LE PATIENT

LE SEUL MAGAZINE DE TOUS LES PROFESSIONNELS DE LA SANTÉ

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LES AVANCÉES MÉDICO-PHARMACOLOGIQUES

MEDICAL AND PHARMACOLOGICAL ADVANCES

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CLINICAL RESEARCH OPPORTUNITY IN COVID-19

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TECHNEGAS™
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Cyclomedica is seeking innovative clinical sites interested in researching the effectiveness of V/Q SPECT/CT scan using Technegas™ in COVID-19 and/or understanding the implication of the disease long-term.

In order to qualify for the research grants, the site must be a current Technegas™ user.
Register your interest here below via the QR code:

Technegas™ is not classified as an Aerosol Generating Procedure and, in more than 30 years of use, there have been no reported viral or other disease cross-contamination events associated with the use of the Technegas™ system.

For more information regarding the use of Ventilation/Perfusion procedures during the current pandemic, please refer to our company's guidance webpage on the COVID-19 situation
www.cyclomedica.com/covid19

NEWS APRIL 2020:

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- Technegas™ is available in 59 countries worldwide with 4 million patient studies performed to date.
- Technegas™ as a diagnostic is innovative in seeding to expand its use beyond diagnosing Pulmonary Embolism.
- The administration of Technegas™ is not an AGP.

For more information about Technegas™ and how V/Q SPECT compares to CTPA in the diagnosis of Pulmonary Embolism, please refer to 2019 EANM guidelines and the 2018 CANM guidelines[1-2].

References: 1. Bajc M, et al. EANM guideline for ventilation/perfusion single photon-emission computed tomography (SPECT) for diagnosis of pulmonary embolism and beyond. Eur J Nucl Med Mol Imaging 2019; 46(12): 2429-245. 2 | 2. Leblanc M, et al. CANM guidelines for Ventilation/Perfusion (V/P SPECT) in Pulmonary Embolism. Nov 2018; available from https://canm-acmn.ca/guidelines

For more information, please visit **www.cyclomedica.com** or email **info@cyclomedica.com.au**
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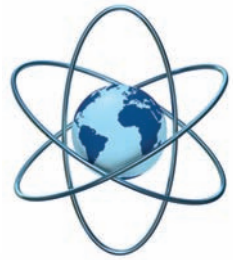

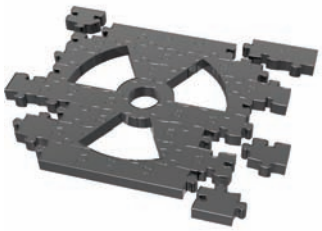

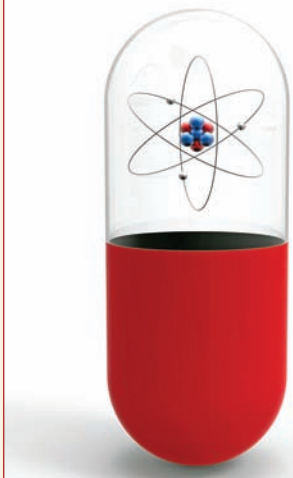

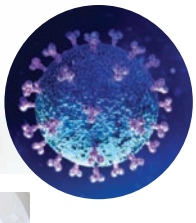

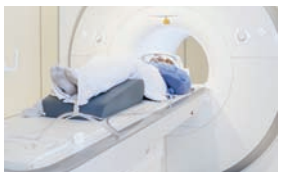

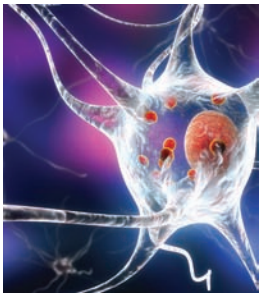

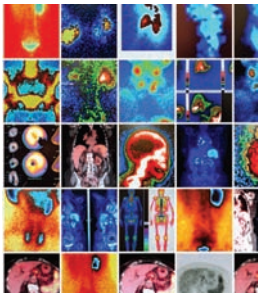

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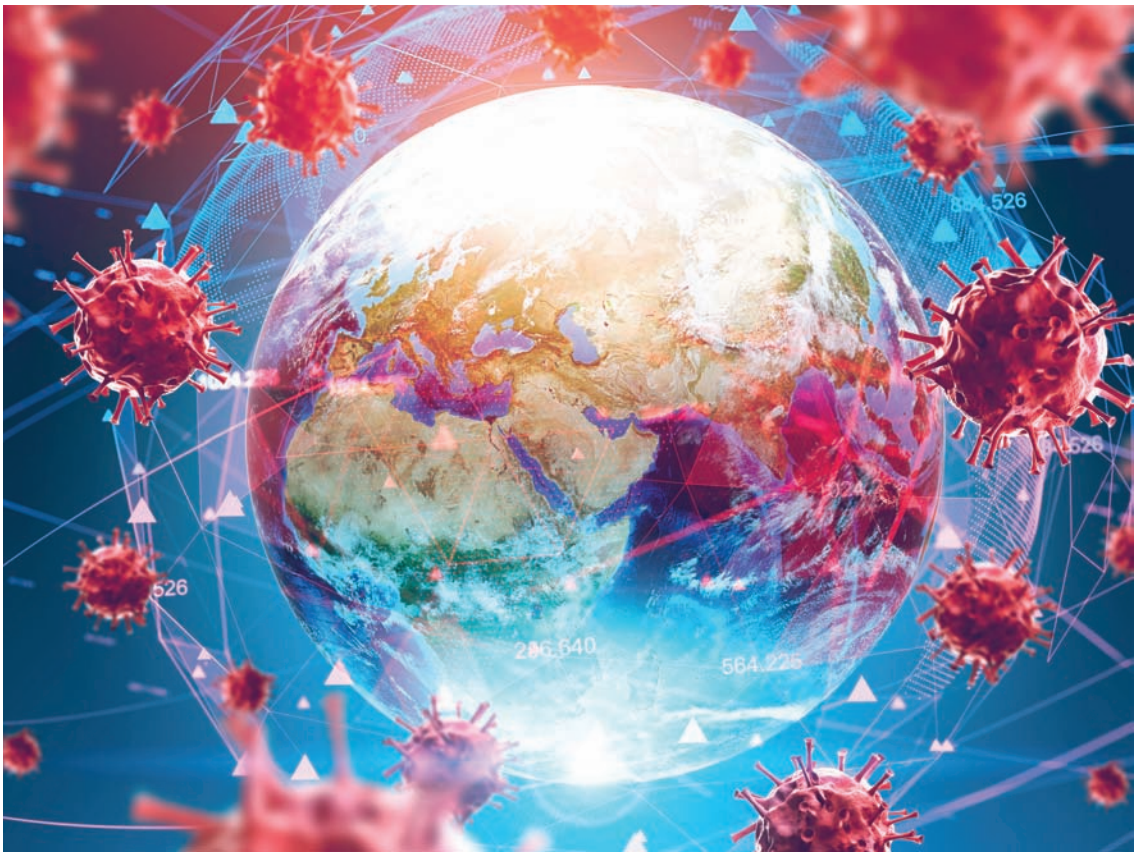


LES AVANCÉES MÉDICO-PHARMACOLOGIQUES
MEDICAL AND PHARMACOLOGICAL ADVANCES

LES VIRUS
CETTE CINQUIÈME COLONNE MALÉFIQUE

Les virus ces délétères mutants tentent continuellement de nous assaillir. Ce sont des spécialistes de la confusion, du furtif.

La cellule humaine se compose d'un noyau dépositaire de l'acide désoxyribonucléique ou ADN. Les messages du noyau de la cellule aux différents éléments du cytoplasme de la cellule sont convoyés par un vecteur l'acide nucléique ou ARN. Comme par exemple pour permettre a la cellule de se reproduire ou de se multiplier.

Les virus lorsqu'ils pénètrent dans une cellule ont la capacité de modifier ou de se substituer à l'ARN original de la cellule pour coder son propre message et amorcer rapidement une multiplication effrénée du virus. Une usine de multiplication extrêmement efficace de production exponentielle de virus est mise en marche. Beaucoup de ce type de virus souvent appelés RIBOVIRUS sont des experts de cette confusion. Par exemple les coronavirus sont de cette famille.

« Contre ces envahisseurs l'organisme humain n'a souvent qu'une seule possibilité de défense soit les anticorps. Ces anticorps c'est comme une CLEF DANS LA SERRURE (ici le virus), c'est spécifique au type de virus. »

VIRUSES
THIS EVIL FIFTH COLUMN

Viruses, these deleterious mutants are constantly trying to attack us. They are stealthy and confusion.

The human cell consists of a nucleus that stores deoxyribonucleic acid or DNA. Messages from the nucleus of the cell to the different elements of the cell's cytoplasm are conveyed by a vector – nucleic acid or RNA. These messages allow the cell to reproduce or multiply.

Viruses, when they enter a cell, have the ability to modify or substitute the original RNA of the cell to encode its own message. Once the virus takes over, it sets in motion a highly efficient unbridled multiplication factory of exponential virus production. Many of the viruses often referred to as RIBOVIRUS are experts at this confusion. Coronaviruses are from this family.

Against these invaders the human body often has only one possibility of defense – antibodies. These antibodies are like a **KEY IN THE LOCK** and are specifically generated to combat each virus.

Contre ces envahisseurs l'organisme humain n'a souvent qu'une seule possibilité de défense soit les anticorps. Ces anticorps c'est comme une CLEF DANS LA SERRURE (ici le virus), c'est spécifique au type de virus.

Après un contact avec le virus les cellules lymphocytes T étudient le virus, l'identifie, le décode et commence a produire ses propres soldats, les anticorps spécifiques a l'envahisseur. Ce processus de défense atteint souvent son efficacité maximale qu'environ 2 mois ou 8 semaines après le premier contact. Pendant cette période ou les défenses sont limitées le virus lui se multiplie rapidement tentant éventuellement de submerger le déploiement des anticorps en production.

LES HUMAINS ONT SUBI A DE MULTIPLES REPRISES L'ASSAUT DE CES MALÉFIQUES ENVAHISSEURS VIRAUX ET DANS CHACUNE DE CES SITUATIONS ILS ONT RÉUSSI A LES VAINCRE.

Que ce soit la grippe espagnole (un coranovirus), la poliomyélite, la variole, la grippe aviaire ou le SARS par exemple.

Certains autres virus peuvent subrepticement coloniser les cellules de l'être humain pour des années et même pour toute la vie de l'être infecté.

Par exemple après en jeune âge d'une attaque de varicelle le virus peut demeurer pour toute la vie du porteur et se remanifester en âge plus avancée sous forme d'une atteinte douloureuse de terminaisons nerveuses comme dans le ZONA.

D'autres virus pourront aussi demeurer à vie dans un être humain comme le virus de l'herpès labial et se remanifester à répétition. Certains autres, comme les papillomavirus, coloniseront à vie des cellules de l'épiderme et réapparaîtront de façon intermittente sur la peau sous forme de verrues. Le virus du SIDA probablement le plus furtif de ces mutants est particulièrement délétère. Il peut demeurer silencieux pendant plusieurs années et en profiter pour affaiblir et même complètement détruire les capacités des lymphocytes T, les producteurs d'anticorps, et ainsi annihiler la seule ligne de défense efficace . Éventuellement il n'y a plus de production de troupes d'assaut, LES ANTICORPS . Dans le cas du SIDA l'être infesté meure finalement de complications comme par une infection bactérienne ou encore par exemple de tuberculose.

La maladie la plus fréquente au monde c'est une maladie virale communément appelée la grippe. L'Organisation Mondiale de la Santé évalue a 650 000 le nombre annuel de décès dans le monde dû à la grippe saisonnière. On tente bien que mal de combattre ces agresseurs, ces mutants très sophistiqués, qui modifient continuellement leur codage génétique. C'est pourquoi à chaque année

After contact with the virus the T-cells study the virus, identify it, decode it and start to produce their own soldiers, the antibodies specific to the invader. This defense process often reaches its maximum effectiveness only about two months to eight weeks after the first contact. During this period when defenses are limited, the virus multiplies rapidly, eventually overwhelming the deployment of antibodies in production.

HUMANS HAVE BEEN REPEATEDLY ASSAULTED BY THESE EVIL VIRAL INVADERS AND IN EACH OF THESE SITUATIONS THEY HAVE SUCCEEDED IN DEFEATING THEM.

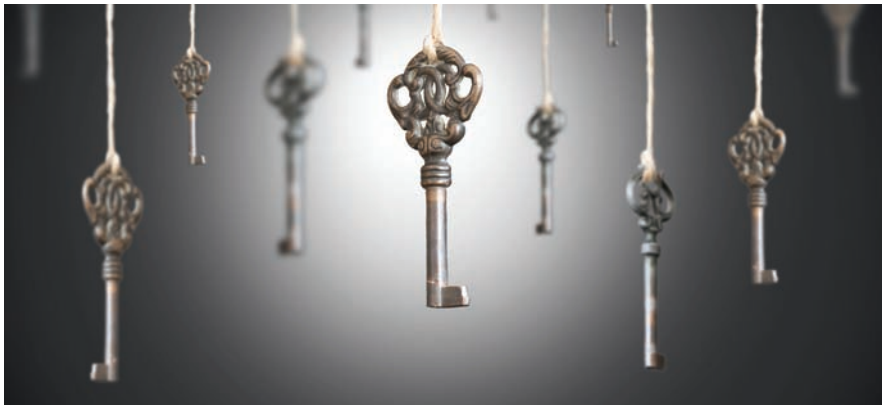
Whether it is the Spanish flu (a coronavirus), poliomyelitis, smallpox, avian flu or SARS for example, some other viruses can surreptitiously colonize the cells of the human being for years and even for the whole life of the infected person.

For example, after a chicken pox attack at a young age, the virus can remain for the entire life of the carrier and reappear in later life in the form of painful nerve endings as in Shingles.

Other viruses, such as the cold sore virus, can also remain in a human being for life and repeatedly re-occur. Some other viruses, called papillomaviruses, will colonize epidermal cells for life and reappear intermittently on the skin as warts. Probably the stealthiest of these mutants, the AIDS virus, is particularly deleterious. It can remain silent for several years and take advantage of its concealment to weaken and even completely destroy the capacities of the T-lymphocytes, the producers of antibodies, and thus annihilate the only effective line of defense. Eventually there is no more production of assault troops, THE ANTIBODY. In the case of AIDS, the infected person finally dies of complications such as bacterial infection or tuberculosis.

