron with an electron (Table 2). Fluorine F18 atom decays to stable 18O-oxygen.

Table 2. Principal Radiation Emission Data for Fluoride F18

Radiation/Emission	% Per Disintegration	Mean Energy
Positron (b+)	96.73	249.8 keV
Gamma (±)*	193.46	511.0 keV

*Produced by positron annihilation

[3] Kocher, D.C. Radioactive Decay Data Tables DOE/TIC-11026, 69, 1981.

The specific gamma ray constant for fluoride F18 is 5.7 R/hr/mCi (1.35 x 10-6 Gy/hr/kBq) at 1 cm. The half-value layer (HVL) for the 511 keV photons is 4.1 mm lead (Pb). A range of values for the attenuation of radiation results from the interposition of various thickness of Pb. The range of attenuation coefficients for this radionuclide is shown in Table 3. For example, the interposition of an 8.3 mm thickness of Pb with a coefficient of attenuation of 0.25 will decrease the external radiation by 75%.

Table 3. Radiation Attenuation of 511 keV Photons by lead (Pb) shielding

Shield thickness (Pb) mm	Coefficient of attenuation
0	0.00
4	0.50
8	0.25
13	0.10
26	0.01
39	0.001
52	0.0001

Table 4 lists the fraction of radioactivity remaining at selected time intervals from the calibration time. This information may be used to correct for physical decay of the radionuclide.

Table 4. Physical Decay Chart for Fluoride F18

Time Since Calibration	Fraction Remaining
0*	1.00
15 minutes	0.909
30 minutes	0.826
60 minutes	0.683
110 minutes	0.500
220 minutes	0.250
440 minutes	0.060
12 hours	0.011
24 hours	0.0001

*calibration time

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action
Fluoride F18 ion normally accumulates in the skeleton in an even fashion, with greater deposition in the axial skeleton (e.g. vertebrae and pelvis) than in the appendicular skeleton and greater deposition in the bones around joints than in the shafts of long bones.

12.2 Pharmacodynamics
Increased fluoride F18 ion deposition in bone can occur in areas of increased osteogenic activity during growth, infection, malignancy (primary or metastatic) following trauma, or inflammation of bone.

12.3 Pharmacokinetics
After intravenous administration, fluoride F18 ion is rapidly cleared from the plasma in a biexponential manner. The first phase has a half-life of 0.4 h, and the second phase has a half-life of 2.6 h. Essentially all the fluoride F18 that is delivered to bone by the blood is retained in the bone. One hour after administration of fluoride, F18 only about 10% of the injected dose remains in the blood. Fluoride F18 diffuses through capillaries into bone extracellular fluid space, where it becomes bound by chemisorption at the surface of bone crystals, preferentially at sites of newly mineralizing bone. Deposition of fluoride F18 in bone appears to be primarily a function of blood flow to the bone and the efficiency of the bone in extracting the fluoride F18. Fluoride F18 does not appear to be bound to serum proteins. In patients with normal renal function, 20% or more of the fluorine ion is cleared from the body in the urine within the first 2 hours after intravenous administration.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
Studies to assess reproductive toxicity, mutagenesis and carcinogenesis potential of Sodium Fluoride F 18 Injection have not been performed.

14 CLINICAL STUDIES

14.1 Metastatic Bone Disease
The doses used in reported studies ranged from 2.7 mCi to 20 mCi (100 MBq to 740 MBq), with an average median dose of 10 mCi (370 MBq) and an average mean dose of 9.2 mCi (340 MBq). In PET imaging of bone metastases with Sodium Fluoride F 18 Injection, focally increased tracer uptake is seen in both osteolytic and osteoblastic bone lesions. Negative PET imaging results with Sodium Fluoride F 18 Injection do not preclude the diagnosis of bone metastases. Also, as benign bone lesions are also detected by Sodium Fluoride F 18 Injection, positive PET imaging results cannot replace biopsy to confirm a diagnosis of cancer.

14.2 Other Bone Disorders
The doses used in reported studies ranged from 2.43 mCi to 15 mCi (90 MBq to 555 MBq), with an average median dose of 8.0 mCi (300 MBq) and an average mean dose of 7.6 mCi (280 MBq).

15 REFERENCES

1. Stabin, M.G., Stubbs, J.B. and Toohey R.E., Radiation Dose Estimates for Radiopharmaceuticals, U.S. Nuclear Regulatory Commission report NUREG/CR¬6345, page 10, 1996.
2. Radiation Dose to Patients from Radiopharmaceuticals, ICRP publication 53, Ann ICRP, 18 pages 15 and 74, 1987
3. Kocher, D.C., „Radioactive Decay Data Tables: A Handbook of decay data for application to radiation dosimetry and radiological assessments" DOE/TIC-11026, page 69, 1981.

16 HOW SUPPLIED/STORAGE AND HANDLING
Sodium Fluoride F 18 Injection is supplied in a multiple-dose Type I glass vial with elastomeric stopper and aluminum crimp seal containing between 370 and 7,400 MBq/mL (10–200 mCi/mL) of no carrier-added sodium fluoride F18, at the EOS reference time, in aqueous 0.9% sodium chloride solution. The total volume and total radioactivity per vial are variable. Each vial is enclosed in a shielded container of appropriate thickness. The product is available in a 30 mL vial configuration with a variable fill volume. The NDC number is: 40028-512-30 (30 mL)

Storage
Store at 25°C (77°F) in a shielded container; excursions permitted to 15–30°C (59–86°F). Use the solution within 12 hours of the EOS reference time.

Handling
Receipt, transfer, handling, possession, or use of this product is subject to the radioactive material regulations and licensing requirements of the U.S. Nuclear Regulatory Commission, Agreement States or Licensing States as appropriate.

17 PATIENT COUNSELING INFORMATION

17.1 Pre-study Hydration
Encourage patients to drink at least 500 mL of water prior to drug administration.

17.2 Post-study Voiding
To help protect themselves and others in their environment, patients should take the following precautions for 12 hours after injection: whenever possible, use a toilet and flush several times after each use; wash hands thoroughly after each voiding or fecal elimination. If blood, urine or feces soil clothing, wash the clothing separately.

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