The most abundant viral disease in the world is commonly called influenza. According to the World Health Organisation the seasonal influenza kill 650 000 persons in the world annually. There is little attempt by the body to fight these aggressors, very sophisticated mutants that are constantly changing

" Against these invaders the human body often has only one possibility of defense – antibodies. These antibodies are like a KEY IN THE LOCK and are specifically generated to combat each virus. "



on doit étudier attentivement le génome du virus et y adapter un nouveau vaccin qui permettra par les lymphocytes T la production d'anticorps spécifiques, LA CLEF, et seulement ceux-ci seront efficaces. Mais les lymphocytes T ont besoin de temps pour produire efficacement ces anticorps.

« Mais ces experts de la mutation tenteront toujours de nous envahir pour assurer leur multiplication. L'être humain est un hôte idéal pour assurer leur survie et se multiplier. Car un virus seul sans coloniser une cellule ne peut survivre. »

C'est pourquoi lorsqu'une attaque de grande envergure survient, la période de 2 mois ou 8 semaines peut expliquer un type de courbe à surveiller.

D'autres virus s'attaquent également à l'être humain que l'on pense aux virus responsable de l'hépatite A ou B ou encore de la fièvre hémorragique, l'ÉBOLA.

L'humanité a eu, a et aura toujours à subir périodiquement l'assaut de ces envahisseurs mutants maléfiques. Certaines batailles ont été gagnées par l'homme. Certaines mesures de protection sont régulièrement mises en place comme les VACCINS.

Mais ces experts de la mutation tenteront toujours de nous envahir pour assurer leur multiplication. L'être humain est un hôte idéal pour assurer leur survie et se multiplier. Car un virus seul sans coloniser une cellule ne peut survivre.

VOILA LE VRAI ENNEMI DE L'HOMME PAS SES CONGÉNÈRES HUMAINS.

" However, these mutation experts will always try to invade us to ensure their existence. Humans are an ideal host to ensure their survival and multiplication. After all, a virus alone without colonizing a cell cannot survive. "

Bien sûr on vit presqu'en symbiose avec ces méchants mais certains virus peuvent devenir nos amis et nos alliés.

Comme les virus bactériophages qui eux attaquent de façon très efficace des bactéries comme par exemple les escherichia coli qui chez certains individus peuvent provoquer des diarrhées mortelles.

On vaincra cette attaque virale sans précédent. Pour la première fois l'ensemble de l'humanité réalise que l'être humain sera toujours en guerre contre cet envahisseur. Seulement une attention continuelle, actuelle et future permettra à l'homme de sortir vainqueur contre chacun de ces assauts viraux.

their genetic coding. This is why every year the genome of the virus must be carefully studied. Each year a new vaccine must be adapted to it, which will allow the T-lymphocytes to produce specific antibodies (THE KEY) that is specific only to that virus. The challenge for the human organism is that the T-lymphocytes need time to produce these antibodies efficiently.

This delay is why when a large-scale attack occurs, we must observe the infection curve over a period of two months or eight weeks.

Other viruses also attack humans, such as the viruses responsible for hepatitis A or B or the hemorrhagic fever, EBOLA.

Humanity has, and always will have, to suffer periodically from these evil mutant invaders. Some battles have been won by mankind. Humanity may attempt to intervene by placing certain protective measures in place such as the VACCINES.

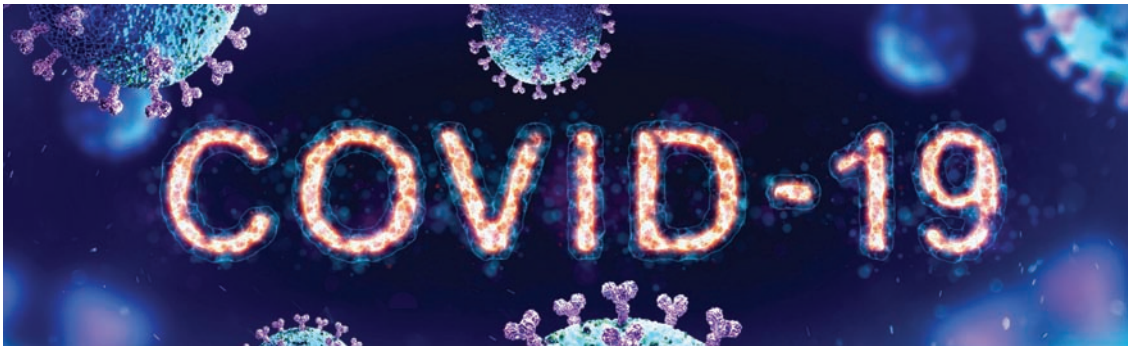
However, these mutation experts will always try to invade us to ensure their existence. Humans are an ideal host to ensure their survival and multiplication. After all, a virus alone without colonizing a cell cannot survive.

THIS IS MAN'S REAL ENEMY, NOT HIS FELLOW HUMANS.

Of course, whilst we live as hosts to these parasitic these villains we also symbiotically live with others as both friends and allies.

An example of one of these friendly viruses to humanity are the bacteriophage viruses that attack bacteria in a very efficient and helpful way; for example, bacteriophages viruses help our body attack the Escherichia Coli that in some individuals can cause deadly diarrhea.

We will defeat this unprecedented viral attack of COVID-19. For the first time the whole of humanity realizes that human beings will always be at war with this invader. Only continuous attention, present and future, will enable mankind to emerge victorious against each and every one of these viral assaults.



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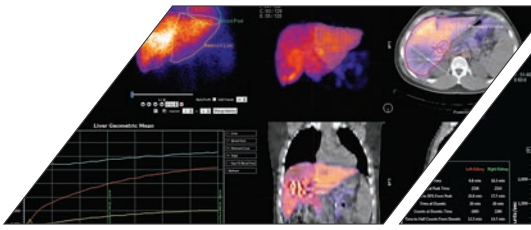
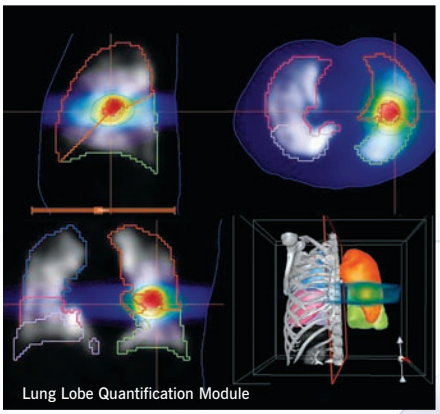


ENTERPRISE CLASS SOLUTIONS FOR MOLECULAR IMAGING

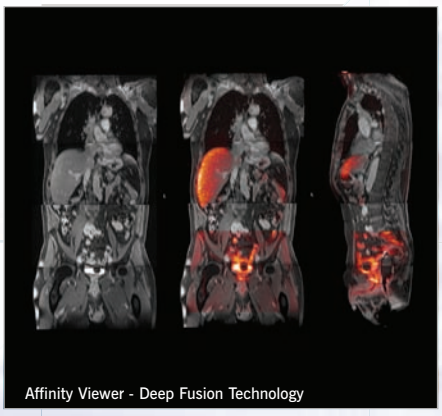
With more than 40 years of recognition for Clinical Excellence and innovation in Molecular Imaging, HERMES delivers Enterprise Class systems and software for integrating, visualizing, processing, reporting and archiving imaging data from different imaging modalities and devices within Molecular Imaging and Radiology. HERMES solutions are empowering physicians by enabling faster and more accurate diagnosis and treatment of patients, thereby improving patient outcomes and increasing efficiency. HERMES leadership within Molecular Imaging has been built on leading technological innovation, financial stability, and historical success. HERMES is committed to the continuous development of cutting-edge accessible software solutions for clinical environments, academic institutions and industry partners. HERMES will continue to offer its customers and proSPECTive clients, the most comprehensive Enterprise Molecular Imaging solutions available for diagnosis and treatment planning as healthcare moves into the new frontiers of Precision Medicine.

DISPLAYED BY HERMES™

Historically, nuclear medicine has benefited from excellent software but, rarely on a single platform. One computer is generally used to display a certain type of exam, another to archive the data and, another is used for specific or dedicated applications. This lack of integration and the non-uniformity of components, continues to cause serious workflow obstacles for professionals working in imaging departments.



Lung Lobe Quantification Module



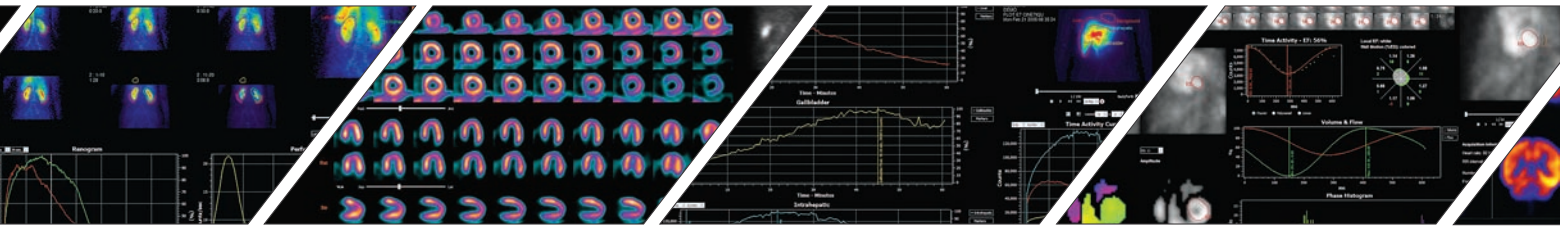
Affinity Viewer - Deep Fusion Technology

With crucial input from customers around the world, nuclear medicine pioneers, the HERMES R&D team has developed Hybrid Viewer PDR™ and Affinity Viewer: A unique and user-friendly software suite for Processing, Display and Reporting (PDR). This all-in-one tool allows the display of all medical imaging modalities (including angiography and ultrasound), image fusion (SPECT-PET-CT-MR) including analysis of this data, processing of conventional nuclear medicine and, the ability to generate medical reports. This technology is used on 6 continents and present in a majority of state-of-the-art NM Departments.

The raw and processed data is stored in a metadata VNA in DICOM, native format, MS-Word™, MS-Excel™, .wav audio files, Adobe PDF™, etc. fully integrating with existing equipment in today's departments under a single master worklist.

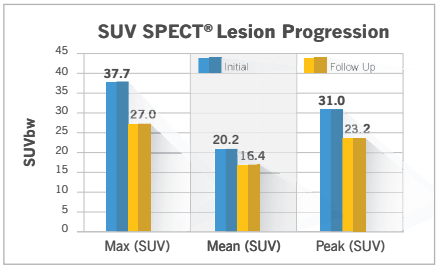
CONNECTED BY HERMES™

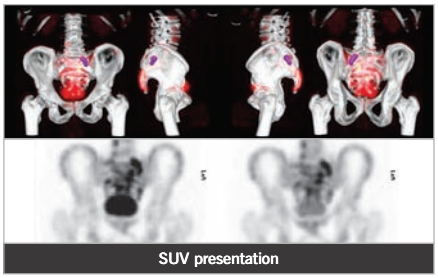
From the early days of nuclear medicine, quantification has been a key aspect; self-defining the practice and at the same time distinguishing from other imaging modalities. The arrival of Positron Emission Tomography (PET and its SUV scale) certainly contributed to advances in the field, but the essence of nuclear medicine still remains the SPECT environment for a vast majority of medical centers. The new breed of cameras coupled with CT components and optimized with advanced reconstruction tools started paving the way for the day when a SUV scale, similar to the one used in PET, would help us quantify images obtained from SPECT-CT scanners. Despite the increasing availability of PET, the number of specific tracers used with this technique is still suboptimal. Absolute SPECT-CT quantification (SUV) is now available and opens the door to a plethora of possibilities with dozens of proven tracers already in use.



RECONSTRUCTED BY HERMES™

The HERMES SUV SPECT® revolutionizes quantitative imaging by exploiting the use of SPECT's full potential in regions where a large portion of the population still does not have access to PET and/or associated reimbursements. HERMES SUV SPECT® software algorithms enable a conversion of the recorded counts per voxel into activity per unit volume with SUV calculations, providing essential and accurate quantitative results.





SUV presentation

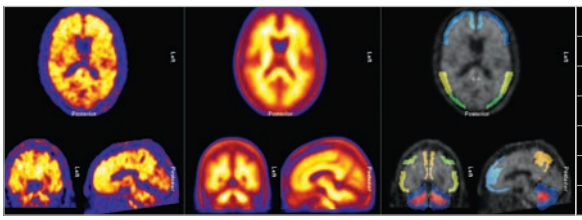
Combined with attenuation correction from a hybrid SPECT-CT scanner or SPECT-only camera (utilizing an independent CT) and a Monte Carlo-modeled scatter correction, HERMES SUV SPECT® brings SPECT-CT scanners from any manufacturer to the next level.

QUANTIFIED BY HERMES™

Mostly used for teaching purposes or display modelling, 3D applications enable automatic lesions detection or the ability to establish more accurate diagnostics in comparison with still largely used 2D tools. These amazing results can be obtained with the help of advanced segmentation methods especially useful with quantitative pulmonary studies. The Hybrid Viewer™ 3D module proceeds with an automatic co-registration of the SPECT-CT (and separate diagnostic CT if needed), an automatic L/R Lung and airways segmentation, a quick inter-lobar fissure definition, a fissure definition quality control, a lobar ventilation and perfusion quantification and an automatic report generation. Knowing that accurate results can drastically change the optimal surgical approach, comparative studies have been conducted between current 2D techniques (planar anterior image or real anterior reprojection divided in 6 segments) and 3D segmentation techniques. Preliminary results have shown differences ranging between -10% to +48% in the assessment of accurate volume calculation in ml. Similar tools for automatic hepatic and kidney segmentation are now available and will help promoting for a closer collaboration between quantitative imaging and surgical departments.

HERMES is extremely proud to participate in high-level research to support healthcare professionals in the detection and treatment follow-up of diseases such as epilepsy, brain tumors, schizophrenia, Parkinson's and most recently Alzheimer's. The market debut of NeuraCeq™, recently approved by Health Canada and commercialized by Isologic, synergizes HERMES efforts in assisting nuclear medicine physicians in university facilities as well as in community hospitals, by providing them with normal templates for a precise and reliable quantification of the patient illness state. This Isologic-HERMES partnership facilitates the utilization of the renown BRASS™ (Brain Registration & Analysis Software Suite) application, appearing in more than 350 scientific publications and presentations around the world and validated with over 2 million patients.

HERMES BRASS™ Quantification with NeuraCeq™ from Isologic



Region Name	SUVr (Z)
Average SUVr	1.65 (2.13)
L Frontal Ctx	1.52 (2.92)
R Frontal Ctx	1.68 (4.24)
L Ant Cingulate	2.15 (5.50)
R Ant Cingulate	2.31 (5.12)
L Occipital Ctx	1.30 (1.00)

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L'APPORT DE LA MÉDECINE NUCLÉAIRE DANS LA DÉTECTION DE L'AMYLOÏDOSE CARDIAQUE

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L'amyloïdose cardiaque est une maladie systémique rare qui est classifiée en plusieurs types. Il s'agit d'un groupe de maladies qui résultent de dépôts d'une protéine anormale appelée amyloïde, dans différents tissus du corps. Il existe plusieurs types de protéines amyloïdes produites par la moelle osseuse. Selon la structure de l'amyloïde en question, la protéine anormale peut s'accumuler dans un tissus isolé (amyloïdose localisée) ou peut affecter plusieurs organes ou tissus (amyloïdose systémique). Tandis que la forme localisée peut être moins nocive, la forme systémique peut causer de sérieux changements dans presque tous les organes du corps. Les organes les plus souvent atteints sont les reins, le cœur, la peau, les poumons, le foie, la rate, les nerfs, la langue et le tractus digestif.

1- TYPES D'AMYLOÏDOSE

L'amyloïdose systémique est habituellement classifiée en trois types principaux qui sont très différents les uns des autres.

A- Le type le plus commun d'amyloïdose systémique est l'amyloïdose **AL** (immunoglobuline à chaine **légère**). L'incidence annuelle de cette forme est d'environ 8-10 cas par million en Amérique du Nord. Cette forme d'amyloïdose est le résultat d'une anomalie des cellules plasmatiques de la moelle osseuse et est intimement reliée au myélome multiple. L'incidence la plus élevée survient entre les âges de 60-70 ans, même si elle peut parfois survenir à un âge plus jeune et environ 70% des patients atteints sont des hommes.

B- L'amyloïdose **AA**, habituellement connue sous le nom d'amyloïdose secondaire est dérivée d'une protéine inflammatoire sérique anormale, l'**amyloïde A**, qui survient en association avec une maladie inflammatoire chronique telle une maladie intestinale inflammatoire chronique ou une maladie rhumatismale.

C- L'amyloïdose héréditaire est causée par un gène anormal. Même si plusieurs gènes peuvent causer la maladie, le type le plus commun d'amyloïdose héréditaire est appelée **ATTR**. Cette forme est causée par des mutations du gène transthyrétine (**TTR**). La transthyrétine, une préalbumine, est une protéine abondante produite par le foie et agit comme **trans**porteur de la **thyr**oxine et du **rétin**ol. Dans sa forme monomérique, la transthyrétine a tendance à se replier et se concentrer progressivement en dépôts d'amyloïde. Les deux principaux sous-types d'amyloïdose ATTR sont l'ATTR mutant (ATTRm) et le

ATTR « wild-type » (ATTRwt) aussi décrite sous le nom d'amyloïdose sénile (ou la transthyrétine est normale mais plus abondante).

2- L'AMYLOÏDOSE CARDIAQUE

La grande majorité des cas d'amyloïdose cardiaque sont causés par une des deux protéines : la chaine légère (AL) ou la transthyrétine (ATTR). L'amyloïdose reliée à l'âge (dans laquelle l'amyloïde provient de la transthyrétine « wild-type » normale est une maladie lentement progressive qui affecte le cœur surtout des hommes plus âgés.

Le diagnostic d'amyloïdose cardiaque est fréquemment manqué ou sous-évalué car sa présentation clinique est souvent similaire à plusieurs autres maladies cardiaques. Les manifestations cardiaques de l'amyloïdose incluent principalement l'insuffisance cardiaque et les arythmies cardiaques. L'hypertrophie ventriculaire avec un voltage électrique anormalement faible à l'électrocardiogramme (ECG) sont des indices de la présence de la maladie. L'amyloïdose AL survient habituellement entre l'âge de 40-80 ans avec une incidence presque égale entre les hommes et les femmes et montre une légère hypertrophie. Cependant, l'hypertrophie des ventricules est plus significative dans les deux formes ATTRwt et ATTRm. Dans ces deux formes d'amyloïdose les hommes sont beaucoup plus fréquemment atteints que les femmes et l'âge de l'incidence varie entre 65-95 ans pour

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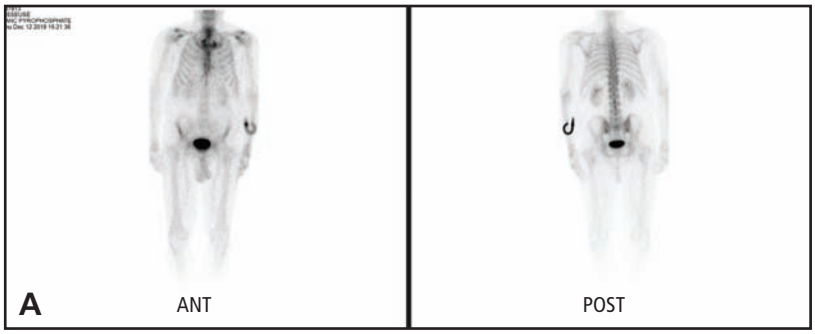
l'ATTRwt et de 55 à 75 ans pour l'ATTRm. La forme ATTRm est très sous-estimée puisque presque un quart des patients âgés ont un certain degré de dépôts d'amyloïde dans le cœur à l'autopsie. De plus, environ 3-4 % des afro-américains ont une mutation commune héréditaire du gène TTR.

3- PRONOSTIC ET DIAGNOSTIC DE L'AMYLOÏDOSE CARDIAQUE.

La mortalité secondaire à l'amyloïdose demeure élevée chez les patients avec une atteinte cardiaque avancée. La détection précoce avec une classification appropriée est primordiale pour un meilleur traitement et un meilleur pronostic. Ceci est d'autant plus important que le traitement va être différent selon le type d'amyloïdose. Le pronostic de l'amyloïdose est intimement relié au degré de l'atteinte cardiaque. Même si le pronostic est habituellement meilleur avec la forme ATTR que la forme AL de la maladie, les deux formes montrent un taux de mortalité annuelle élevé.

Le traitement de la forme AL a deux buts principaux : premièrement, tenter de ralentir la progression de la maladie en éliminant les cellules clonales plasmatiques et leur progression de chaines légères anormales à l'aide de la chimiothérapie et deuxièmement de traiter l'atteinte de la fonction de l'organe. Contrairement à la forme AL, la chimiothérapie n'a aucun rôle dans le traitement de l'amyloïdose ATTR car cette forme de maladie n'est pas maligne. Plusieurs agents ont été ou sont en investigation actuellement pour le traitement de l'amyloïdose tels les anti-inflammatoires non stéroïdiens (toutefois, les anti-inflammatoires sont relativement contre-indiqués en présence d'une insuffisance cardiaque) ou les médicaments interférant avec le RNA qui aident à réduire la production de la transthyrétine par le foie. En mai 2019, la compagnie Pfizer a reçu l'aval du Food and Drug Américain (FDA) pour commercialiser le Tafamidis, un médicament prometteur dans les cas de cardiomyopathie amyloïde de la forme ATTR. Cet agent était déjà approuvé en Europe et au Japon dans le traitement de la polyneuropathie reliée à l'amyloïdose ATTRm.

Le diagnostic définitif de l'amyloïdose requiert une biopsie tissulaire de l'organe cliniquement atteint. Pour l'amyloïdose cardiaque, une biopsie endomyocardique avec coloration spéciales vont révéler la présence de dépôts d'amyloïde dans les cellules cardiaques et confirmer le diagnostic. D'autres tests de laboratoire peuvent aussi être utiles afin de confirmer le type d'amyloïdose et de monitorer la réponse de la maladie au traitement. Compte tenu de la nature plus effractive de la biopsie cardiaque, les recherches se sont penchées sur des méthodes d'imagerie non effractives afin de détecter et de différentier les types d'amyloïdose. L'échocardiographie et la résonnance magnétique (MRI) sont très utiles pour identifier l'état fonctionnel et morphologique mais ne peuvent pas facilement faire la distinction entre les deux types d'amyloïdose cardiaque. De récentes données



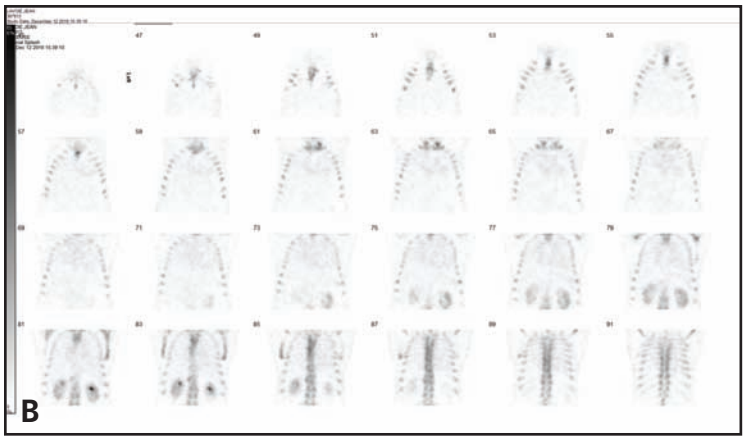


Figure 1
Scintigraphie pancorporelle au 99mTc-PYP en mode planaire (A) et en mode tomoscintigraphique (B) chez un patient avec une amyloïdose cardiaque de type AL. Il n'y a aucune captation anormale du radiotraceur au niveau du muscle cardiaque, ce qui est normal pour ce type de pathologie. L'étude est interprétée comme étant normale.

scientifiques ont démontré que la médecine nucléaire pouvait être utile afin d'améliorer et de différentier le diagnostic non effractif de l'amyloïdose cardiaque : la scintigraphie myocardique au 99mTc-Pyrophosphate.

4- LA SCINTIGRAPHIE MYOCARDIQUE

Les études scientifiques récentes au sujet de l'amyloïdose cardiaque et son traitement possible ont renouvelé l'intérêt pour une technique de médecine nucléaire qui existe depuis plus de cinquante ans, soit la scintigraphie osseuse. Il est connu depuis des décennies que les radiotraceurs utilisés pour obtenir des scintigraphies osseuses tels le 99mTc-Methylene Diphosphonate (99mTc-MDP) ou le 99mTc-Pyrophosphate (99mTc-PYP) montrent une affinité élevée pour la protéine amyloïde, ce qui se traduit par une hypercaptation cardiaque du radiotraceur chez les patients atteints d'amyloïdose cardiaque alors que le radiotraceur ne se fixe pas dans un cœur normal. Il a été démontré que le 99mTc-PYP était le meilleur agent à cet égard. Même si une captation anormale du 99mTc-PYP peut être décelée dans certaines pathologies telles l'infarctus aigu du myocarde ou la péricardite, ces conditions peuvent être reconnues relativement facilement de l'amyloïdose à l'aide de simples test cliniques. Plusieurs études ont démontré que le 99mTc-PYP s'accumulait à différents degrés dans le cœur des patients avec l'amyloïdose ATTR mais non chez les patients avec le type AL. Même si les

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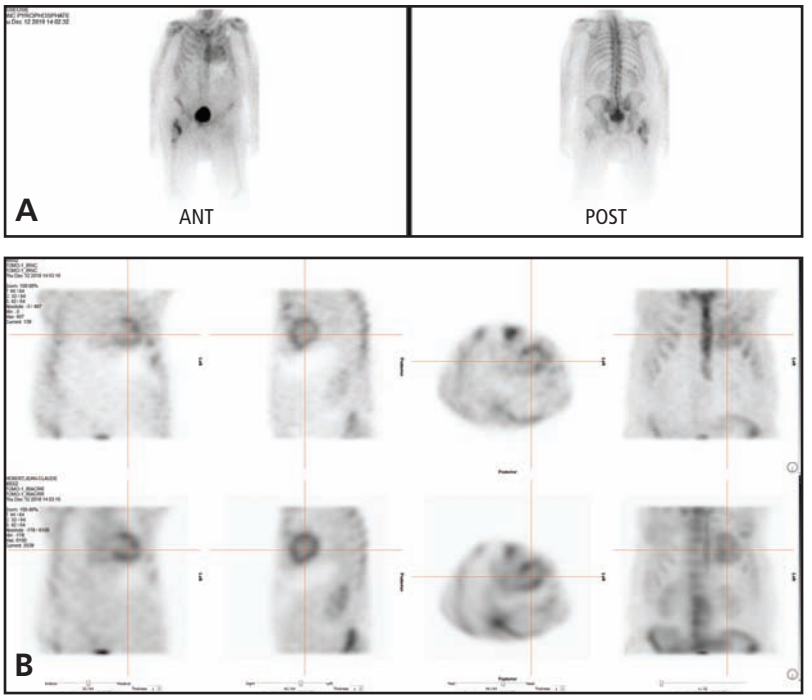

Figure 2
Scintigraphie pancorporelle au 99mTc-PYP en mode planaire (A) et en mode tomoscintigraphique (B) chez un patient avec une amyloïdose cardiaque de type ATTR. Il y a une importante captation anormale du radiotraceur au niveau du muscle cardiaque, bien délimitée sur les études tomographiques (flèches). Ceci représente un cas typique d'amyloïdose cardiaque de type ATTR.

« Les études scientifiques récentes au sujet de l'amyloïdose cardiaque et son traitement possible ont renouvelé l'intérêt pour une technique de médecine nucléaire qui existe depuis plus de cinquante ans, soit la scintigraphie osseuse. »

mécanismes exacts de la captation cardiaque du 99mTc-PYP dans les cas d'amyloïdose ATTR (et l'absence ou le peu de captation dans les cas d'amyloïdose AL) sont actuellement inconnus, les hypothèses sont à l'effet que la captation accrue des radiotraceurs est reliée aux niveaux de calcium élevés dans les dépôts d'amyloïde chez les patients avec l'amyloïdose cardiaque ATTR. Un avantage distinct de la scintigraphie cardiaque au 99mTc-PYP est sa capacité d'identifier spécifiquement l'amyloïdose cardiaque ATTR de façon non effractive.

Il n'y a pas de préparation spéciale pour la scintigraphie myocardiaque au 99mTc-PYP. Cette technique est disponible dans tous les départements de médecine nucléaire. Cette technique non-effractive et sans effet secondaire ne requiert qu'une simple injection intraveineuse du 99mTc-PYP. Trois à quatre heures après l'injection, des images planaires pancorporelles de même qu'une tomoscintigraphie SPECT (**S**ingle **P**hoton **E**mission **T**omography) du cœur, qui consiste à faire tourner autour du patient une gamma caméra qui détecte les rayons gammas provenant du radiotraceur dans le cœur, seront obtenues. La technique entière prend environ 45 minutes. La tomoscintigraphie permet d'obtenir de fines images de la région cardiaque et permet d'évaluer la captation du 99mTc-PYP au niveau de l'apex du cœur qui est habituellement épargnée jusqu'à un stade avancé de la maladie.

Des analyses quantitatives et semi-quantitatives sont obtenues par la suite. Cette analyse permet de classifier plus objectivement le degré de captation cardiaque qui peut être proportionnel au degré des dépôts d'amyloïdose dans le cœur.

La scintigraphie cardiaque au 99mTc-PYP est indiquée chez les patients avec une insuffisance cardiaque et une augmentation inexpliquée de l'épaisseur du ventricule gauche, spécialement chez les patients âgés de plus de 60 ans ayant une fraction d'éjection ventriculaire gauche normale. D'autres indications incluent l'évaluation de l'atteinte cardiaque chez les individus avec une amyloïdose familiale connue ou suspectée, dans le diagnostic d'amyloïdose cardiaque ATTR chez les patients avec une échocardiographie ou une MRI compatibles avec une amyloïdose cardiaque ou chez les patients chez qui une amyloïdose cardiaque ATTR est suspectée mais qui présentent des contre-indications à la MRI telles une insuffisance rénale ou la présence d'implants métalliques.

D'autres radiotraceurs peuvent être utilisés dans le diagnostic non effractif de l'amyloïdose cardiaque. Les pays européens utilisent en clinique un nouveau radiotraceur, le 99mTc-DPD (99mTc-3,3-diphosphono-1,2-propanodicarboxylic acid) avec de très bons résultats. Certains auteurs ont rapporté également l'utilisation du 123 Iode-mIBG (**m**eta **i**odo**b**enzyl **g**uanidine). Ce radiotraceur est utilisé afin d'évaluer le degré d'innervation du cœur. Les patients au stade précoce d'amyloïdose cardiaque, spécialement ceux du type ATTR, démontrent un certain degré de dénervation et peut être détecté à l'aide de la scintigraphie cardiaque au 123 Iode-mIBG. Il est possible que l'utilisation plus répandue de ce test pourrait aider à identifier les patients à un stade plus précoce de la maladie, pouvant ainsi améliorer le pronostic.

CONCLUSION

Le paradigme de l'amyloïdose cardiaque s'est significativement modifié au cours de la dernière décennie. Une meilleure compréhension de la maladie, une reconnaissance accrue de son incidence, une amélioration significative à la fois dans le traitement et les outils diagnostiques ont modifié l'approche médicale de l'amyloïdose cardiaque. Même si la scintigraphie cardiaque au 99mTc-PYP est considérée comme une « vielle » technique, sa haute sensibilité dans le diagnostic de l'amyloïdose cardiaque et son potentiel unique de différentier les formes ATTR et AL, elle est reconnue comme étant un outil diagnostique important pouvant aider à guider la prise en charge de ces patients. La médecine nucléaire peut donc jouer un rôle important dans cette maladie souvent sous-diagnostiquée. ■

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THE ROLE OF NUCLEAR MEDICINE IN DETECTION OF CARDIAC AMYLOIDOSIS

Amyloidosis is a rare systemic disorder that is classified into several types. This is a group of diseases that are a consequence of abnormal protein deposits, called amyloid, in various tissues of the body. There are several types of amyloid proteins produced by the bone marrow. Depending on the structure of the particular amyloid, the abnormal protein can accumulate in an isolated tissue (localized amyloidosis) or can affect many organs or tissues (systemic amyloidosis). While the localized form of the disease can be less harmful, the systemic form can cause serious changes in almost every organs of the body. The most frequently involved organs are the kidneys, heart, skin, lungs, liver, spleen, nerves, tongue and digestive tract.

1- TYPES OF AMYLOIDOSIS

Systemic amyloidosis is usually classified into three major types that significantly differ from each other.

A- The most common type of systemic amyloidosis is **AL** amyloidosis (immunoglobulin **light** chain). The annual incidence of this for mis approximately 8-10 cases per million in North America. This form of amyloidosis results from an abnormality of the plasma cells in the bone marrow and is closely related to multiple myeloma. Although earlier onset may occur, the higher incidence is seen between the ages of 60 to 70 with nearly 70% being male patients.

B- AA amyloidosis, usually known as secondary amyloidosis is derived from an inflammatory protein serum **amyloid A** which occurs in association with chronic inflammatory disease such as chronic inflammatory bowel disease or rheumatic diseases.

C- Hereditary amyloidosis is caused by an abnormal gene. Although many genes can cause the disease, the most common type of hereditary amyloidosis is called **ATTR**. This form is caused by mutations in the transthyretin (**TTR**) gene. Transthyretin, a prealbumin, is an abundant protein produced by the liver and is a **trans**porter of **thy**roxine and **retin**ol. In its monomeric form, transthyretin is prone to misfold and gradually concentrate as amyloid deposits. The two main subtypes of ATTR amyloidosis are the mutant ATTR (ATTRm) and the wild-type ATTR (ATTRwt), previously described as senile amyloidosis.

2- CARDIAC AMYLOIDOSIS

The vast majority of cardiac amyloidosis is caused by one of the two proteins: light chain (AL) or transthyretin (ATTR). Age related amyloidosis (in which amyloid is derived from wild-type normal transthyretin) is a slowly progressive disease that affect the heart of elderly men.

" Cardiac amyloidosis is frequently misdiagnosed initially since its clinical presentation is similar to that of many other cardiac diseases. "

Cardiac amyloidosis is frequently misdiagnosed initially since its clinical presentation is similar to that of many other cardiac diseases. Cardiac manifestations of amyloidosis include heart failure and cardiac arrhythmias. Ventricular hypertrophy with inappropriately low electrical voltages on the electrocardiogram is clues to diagnosis. The AL amyloidosis is usually seen between the ages of 40 to 80 with an incidence in men and women almost equal and shows mild left ventricular hypertrophy. However, left ventricular hypertrophy can be significant in both ATTRwt and ATTRm amyloidosis. In these two forms, men are significantly more affected than women and the age of occurrence is between 65 to 95 years. for ATTRwt and 55 to 75 years. for ATTRm. ATTRwt form is quite underestimated since almost a quarter of elderly patients at autopsy has some degree of cardiac amyloid deposits. Approximately 3-4% among US African Americans have a common inherited mutation of the TTR gene.

3- PROGNOSIS AND DIAGNOSIS OF CARDIAC AMYLOIDOSIS

Mortality from amyloidosis remains high for patients with advanced cardiac involvement. Early detection with appropriate classification is crucial for a better treatment and prognosis. This is very important since the treatment will differ according to the type of amyloidosis. Prognosis in amyloidosis is mainly dependent on the degree of cardiac involvement. Although the prognosis is generally better in the ATTR form than in the AL form of the disease, both forms still show a high annual mortality rate. The treatment of AL amyloidosis has two goals: attempting to slow the progression of the disease by eliminating the clonal plasma cells and their production of abnormal light chains with chemotherapy and treating the organ dysfunction. On the contrary, chemotherapy has no role in the treatment of ATTR amyloidosis as it is not a malignant process. Several agents have been and are currently under investigation for the treatment of amyloidosis such as nonsteroidal anti-inflammatory drug (however anti-inflammatory drugs are relatively contraindicated in heart failure) or RNA interference medications which help reducing the production of transthyretin by the liver. In May 2019 the US Food and Drug Administration (FDA) approved Pfizer Inc's oral drug, Tafamidis, for ATTR amyloid cardiomyopathy. This agent has been previously approved in Europe and Japan for treatment of ATTRm amyloidosis polyneuropathy.

Definitive diagnosis of amyloidosis requires a tissue biopsy of the clinically involved organ. For cardiac amyloidosis an endomyocardial biopsy with special stainings will reveal the amyloid deposits and confirm the diagnosis. Other adjunctive laboratory tests will be also helpful to confirm the type of amyloidosis and monitor the disease response to treatment. Due to the rather "aggressive" nature of the myocardial biopsy, researches have been focused on non-invasive imaging methods to detect and differentiate the different types of amyloidosis. Echocardiography and MRI (magnetic resonance imaging) are very useful in identifying the morphological and functional status of the heart but cannot always make the distinction between the two types of cardiac amyloidosis. Recent scientific data showed that a nuclear medicine procedure could help to improve and differentiate the non-invasive diagnosis of cardiac amyloidosis: myocardial scintigraphy with 99mTc-Pyrophosphate.

4- MYOCARDIAL SCINTIGRAPHY

Recent scientific awareness about cardiac amyloidosis and its possible treatment renewed the interest in a nuclear medicine diagnostic test which is used since more than 50 years, bone scintigraphy. It is known since several decades that the radiotracers used in bone scintigraphy, 99mTc-Methylene Diphosphonate (99mTc-MDP) or 99mTc-Pyrophosphate (99mTc-PYP) show a high affinity for amyloid protein resulting in a diffuse myocardial uptake of the radiotracer in patients with cardiac amyloidosis. 99mTC-PYP has been shown to be the best agent in that purpose. Although myocardial increased uptake of 99mTC-PYP can be seen in different conditions such as an acute myocardial infarction or pericarditis, these conditions can be relatively easily differentiated from amyloidosis with simple clinical tests. Many studies have shown that 99mTc-PYP accumulate at various degrees in the heart of patients with ATTR amyloidosis but not in those with the AL type. Although the exact mechanisms of 99mTc-PYP uptake in ATTR cardiac amyloidosis (and the lower or no uptake in AL amyloidosis) are currently unknown, it is thought that this increased radiotracer uptake is related to the high calcium levels in the amyloid deposits of patients with ATTR cardiac amyloidosis. A distinct advantage of 99mTc-PYP myocardial imaging is its ability to specifically identify ATTR cardiac amyloidosis non-invasively.

No specific test preparation is required. This procedure is available in every department of nuclear medicine. This non-invasive procedure requires a single

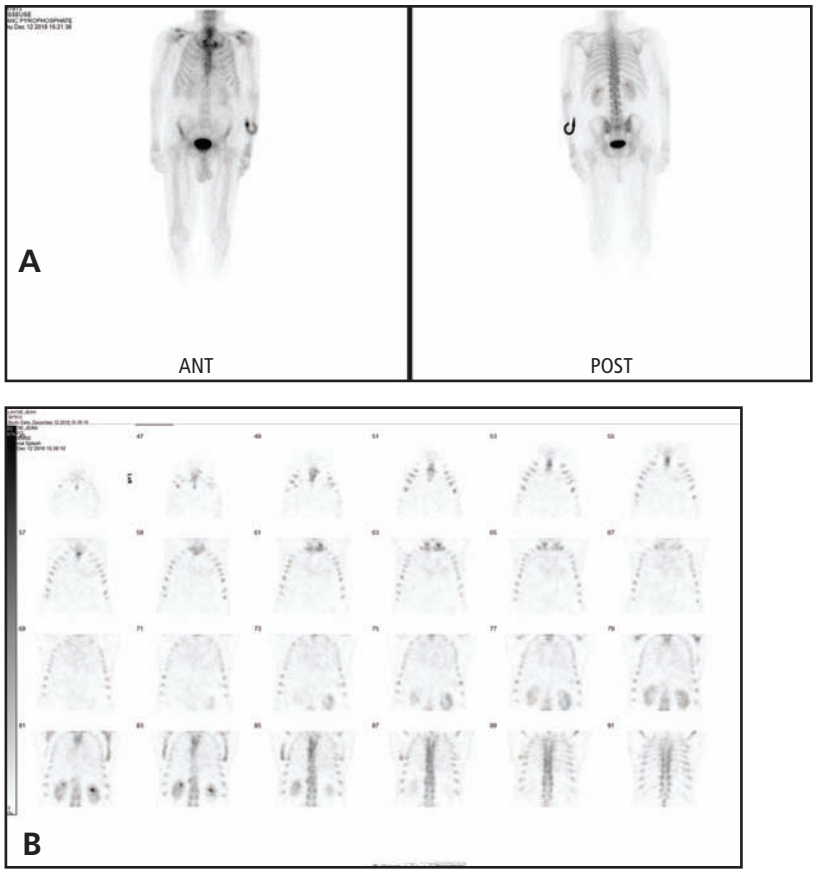

Figure 1
99mTc-PYP whole-body planar images (A) and SPECT images (B) in a patient with cardiac AL type of amyloidosis. There is no focalized increased cardiac uptake of the radiotracer and thus represents a normal finding. This study is interpreted as normal.

" Mortality from amyloidosis remains high for patients with advanced cardiac involvement. Early detection with appropriate classification is crucial for a better treatment and prognosis. "

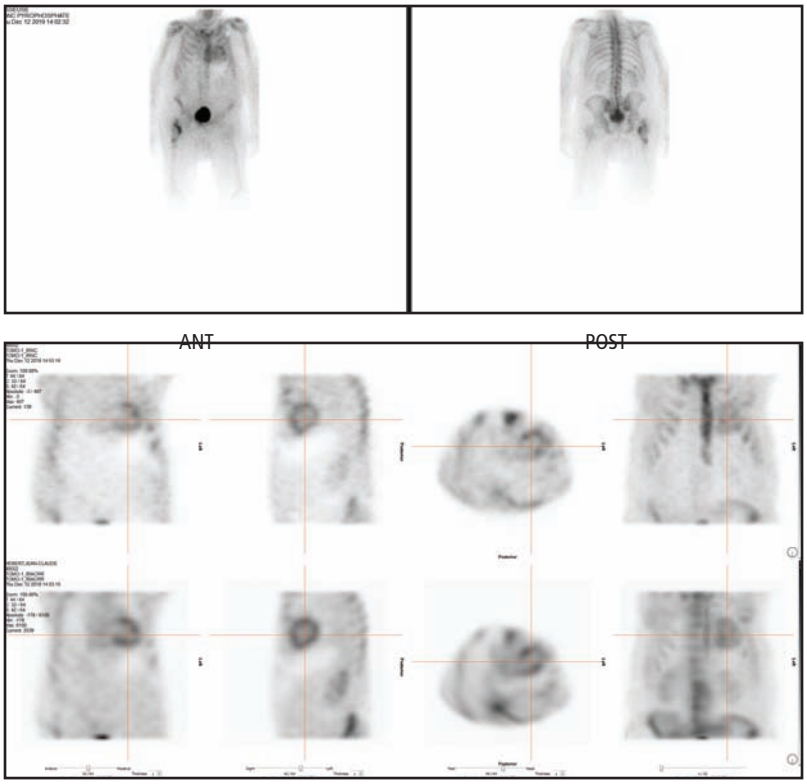

Figure 2
99mTc-PYP whole-body planar images (A) and SPECT images (B) in a patient with cardiac ATTR type of amyloidosis. Note the intense myocardial increased uptake which is well delineated in the SPECT study slices (arrows). This is a typical finding in ATTR cardiac amyloidosis.

" Recent scientific awareness about cardiac amyloidosis and its possible treatment renewed the interest in a nuclear medicine diagnostic test which is used since more than 50 years, bone scintigraphy. "

intravenous injection of the radiotracer with no side effect. Three to four hours after the injection, planar whole-body images and SPECT study (Single Photon Emission Tomography) which consists of a gamma camera detecting the gamma rays emitted by the radiotracer from the heart and rotating around the patient (allowing for more precise localization of the radiotracer uptake) are obtained. The entire procedure lasts for approximately 45 minutes. SPECT imaging can help to evaluate the uptake of the radiotracer at the apex of the heart which is usually spared until the disease is very advanced. Quantitative or semi-quantitative analysis can be obtained from computer image analysis. This serves to categorize more objectively the degree of myocardial uptake which can be proportional to the degree of amyloid deposits into the myocardium.

99mTc-PYP myocardial imaging is indicated in patients with heart failure and unexplained increase in left ventricular thickness, especially over the age of 60 years with preserved left ventricular ejection fraction. Other indications include the evaluation of cardiac involvement in individuals with known or suspected familial amyloidosis, diagnosis of cardiac ATTR in patients with MRI or echocardiography consistent with cardiac amyloidosis or in patients with suspected cardiac ATTR amyloidosis and contraindications to MRI such as renal insufficiency or implantable cardiac devices.

Other radiotracers are used in the non-invasive diagnosis of cardiac amyloidosis. European countries currently used in clinical practice a new radiotracer, 99mTc-DPD (99mTc-3,3-diphosphono-1,2-propan-odicarboxylic acid) with very good results. Some authors have reported the use of 123 Iodine-mIBG (**m**eta **i**odobenzyl **g**uanidine). This radiotracer is used to evaluate the degree of innervation of the heart. Patients in the early stages of cardiac amyloidosis, especially those with ATTR type, show some degree of denervation and can be detected with 123Iodine-mIBG scintigraphy. It is hoped that more generalized use of this test would help identifying patients in the early stages of the disease, potentially improving the prognosis.

CONCLUSION

The paradigm of cardiac amyloidosis has markedly changed in the last decade. Better understanding of the disease, increased awareness of its incidence, marked improvements in both treatment and in diagnostic tools are modifying the actual medical approach of cardiac amyloidosis. Although 99mTc-PYP imaging is considered as an "old" procedure, its high sensitivity in diagnosing cardiac amyloidosis and its unique ability to differentiate ATTR and AL cardiac amyloidosis is recognized as an important tool in guiding patient management. Nuclear medicine can play a key role in this underdiagnosed disease. ■

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DATSCAN IMAGING IN PARKINSON'S DISEASE

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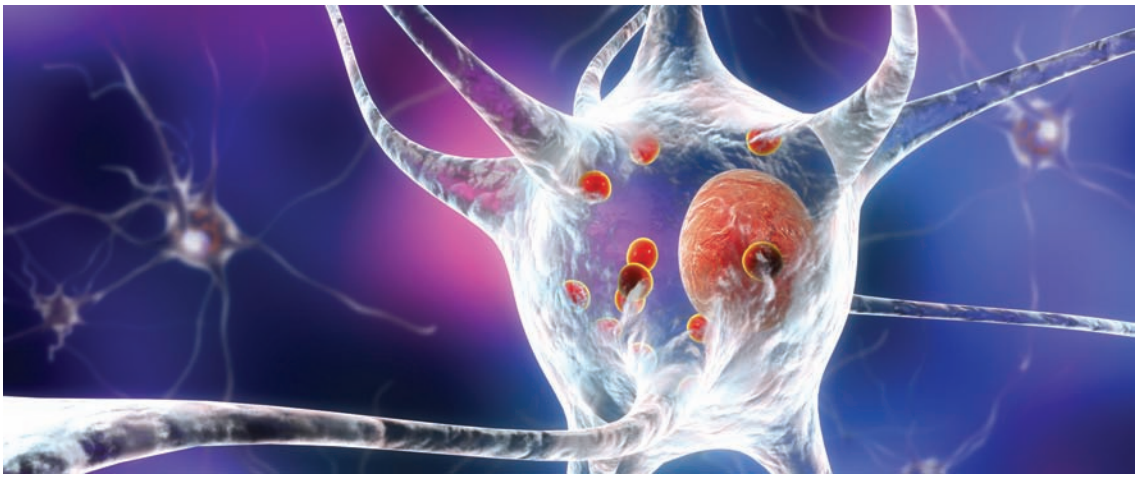
City Hospital, Birmingham, England.



" Brain has great capacity in maintaining its function despite substantial structural and functional cell loss in the brain. This is well recognised in patients following cerebrovascular events (stroke) where remarkable recovery can be achieved despite significant loss of brain tissue."

Ioflupane (DaTSCAN™, GE Healthcare) can be used as an additional imaging tool to establish or confirm the diagnosis of Parkinson's and Parkinsonian syndromes. Parkinson's disease is due to progressive degeneration and loss of dopaminergic nerve terminals in the brain, located in the relatively small nuclei in the brain called the striata. Striata have essential role in maintaining normal movement and the degeneration of these dopaminergic nerve terminals in striata leads to tremor, muscular rigidity, and slow movement. Although the disease starts in the nerve terminals in the striata, it slowly progresses and results in the loss of the nerve cells which reside in another brain nucleus called "substantia nigra" located at the base of the brain. The disease can involve many other organs in the body such as autonomic nerve function and can result in depression and anxiety, memory problems, balance problems, loss of smell and sleep disturbances. Parkinson's disease is the second most common neurodegenerative disease after Alzheimer, affecting 1 in 500 people, with incidence increasing with age, but the symptoms can start as early as age of 40 or even younger. Although at present there is no cure for this condition, the disease can be controlled with appropriate medication or in some with surgery. Patients with Parkinson's should be monitored, and appropriate care and support is an essential component of management of the patients.

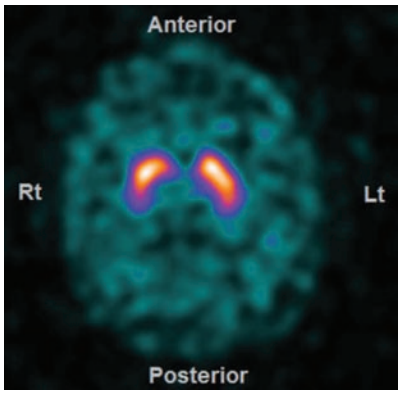


Figure 1
DaTSCAN image showing normal uptake in striata with normal relative background activity.

In patients presenting with classic signs and symptoms, the diagnosis can be made clinically, response to treatment can also help establish the diagnosis. However symptoms can be minimal and non-specific in particular in the early presentation. In some cases the clinical diagnosis can be challenging when minimal symptoms are difficult to assess and can be confused with other more benign conditions such as essential tremor. Even response to treatment can be difficult to assess, as response to treatment is variable, and one should take into account the "placebo" effect of drugs, which may lead to wrong diagnosis of Parkinson's disease.

Brain has great capacity in maintaining its function despite substantial structural and functional cell loss in the brain. This is well recognised in patients following cerebrovascular events (stroke) where remarkable recovery can be achieved despite significant loss of brain tissue. This is also true in Parkinson's disease. There is preservation of normal movement and function despite significant progressive loss of dopaminergic nerve terminals in striata. Imaging and post mortem studies have shown that by the time Parkinsonian symptoms appear almost 60% of the dopaminergic nerve terminals in the striata have already been affected by the disease and lost. This means that even in the very early clinical Parkinson's disease there could be substantial functional damage, so that functional imaging with DaTSCAN can be highly positive, even in patients with minimal and with very early clinical presentation. Establishing diagnosis of PD early on, can minimise the unnecessary investigations and help plan treatment and care, controlling the disease in patients from early on in the

disease. With control and intervention most people with Parkinson's can now achieve a near normal life expectancy.

Ioflupane (DaTSCAN) is a radiopharmaceutical molecule which has been labelled with tiny amount of radioactive iodine 123 (^{123}I). DaTSCAN binds to special transporters (dopamine transporters) in the presynaptic dopaminergic nerve terminals in the striata. In Parkinson's disease and Parkinsonian syndromes, DaTSCAN uptake in the striata is significantly reduced by the time patients exhibit early symptoms, establishing the diagnosis with more certainty than clinical presentation alone.

Ioflupane (DaTSCAN) is injected in to the vein and is then slowly taken up by the dopaminergic nerve terminals in striata. Three hours after the injection, using a special technique called Single Photon Emission Tomography (SPECT imaging), images of the head are acquired to assess DaTSCAN uptake in the striata. SPECT imaging is acquired using special gamma cameras which is widely available in any nuclear medicine department. The imaging itself takes around 40 minutes. The whole procedure is simple, and widely available in most nuclear medicine departments.

DaTSCAN is useful in particular in patient with clinically uncertain diagnosis of Parkinson's disease. Several clinical follow up studies have demonstrated the accuracy of DaTSCAN in patients with uncertain diagnosis of PE, establishing the diagnosis many years before the clinical diagnosis could be made with certainty. This technique may also prove useful in earlier diagnosis, before the symptoms become prominent. The following cases are examples of use of DaTSCAN in patients with clinically uncertain diagnosis of PD.

CASE 1

82-old-man had noticed tremor when he was writing or lifting a cup of coffee. His wife also noticed that he was acting out his dreams (REM sleep disorder). He was referred to movement disorder specialist with possible diagnosis of Parkinson's disease. He drank moderately (<10 units a week), and had only two or three small cups of coffee in a day. On examination he had no obvious speech problems, had normal gait, normal arm swing with no rigidity or bradykinesia. However there was mild action tremor on outstretched hand. There was no dysarthria or dysdiadochokinesia (impaired ability to perform rapid, alternating movements). There was no family history of tremors, Parkinson's disease or other neurological conditions. Possibility of early Parkinson's disease was entertained and referred for a DaTSCAN for further assessment.

DaTSCAN showed normal ioflupane uptake in both striata with normal background activity (figure 1). Quantification confirmed this normal uptake showing normal striatal specific binding ratios (SBR) in both striata (figure 2) with normal putamen to caudate ratios. There was no evidence of loss of dopaminergic nerve terminals. This normal appearance is against the diagnosis of PD, PD+, or DLB. Normal appearance is seen in normal individuals and also in those with essential tremor or drug induced Parkinson's. DaTSCAN excluded Parkinson's disease in this patient.

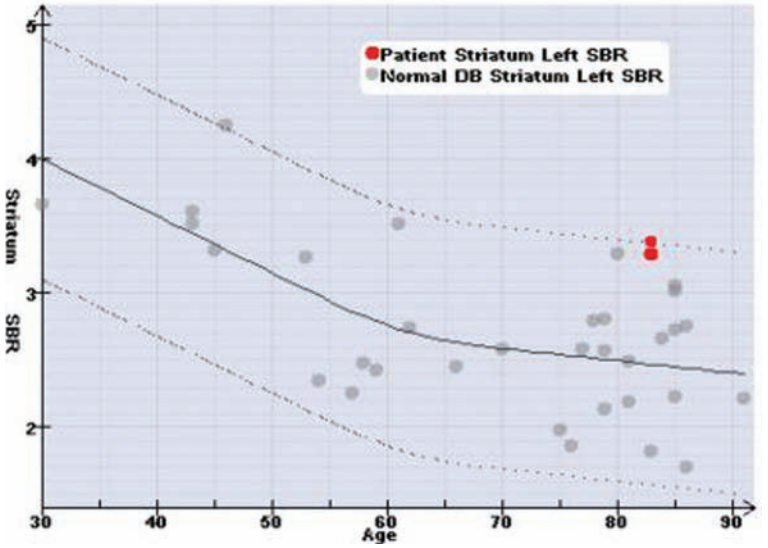


Figure 2
Patient's Striatal specific binding ratios (SBR) are relatively high and well within normal range (red dots). Note that there is no known disease/condition associated with high SBR. The grey dots represent the SBR in participants in the normal database. Solid line is the mean normal SBR and the dotted lines indicate the limits for values within two standard deviations from normal mean. SBR value for most patients (but not all patients) with Parkinson's disease falls below two standard deviations from mean normal.

CASE 2

77-year-old gentleman, a keen retired golfer, was referred to a movement disorder specialist clinic. He is left handed, and noted left hand resting tremor for a few months with no other symptoms. He is an independent person living with his wife. No memory issue was noted. On physical examination he had a mild form of resting tremor at the left hand. No rigidity was noted. A possible mild bradykinesia was noted on left hand. He had a normal gait. No dysphonia was noted. The specialist arranged a DaTSCAN to assess for Parkinson's disease.

DaTSCAN showed reduced ioflupane uptake in both striata with typical abnormal "dot" appearance of the striata (loss of uptake in putamen) (figure 3).

" DaTSCAN is useful in particular in patient with clinically uncertain diagnosis of Parkinson's disease. "

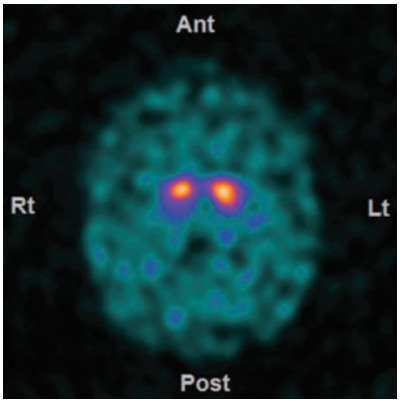


Figure 3
Typical "dot" appearance of striata in a patient's with Parkinson's disease. The loss of normal "comma" shape of striata is due to preferential loss of dopaminergic nerve terminals in the putamen relative to caudate. However a balanced loss of dopaminergic nerve terminal may retain the "comma" shape, with overall reduction in ioflupane uptake in the striata.

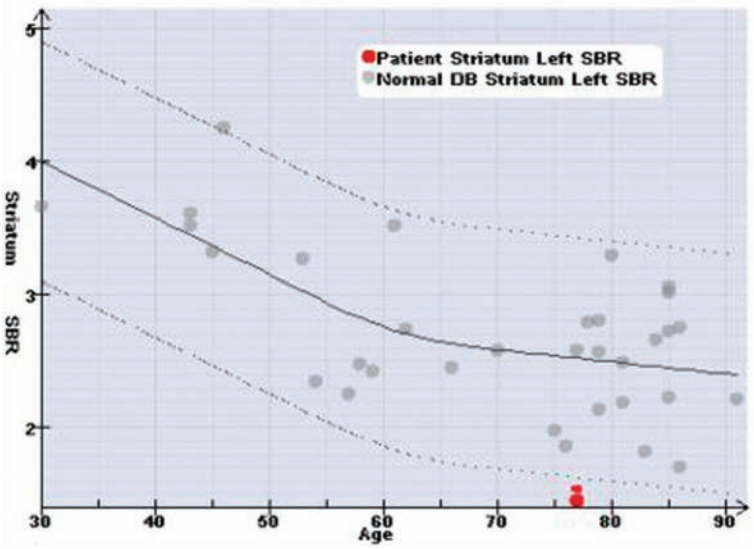


Figure 4
Both right and left striatal SBR is below two standard deviation of the normal range for the patient age (red dots). This is seen in patients with loss of dopaminergic nerve terminals in the striata. Note that the SBR value is age specific as there is also some normal decline of SBR with age and the values have to be matched with patient age.

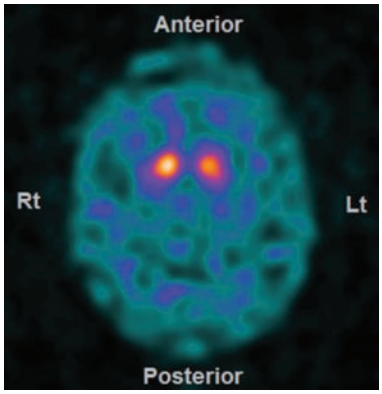


Figure 5:
Typical abnormal appearance of a DaTSCAN with classic abnormal "dot" shaped striata, and relatively high appearance of background activity. Note that the appearance of relatively higher background activity is due to reduced striatal uptake and visual effect of scaling of the images, rather than a true rise in background activity.

Quantification confirmed this showing reduced striatal DaTSCAN specific binding ratios in both striata (figure 4) with bilaterally reduced putamen to caudate ratios (preferential loss of dopaminergic nerve terminals in putamen component of the striata is a classic finding in IPD). The findings confirmed the loss of dopamine allergic terminals in both striata. This is seen in patients with IPD or PD+. One would expect normal uptake in patients with essential tremor or drug-induced (post-synaptic) Parkinsonism.

Patient was reviewed in the clinic with the result of the scan, and commenced on treatment for Parkinson's disease.

CASE 3

72-year-old lady was referred to movement disorder specialist with asymmetric onset tremor at rest, which is high amplitude without much other features of Parkinson's disease and lack of response to Co-careldopa. There are no other features of rigidity or bradykinesia. DaTSCAN was requested to assess further.

DaTSCAN showed visually reduced uptake in putamen on both sides, with typical abnormal "dot" appearance of both striata, and visually relative raised background activity (figure 5). Quantification confirmed the visual findings, showing reduced striatal Specific Binding Ratio (SBR) on both sides (figure 6). Quantification also showed reduced putamen to caudate ratios on both sides. These findings indicate loss of pre-synaptic dopaminergic nerve terminals in both striata consistent with a diagnosis of idiopathic Parkinson's disease or Parkinsonian syndrome.

These cases demonstrate the usefulness of DaTSCAN in patients with mild clinical presentation, when the clinical diagnosis could be difficult. As case 3 demonstrates, even a clinical trial of anti-Parkinsonian drugs may not be diagnostic, as response to treatment could be variable. However it is important to emphasise that in many cases confident clinical diagnosis can be made by experienced clinicians (up to 80% accuracy achieved by movement disorder specialists), and DaTSCAN imaging should be reserved for the more difficult cases with uncertain clinical diagnosis of PD, in particular in those with non-specific early symptoms. ■

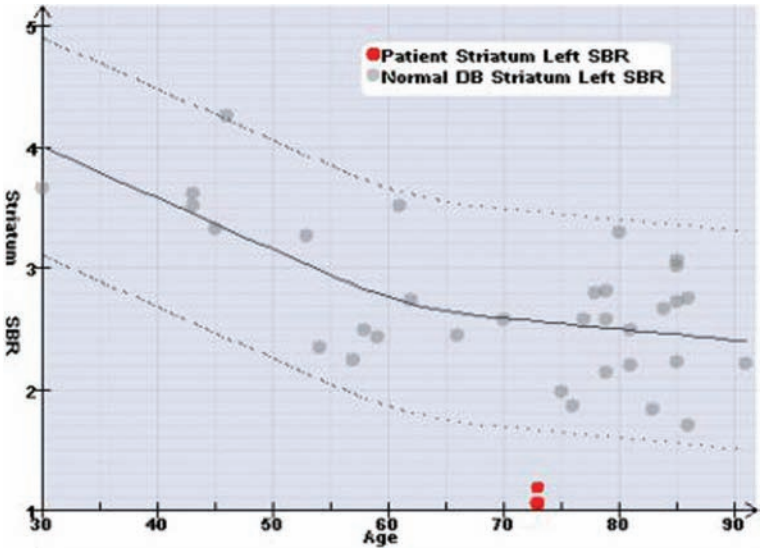


Figure 6
In this patient the SBR value is 3.44 standard deviation below the normal mean (red dots with z-score of -3.44). This indicates severe loss of dopaminergic nerve terminals consistent in both striata. In Parkinson's disease the disease almost always affects both striata, but is often asymmetric. In patients with predominantly one sided symptoms, although the disease affects both striata, the loss of dopaminergic nerve terminals is more severe in striatum contralateral to the side with prominent symptoms.

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References: 1. Bajc M, et al. EANM guideline for ventilation/perfusion single photon-emission computed tomography (SPECT) for diagnosis of pulmonary embolism and beyond. Eur J Nucl Med Mol Imaging 2019; 46(12): 2429-245. 2 | 2. Leblanc M, et al. CANM guidelines for Ventilation/Perfusion (V/P SPECT) in Pulmonary Embolism. Nov 2018; available from https://canm-acmn.ca/guidelines

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CANM Annual Scientific Meeting 2020

October 8-10, 2020

Brookstreet Hotel, Ottawa, Ontario

L'Association canadienne de Médecine nucléaire continue de travailler en étroite collaboration avec les différentes Associations et Sociétés de Médecine nucléaire dans le monde. La survenue de la crise du COVID-19 nous oblige a continuellement nous adapter a la situation. Dans ce contexte nous avons reporté notre congrès annuel au 8-10 octobre 2020 à Ottawa . Nous avons dû reporter la session de formation de nos résidents à 2021. Plus que jamais nos membres collaborent étroitement avec leurs autorités sanitaires pour assurer les services essentiels de Médecine nucléaire.

MERCI À VOUS TOUS

Collègues, technologues, physiciens, ingénieurs, radiochimistes, industriels, préposés a nos patients, personnel du secrétariat, les employés de l'entretien ménagé, les gardiens de sécurité, les bénévoles et beaucoup nos patients pour leur compréhension et leurs escortes, ambulanciers et infirmières, autorités hospitalières.

On ne peut également que remercier nos confrères spécialistes et omnipraticiens et résidents pour leur indéfectible support et disponibilité. L'ACMN continuera de collaborer aux magazines LePatient et le Epatient mais pour le moment seulement en version électronique. Les versions magazine suivront aussitôt que possible. **www.lepatient.ca • www.nmpangea.com**

François Lamoureux
Président

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CANM-ACMN OTTAWA CANADA	8-10 OCTOBRE 2020
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THERANOSTICS WORLD CONGRESS SANTIAGO CHILI	19-21 MARS 2021
CANM-ACMN HALIFAX CANADA	8-10 AVRIL 2021
AMSMNQ ESTÉREL CANADA	27-30 MAI 2021
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WFNMB KYOTO JAPAN	7-11 SEPTEMBRE 2022

The Canadian Association of Nuclear Medicine continues to work in close collaboration with the various Associations and Societies of Nuclear Medicine in the world. The onset of the COVID-19 crisis forces us to continually adapt to the ongoing situation. In this context we have postponed our annual conference to October 8-10, 2020 in Ottawa. We also have had to postpone the training session of our residents to 2021. More than ever, our members are working closely with their respective health authorities to provide essential Nuclear Medicine services.

TO ALL OF YOU, THANK YOU !

Colleagues, technologists, physicists, engineers, radio-chemists, industrialists, patient attendants, secretarial staff, housekeeping staff, security guards, volunteers, paramedics, nurses and hospital authorities.

We also cannot thank our fellow specialists, general practitioners, and residents enough for your unwavering support and availability. CANN will continue to collaborate with the magazine ThePatient and e-Patient, but for now the electronic format only will be available. The magazine version will follow as soon as possible. **www.lepatient.ca • www.nmpangea.com**

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SNMMI NEW ORLEANS	JUNE 13-16 2020 Virtual meeting
CANM-ACMN OTTAWA CANADA	8-10 OCTOBER 2020
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In the investigation of movement disorders in which Dopamine transporter loss is a potential component, most commonly Parkinsonism, and there is diagnostic uncertainty, imaging with 123I-ioflupane can provide important information. As a Health Canada approved imaging agent is now available, the Canadian Association of Nuclear Medicine has produced this set of guidelines to aid clinicians in utilizing and performing the test in the evaluation and treatment of Canadian patients. It has been produced by a group of expert Nuclear Medicine Physicians and Movement Disorder Neurologists assessing best practices in Canada, Europe and the United States.

L'évaluation de la densité des récepteurs dopaminergiques est un paramètre déterminant dans l'évaluation des troubles du mouvement, particulièrement pour le diagnostic de la maladie de Parkinson et des syndromes parkinsoniens. De nombreuses études cliniques ont démontré la contribution de l'imagerie scintigraphique des noyaux caudés et du pallidum au moyen de la molécule d'ioflupane marquée à l'iode 123. L'administration intraveineuse de ce radiopharmaceutique qui est maintenant approuvé par Santé Canada permet de quantifier la densité de ces récepteurs et procure au cliniciens un outil diagnostique précieux pour l'évaluation des troubles du mouvement.

L'Association Canadienne de Médecine Nucléaire a demandé à un groupe d'experts en médecine nucléaire et en neurologie d'établir des lignes directrices pour l'utilisation de l'ioflupane en pratique clinique au Canada sur base des pratiques médicales en vigueur au Canada, en Europe et aux Etats-Unis.

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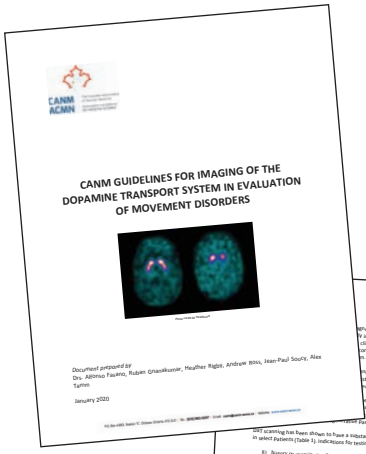

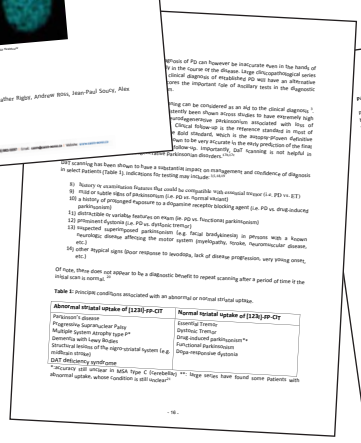

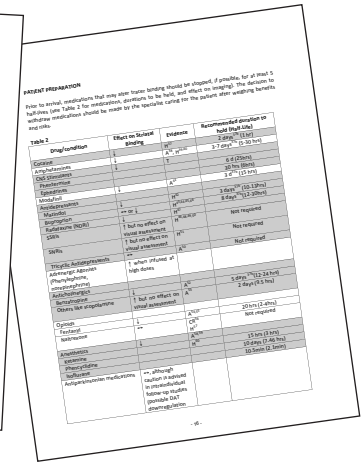

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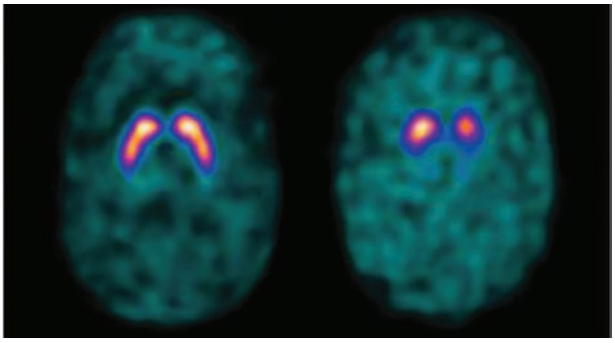
CANM GUIDELINES FOR IMAGING OF THE DOPAMINE TRANSPORT SYSTEM IN EVALUATION OF MOVEMENT DISORDERS



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Document prepared by
Drs. Alfonso Fasano, Ruban Gnanakumar, Heather Rigby, Andrew Ross, Jean-Paul Soucy, Alex Tamm

January 2020

ABSTRACT

In the investigation of movement disorders in which Dopamine transporter loss is a potential component, most commonly Parkinsonism, and when there is diagnostic uncertainty, imaging with 123I-ioflupane can provide important information. It is recommended in the following situations:

1) history or examination features that could be compatible with essential tremor (i.e. PD vs. ET)
2) mild or subtle signs of parkinsonism (i.e. PD vs. normal variant)
3) a history of prolonged exposure to a dopamine receptor blocking agent (i.e. PD vs. drug-induced parkinsonism)
4) distractible or variable features on exam (ie. PD vs. functional parkinsonism)
5) prominent dystonia (i.e. PD vs. dystonic tremor)
6) suspected superimposed parkinsonism (e.g. facial bradykinesia) in persons with a known neurologic disease affecting the motor system (myelopathy, stroke, neuromuscular disease, etc.)
7) other atypical signs (poor response to levodopa, lack of disease progression, very young onset, etc.)

The only contraindications include:

Absolute:

1. Pregnancy.
2. Inability to cooperate with brain imaging.
3. Known hypersensitivity to the active substance or to any of its excipients. An iodine allergy is not an absolute contraindication.

Relative:

1. Breastfeeding.

Patient preparation, obtaining history and ensuring the patient is not on interfering agents is vital. Additionally, exam acquisition parameters and patient positioning are an integral component to obtaining a diagnostic exam and should be followed.

The report should provide an overall impression of scan as Normal or Abnormal.

Interpretation can involve both qualitative assessment and semiquantitative analyses by physicians trained to assess the images.

The referring clinician can then utilize the results of the 123I-ioflupane scan to best manage the patient's condition.

RÉSUMÉ

CANADIAN ASSOCIATION OF NUCLEAR MEDICINE GUIDELINES FOR IMAGING OF THE DOPAMINE TRANSPORT SYSTEM IN EVALUATION OF MOVEMENT DISORDERS

INTRODUCTION

The Canadian Association of Nuclear Medicine (CANM) strives for excellence in the practice of diagnostic and therapeutic nuclear medicine by promoting the continued professional competence of nuclear medicine specialists, establishing guidelines of clinical practice, and encouraging biomedical research. We work with all professionals in

nuclear medicine to ensure that Canadians have access to the highest quality nuclear medicine services.

These practice guidelines have been developed with input from clinician experts in movement disorders as well as neuroimaging through a consensus process and have been extensively reviewed and approved by the CANM Board of Directors. They are proposed as a reference tool to clinicians dealing with patients with movement disorders to help provide appropriate care. They are not considered to be inflexible rules or requirements of practice. The final decision regarding the ordering and use of any procedure or course of action is made by the clinician based on the situation and the clinician's judgement. These guidelines are intended for clinicians as well as nuclear medicine physicians to aid in understanding the test, provide guidance with appropriate ordering as well as for interpretation and reporting.

Clinical diagnosis of Parkinsonism is straightforward and arrived at based on clinical observations without the use of additional tests in the vast majority of cases. However, for incomplete syndromes, or an overlap between multiple concurrent conditions especially in early stage presentation, utilizing imaging of the dopamine transport system provides an improvement in diagnostic accuracy.[1,2,3]

N-v-fluoropropyl-2b-carbomethoxy-3b-(4-123I-iodo-phenyl) nortropane (123I-ioflupane) is a molecular imaging agent used to demonstrate the location and concentration of cell membrane dopamine transporters (DaTs) located on axon terminals of nigral dopaminergic projection neurons. It has shown efficacy for detecting degeneration of the dopaminergic nigro-striatal pathway, allowing better separation of patients with essential tremor from those with Parkinsonian syndromes, as well as differentiating between some causes of Parkinsonism (e.g. functional/psychogenic or iatrogenic forms).

This document provides information and guidance for the indications, technical aspects, interpretation, and reporting of DaT single photon emissions computed tomography (SPECT) scans with 123I-ioflupane. These have been developed using the previous work of the European Association of Nuclear Medicine and the Society of Nuclear Medicine and Molecular Imaging.[4,5,6]

INDICATIONS

Making a diagnosis of idiopathic Parkinson's disease (PD) generally relies on the identification of cardinal motor signs and the absence of features indicative of another disease with the support of levodopa responsiveness. In the vast majority of cases, the diagnosis of PD can be made based entirely on the clinical assessment. Up until 2015, the most widely accepted clinical criteria for PD diagnosis was the UK Brain bank criteria.[6] In 2015, the International Parkinson and Movement Disorder Society published new guidelines that have been implemented in the 2nd edition of the Canadian Guideline for PD.[7,8]

The clinical observations useful in the diagnosis of PD can however be inaccurate even in the hands of experienced neurologists, particularly early in the course of the disease. Large clinicopathological series estimate that 10-25% of patients with a clinical diagnosis of established PD will have an alternative diagnosis at autopsy.[6,9,10,11] This underscores the important role of ancillary tests in the diagnostic work-up of select patients with Parkinsonism.

In cases of diagnostic uncertainty, DaT scanning can be considered as an aid to the clinical diagnosis[3]. Abnormal uptake of [123I]-FP-CIT has consistently been shown across studies to have extremely high sensitivity and specificity in cases of neurodegenerative parkinsonism associated with loss of nigrostriatal dopamine neurons.[12,13,14,15,16,17]

Clinical follow-up is the reference standard in most of these studies but is only a surrogate of the gold standard, which is the autopsy-proven definitive diagnosis. However, DaT imaging has been shown to be very accurate in the early prediction of the final clinical diagnosis obtained after long term follow-up. Importantly, DaT scanning is not helpful in differentiating between neurodegenerative parkinsonian disorders.[17b,17c]

DaT scanning has been shown to have a substantial impact on management and confidence of diagnosis in select patients (Table 1). Indications for testing may include:[3,5,18,19]

1) history or examination features that could be compatible with essential tremor (i.e. PD vs. ET)
2) mild or subtle signs of parkinsonism (i.e. PD vs. normal variant)
3) a history of prolonged exposure to a dopamine receptor blocking agent (i.e. PD vs. drug-induced parkinsonism)
4) distractible or variable features on exam (ie. PD vs. functional parkinsonism)
5) prominent dystonia (i.e. PD vs. dystonic tremor)
6) suspected superimposed parkinsonism (e.g. facial bradykinesia) in persons with a known neurologic disease affecting the motor system (myelopathy, stroke, neuromuscular disease, etc.)
7) other atypical signs (poor response to levodopa, lack of disease progression, very young onset, etc.)

Of note, there does not appear to be a diagnostic benefit to repeat scanning after a period of time if the initial scan is normal.[20]

Table 1: Principal conditions associated with an abnormal or normal striatal uptake.

Abnormal striatal uptake of [123I]-FP-CIT	Normal striatal uptake of [123I]-FP-CIT
Parkinson's disease	Essential Tremor
Progressive Supranuclear Palsy	Dystonic Tremor
Multiple System Atrophy type P*	Drug-induced parkinsonism**
Dementia with Lewy Bodies	Functional parkinsonism
Structural lesions of the nigro-striatal system (e.g. midbrain stroke)	Dopa-responsive dystonia
DAT deficiency syndrome	

*:accuracy still unclear in MSA type C (cerebellar) **: large series have found some patients with abnormal uptake, whose condition is still unclear

Variable findings

DaT imaging is a reliable surrogate of nigro-striatal degeneration and some conditions (PD in particular) are always associated with it, thus explaining the diagnostic role of SPECT scans with ^{123}I-ioflupane. In some condition however, the impairment of the nigro-striatal fiber is variable and so is the striatal uptake.

'Vascular parkinsonism' has undergone a drastic nosologic revision in recent years and it is now acknowledged that it is often an over-

diagnosed condition in patients with degenerative diseases also featuring vascular changes of the white matter (the so-called "pseudovascular parkinsonism").[22] In some cases of pseudovascular parkinsonism a more diffuse and symmetrical reduction of uptake is observed[23] often with irregularities in the profile of the putamen. In "definite" vascular parkinsonism there is an ischemic or hemorrhagic stroke involving the substantia nigra and/or nigrostriatal pathway and DaT imaging is positive. Most of these cases are unilateral parkinsonism. By contrast, DaT is normal in "vascular pseudoparkinsonism" (e.g., akinetic mutism resulting from bilateral mesial frontal strokes or apathetic depression from bilateral striatal lacunar strokes).[24]

Cortico-basal syndrome (CBS) is the most challenging movement disorder from a diagnostic standpoint as its underlying pathology is cortico-basal degeneration only in a minority of cases (other being caused by progressive supranuclear palsy (PSP), Alzheimer or even prion pathology). Not surprisingly DaT imaging is variable depending on the underlying pathology, with some cases showing normal uptake.[25]

A similar scenario is seen in **orthostatic tremor** (OT), in which an abnormal DaT is supposed to be found in the so-called 'plus' forms (as opposed to primary or secondary forms), occurring when OT is associated with PD or other cases of degenerative parkinsonism.[26]

Likewise, **primary progressive freezing of gait** may herald many different degenerative processes and an abnormal DaT is seen in cases caused by PSP pathology while a normal uptake is more often seen in cases evolving towards CBS or motor neuron diseases.[27]

Holmes tremor is another heterogenous condition supposedly caused by a strategic (usually vascular) lesion involving both the nigrostriatal system and the cerebello-thalamic fibers. However, due to the variability of lesions, a normal DaT study is still possible (e.g. in case of lesions not involving the midbrain).[28]

Many other conditions are associated with variable involvement of the nigra which therefore present with different DaT imaging appearances (e.g. Huntington disease) and in some cases an improvement of the uptake has been reported following treatment, such as in Normal Pressure Hydrocephalus (NPH). Not many papers have explored the role of DaT imaging in NPH but the following scenarios can be hypothesized: 1) an abnormal uptake in patients with co-existing PD or other degenerative conditions involving the pars compacta of the substantia nigra, 2) an abnormal uptake in patients mistakenly diagnosed with NPH while having PD or other degenerative conditions involving the pars compacta of the substantia nigra, 3) a normal uptake (e.g. in the so-called "pseudovascular pseudoparkinsonism"[29], and 4) an abnormal uptake caused by the mechanical compression of the fiber reaching the putamen.

The role of DaT imaging in research

DaT imaging has different roles in research protocols, some of which is still not fully explored but at least 5 principal applications can be listed here:

1. DaT imaging as a biomarker to assess PD progression, for example, in the Parkinson Progression Marker Initiative funded by the Michael J Fox Foundation[30]
2. Study of the regional differences in uptake to understand different PD presentations
3. Use of DaT imaging as endophenotype in populations at risk of developing PD, such as carriers of genetic mutation[31] or patients with REM sleep behavioral disorder
4. DaT scanning can be used as a marker of the protective effect of surgical[32] or pharmacological treatment.[33]

As for the last point, it should be emphasized that the DaT expression is influenced by factors other than number of dopaminergic neurons (e.g. up or downregulation influenced by drugs), thus its role in proving a disease modifying effect is object of debate.

CONTRAINDICATIONS

Absolute:

1. Pregnancy.
2. Inability to cooperate with brain imaging.
3. Known hypersensitivity to the active substance or to any of its excipients. An iodine allergy is, however, not an absolute contraindication to receiving this radiotracer.

Relative:

Breastfeeding. If possible, consider delaying the examination until breastfeeding has ceased. It is unknown if ioflupane is secreted in human milk, therefore, if administration is considered necessary, breast-feeding should be interrupted for a minimum of 1 day and up to 6 days.[34,35,36]

REQUEST/REQUISITION SUGGESTED FORMAT

The suggested format for the requisition is to have boxes to allow the referring clinician to provide the following information:

a. Description of patient symptoms and clinical question
   - For neurological symptoms, specify the type, duration, and right or left sidedness

b. Relevant past medical history
   - This would include history of brain surgery, trauma or tumor, stroke, psychiatric illness and epilepsy

c. List of current medications
   - For any medications that may affect tracer binding (see below), indicate when the medication was last taken

d. History of use of recreational drugs that affect tracer binding (see below)
   - If so, indicate when it was last taken

e. Previous brain imaging studies, including date and location of study
   - This should include CT, MRI, SPECT, PET

f. Can the patient lie still for 30-45 minutes for the test?

PATIENT PREPARATION

Prior to arrival, medications that may alter tracer binding should be stopped, if possible, for at least 5 half-lives (see Table 2 for medications, durations to be held, and effect on imaging). The decision to withdraw medications should be made by the specialist caring for the patient after weighing benefits and risks.

Table 2

Drug/condition	Effect on Striatal Binding	Evidence	Recommended duration to hold (Half-Life)
Cocaine	↓	H[37]	2 days[37b] (1 hr)
Amphetamines	↓	A[38], H[39,40]	3-7 days[37b] (5-30 hrs)
CNS Stimulants	↓	T	
Phentermine			6 d (25hrs)
Ephedrines			30 hrs (6hrs)
Modafinil	↓	A[41]	3 d[37b] (15 hrs)
Antidepressants			
Mazindol	↓	H[42]	3 days[37b] (10-13hrs)
Buproprion	↔ or ↓	H[43,44,45,46]	8 days[37b] (12-30hrs)
Radafaxine (NDRI)	↓	H[47]	
SSRIs	↑ but no effect on visual assessment	H[46,48,49,50]	Not required
SNRIs	↑ but no effect on visual assessment	H[51]	Not required
Tricyclic	↔	A[50]	Not required
Antidepressents			
Adrenergic Agonists (Phenylephrine, norepinephrine)	↑ when infused at high doses		
Anticholinergics			
Benzatropine	↓	A[52]	5 days [37b](12-24 hrs)
Others like scopolamine	↑ but no effect on visual assessment	A[53]	2 days (9.5 hrs)
Opioids			
Fentanyl	↓	A[54,55]	20 hrs (2-4hrs)
Naltrexone	↔	CR[56] H[57]	Not required
Anesthetics	↓	A[58,59]	
Ketamine		H[60]	15 hrs (3 hrs)
Phencyclidine			10 days (7-46 hrs)
Isoflurane			10.5min (2.1min)
Antiparkinsonian medications	↔, although caution is advised in intraindividual follow-up studies (possible DAT downregulation with L-DOPA)		
L-DOPA60		H[61,62]	Not required
Dopamine agonists		H[63,64]	Not required
NMDA receptor blockers		T	Not required
MAO-B inhibitors		H[65,66]	Not required
COMT inhibitors		T	Not required
Cholinesterase Inhibitors	↔	H[67]	Not required
Neuroleptics/ Antipsychotics	↔	A[68], H[69]	Not required
Estrogen replacement post menopause	↑ but no effect on visual assessment	H[70]	Not required
Menstrual cycle	↔		
Lithium	↓	CR[71]	5 days (24 hrs)

↑ increase binding, ↓ decrease binding, ↔ no effect, NDRI = norepinephrine-dopamine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitors, SNRIs = Serotonin-norepinephrine reuptake inhibitors, MAO-B = monoamine oxidase-B, COMT = catechol-O-methyltransferase, DAT = dopamine transporter. T = theoretical, H = human data, A = animal data., CR = case report

At least 1 hour prior to radiotracer injection, a single 400mg dose of potassium perchlorate or 100mg equivalent of iodide in Lugol's solution should be administered to reduce exposure of the thyroid to free ^{123}I. This is not mandatory as the radiation dose expected to the thyroid gland would be very low and it may be avoided if patients are known to have sensitivities. A dim or quiet environment is not necessary for the uptake period.

IMAGING

Set Up and Positioning

2.5 or 5-mL solution containing 185 or 370MBq of ^{123}I-ioflupane is administered intravenously as a slow bolus over roughly 20 s followed by a saline flush.[3] Binding of the radiotracer is stable between 3 and 6 hours after injection, at which point SPECT imaging can be acquired. It is encouraged that each centre optimize reproducibility and reduce variability by maintaining the same interval.[56,72,73]

Voiding is recommended prior to scanning to avoid interruptions and frequently after imaging to reduce radiation exposure. All eyeglasses, earrings, hair clips, combs or hearing aids should be removed if possible.[74] The patient should be supine with the head straight (chin in neutral position and vertical canthomeatal line) and instructed to remain still during the image acquisition. Reducing head tilt is desirable but should not jeopardize patient comfort as images can be reoriented following acquisition. The corpus striatum(caudate nucleus and putamen) and occiput are required in the field of view. A case by case strategic decision should be considered in patients with L-DOPA induced dyskinesias as whether to hold the drug. Patients with severe tremor should likely be scanned under the effect of the therapy but this noted in the report. Although rarely of use, restraint devices can be utilized to minimize movement. If movement is an issue, short-acting benzodiazepine sedation does not affect image quality and can be used if agreed upon by the patient or patient's legal representative, referring physician and the patient has arranged appropriate transport following the exam.[35]

Equipment & Image Acquisition

Detector:
Multiple detector or dedicated SPECT camera are strongly preferred over single headed cameras due to shortened scan time to achieve adequate counts at the routine doses administered for data acquisition.[35] The field of view should include the entire brain and the smallest possible, safe rotation radius should be used (typically 11-15cm).[35]

Collimator:
Low Energy High Resolution (LEHR) parallel-hole collimation is adequate, but, if available, fan-beam collimators may be preferred for improved resolution at the cost of count rate capability.

Photopeak:
The photopeak should be 159keV +/- 10%. Additional energy windows can be used for scatter correction.

Matrix:
A 128 x 128 matrix is recommended. Acquisition pixel size should be one-third to one-half of the expected resolution. Hardware

zoom may be necessary to achieve an appropriate pixel size of 3.5-4.5mm. Slices should be 1 pixel thick.

Angular Sampling, Scan Time and Total Detected Events:
3-degree angular sampling for 360 degrees of coverage (180 degrees for each head in a dual head camera) is recommended, although continuous rotation may also be used. The number of seconds per position depends on the sensitivity of the system, but usually 30-40s are required.

A minimum of 1.5 million total counts should be collected for optimal images if scatter correction is applied (otherwise >3 million). Total acquisition time will vary according to camera specifications, but is often between 30-45 minutes. Consider segmenting data acquisition into multiple sequential acquisitions which may permit exclusion of data with artefacts (i.e. exclude segments with movement artifact).

Image Processing:
Projection data in cine mode and sinograms should be displayed to assess scan quality of data, patient motion, and artifacts. Rescanning will be required for large movements, but motion correction can be applied to correct for minor movements.

Iterative reconstruction is preferred but filtered back projection is adequate. The entire brain volume should be reconstructed at the highest pixel resolution (i.e. one-pixel slice thickness).

A low-pass filter (i.e. Butterworth) is recommended and should preserve the linearity of the count rate response. Other filters may introduce artifact and are not recommended for general use. All 3 dimensions should be filtered either by 2D prefiltering of the projection data or by applying a 3D postfilter to the reconstructed data.

Attenuation correction is recommended. Attenuation maps can be measured from a sequentially or simultaneously acquired CT or transmission scan or calculated according to the Chang technique (broad beam linear correction coefficient for ^{123}I: $= 0.11 cm^{-1}$). Variance may occur with fan-beam collimators and accuracy should be verified with an appropriate phantom.

Images are reconstructed into slices in 3 standard planes (axial, coronal, sagittal). Transverse slices should be parallel to a standard, reproducible anatomic orientation, such as the anterior commissure-posterior commissure line. Correct reorientation aids visual assessment and is crucial for quantitative assessments.

Quantification assesses the ratio of activity in a structure/region of interest to activity in a reference region (generally striatum or striatal subregions compared to the occipital area (or possibly cerebellum)). Regions/volumes of interest may be drawn manually, using automated systems or voxel-based mathematical systems. For both manual and automated semiquantification, the left and right striatum as well as the caudate and putamen should be quantified separately.

INTERPRETATION

In general, visual assessment of the images is sufficient to make an accurate diagnosis when the uptake is clearly abnormal. However, the addition of semiquantification has been shown to allow readers with limited experience in the interpretation of DaT imaging to perform as well as more experienced readers. The addition of semiquantification and comparison to age matched normal values has also been shown to increase reader confidence in the interpretation of DaT imaging.

The images should be viewed using appropriate computer software, which allows for adjustment of the alignment, colour table, background subtraction or contrast. It is recommended that readers become familiar with one color scale to allow for consistency in interpretation between studies.

Visual interpretation should begin by assessing the quality of the images. Alignment of the head should be checked, as a misalignment could result in artificial asymmetry and a misinterpretation of the images. The raw images of the SPECT scan should be viewed in the cine mode or sinogram mode to assess for movement or other technical artifacts. If applicable, the possible affect of any medications known to interfere with 123I-ioflupane striatal binding should be considered. Using a fixed set of reference images at all levels (Normal to severe decrease) can aid in providing a qualitative assessment of uptake.

The striata should be assessed for their shape, extent, symmetry and intensity. On axial images in a normal study the striata will be symmetric with well defined borders and have a comma or crescent shape. Abnormal studies are characterized by decreased intensity of the striatum on one or both sides, as well as decrease in size to a circle or oval shape.

The head of the caudate and the putamen should have high contrast to the background in patients of all ages and for all colour scales. With normal aging, some decrease in striatal binding occurs in both the caudate and putamen and should be recognized to avoid overinterpretation. Activity in the head of the caudate should be compared to activity in the putamen, as when abnormal, the putamen is usually more severely affected than the caudate nucleus, especially in iPD. In a normal healthy patient, the striata should be fairly symmetric although mild asymmetry may be seen. In the disease state, abnormalities usually first become visible in the putamen contralateral to the neurological signs.

Some common patterns can be seen on visual interpretation. In Parkinson's disease, there is usually a decrease in activity in the dorsal putamen contralateral to the neurological signs and this progresses anteriorly ipsilaterally over time. In contrast, in atypical Parkinson's syndromes the abnormalities tend to be more symmetric and involve more of the caudate.

In cases of vascular parkinsonism, striatal uptake is usually normal or only slightly decreased except in cases of striatal infarcts. An infarct usually appears as a punched out defect when compared to the neurodegenerative syndrome abnormalities described above.

Correlation with available CT or MRI studies of the brain should occur and may provide additional information that could aid in accurate interpretation of studies, in particular by showing anatomic lesions that may alter the appearance of the striatal structures.

QUANTITATIVE ANALYSES

Quantification with use of validated age-matched reference values may be helpful to accurately interpret DaT imaging. Further benefits of quantification include earlier detection of disease, the ability to objectively assess loss of presynaptic dopaminergic neurons over subsequent studies and providing useful data for research and multicenter studies.

There is no universally accepted cut-off value for normal or abnormal, as quantitative data can be affected by the camera system, calibra-

tion, image acquisition protocol, post-acquisition processing including corrections and quantification protocol. Quantitative data needs to be compared to a suitable database of reference values, ideally age-matched. To use quantification, each site needs to determine a reference range by scanning a population of healthy controls or alternatively calibrate its procedure with a site that has a reference database. Cross-calibration can be done by establishing the relationship between measured uptake ratio and true activity using an anthropomorphic phantom filled with different concentrations of activity and comparing to the same done at another site.

Quantification is subject to interobserver variability especially for inexperienced readers, which may be secondary to differences in reorientation of the head and errors in placement of the reference regions of interest. However, this can be overcome with the use of automated systems to analyze volumes of interest.

For manual quantification, standardized alignment of the head should be used and the sum of at least 3 consecutive slices with standardized region of interests of at least twice the full width and half maximum represents the minimum requirement of tissue volume sampling. A consistent number of slices should be used. For automated quantification, a 3D volume of interest is preferred but the placement of the region of interest should be checked visually.

Quantitative data can be reported as striatal binding expressed as percentage of normal binding for age-matched reference uptake.

REPORT

The report should include the usual demographic information used in imaging reports at the imaging site for example the patient's name, date of birth and hospital identification number. The name of the referring physician and date of the scan should also be included.

a) History
The provided clinical history should be included in the report, including the type, duration and side of neurological symptoms and any relevant past medical history.

State whether the patient is on any drugs known to interfere with 123I-ioflupane binding, and if so which drugs.

If sedation was used, state the dosage, route and timing in relation to the scan.

b) Technique
State the injected dose the radiopharmaceutical, the elapsed time between the injection of the radiopharmaceutical and image acquisition.

c) Findings
Describe any factors that limit image quality, such as patient motion.

Describe the visual interpretation of striatal binding as normal or abnormal. If abnormal, report the location and severity of reduced striatal binding. For severity of reduced binding descriptions such as mild, moderate and severe are suggested. If relevant, compare the findings with any previous 123I-ioflupane studies for the patient. Correlate with previous ^{18}F-FDG PET, CT or MRI studies of the brain, as applicable.

If semiquantitative analysis was performed, report the values and reference range. An age matched reference range is preferred.

d) Impression
State overall impression of scan as Normal or Abnormal.

An abnormal study indicates that a presynaptic striatal dopaminergic terminals deficit is present and can be seen in conditions such as PD, PSP, multiple system atrophy, and dementia with Lewy bodies. The reporting physician should avoid referring to a clear diagnosis for example, PD, as these remain a clinical diagnosis for which. DATscan provides supportive information. If required to clarify the diagnosis, further studies such as ^{18}F-FDG PET may be recommended.

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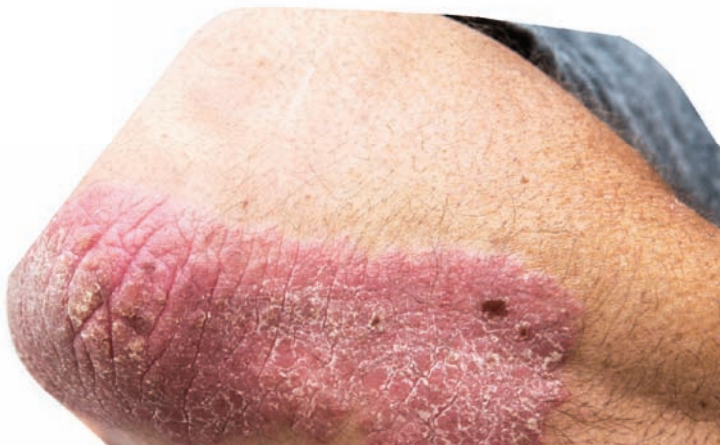

THERANOSTICS A PORTMANTEAU OF THERAPEUTICS AND DIAGNOSTICS

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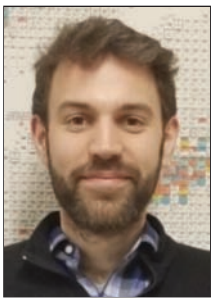

Guillaume Chaussé MD, FRCPC
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Background

Theranostics, a portmanteau of therapeutics and diagnostics, is a field of medicine which combines targeted therapy based on similarly targeted diagnostic tests. In the context of nuclear medicine this usually means molecular ligands targeting a specific part of a cancer cell which are then attached either to an imaging or a therapeutic radioisotope. Of course, both imaging performance and treatment delivery require the identification of a highly expressed and specific tumor target.

Neuroendocrine tumors arise from a network of cells that are widely spread throughout the human body. These cells have nerve-like and hormone-secreting features and give rise to tumours of various aggressiveness, with or without the ability to secrete hormones such as insulin, serotonin and others. Gastro-intestinal tract, pancreas and lungs are the most common primary sites of neuroendocrine tumor occurrence; the liver is often involved when metastases occur. The cancer can manifest itself either in the form of growth of a mass (primary lesion or metastases), effects of the secreted hormones or be found incidentally, usually on imaging done for other reasons. The diagnosis of neuroendocrine tumours is often delayed by years, because the symptoms associated with NETs can also be typical for dozens of other diseases and conditions. Characteristics of the better differentiated NETs include expression at the cellular surface of the so-called somatostatin receptor. This receptor binds strongly to the naturally occurring hormone somatostatin and also to similar man-made molecules known as somatostatin analogs (SSA).

SSTR Imaging

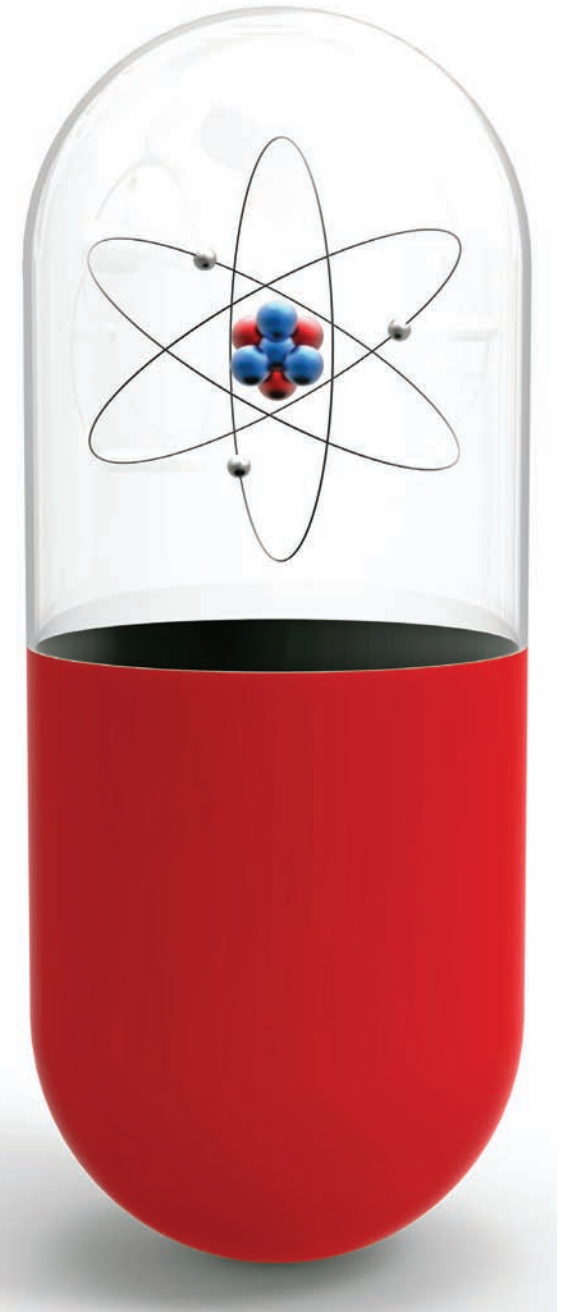
Somatostatin transmembrane receptors (SSTR) can be targeted with imaging probes to yield specific imaging techniques to stage and follow neuroendocrine tumors. The first widely used radiotracer for was ^{111}In-Octreotide. Indium-111 emits gamma photons and is imaged with lower resolution gamma cameras; it has a relatively long half-life of 67 hours. It often requires delayed imaging over a few days to account for slower tumor uptake and delayed clearance and lacks strong accumulation in many neuroendocrine tumors.

New somatostatin analog imaging agents such as 68Ga-DOTATOC, ^{68}Ga -DOTATANOC and ^{68}Ga -DOTATATE use higher resolution positron emission tomography (PET) scanners and have a higher affinity to the receptor itself, resulting in higher levels of accumulation at tumor sites and therefore easier detectability. It has been reported that SSTR PET impacts patient management in more than 50% of cases.

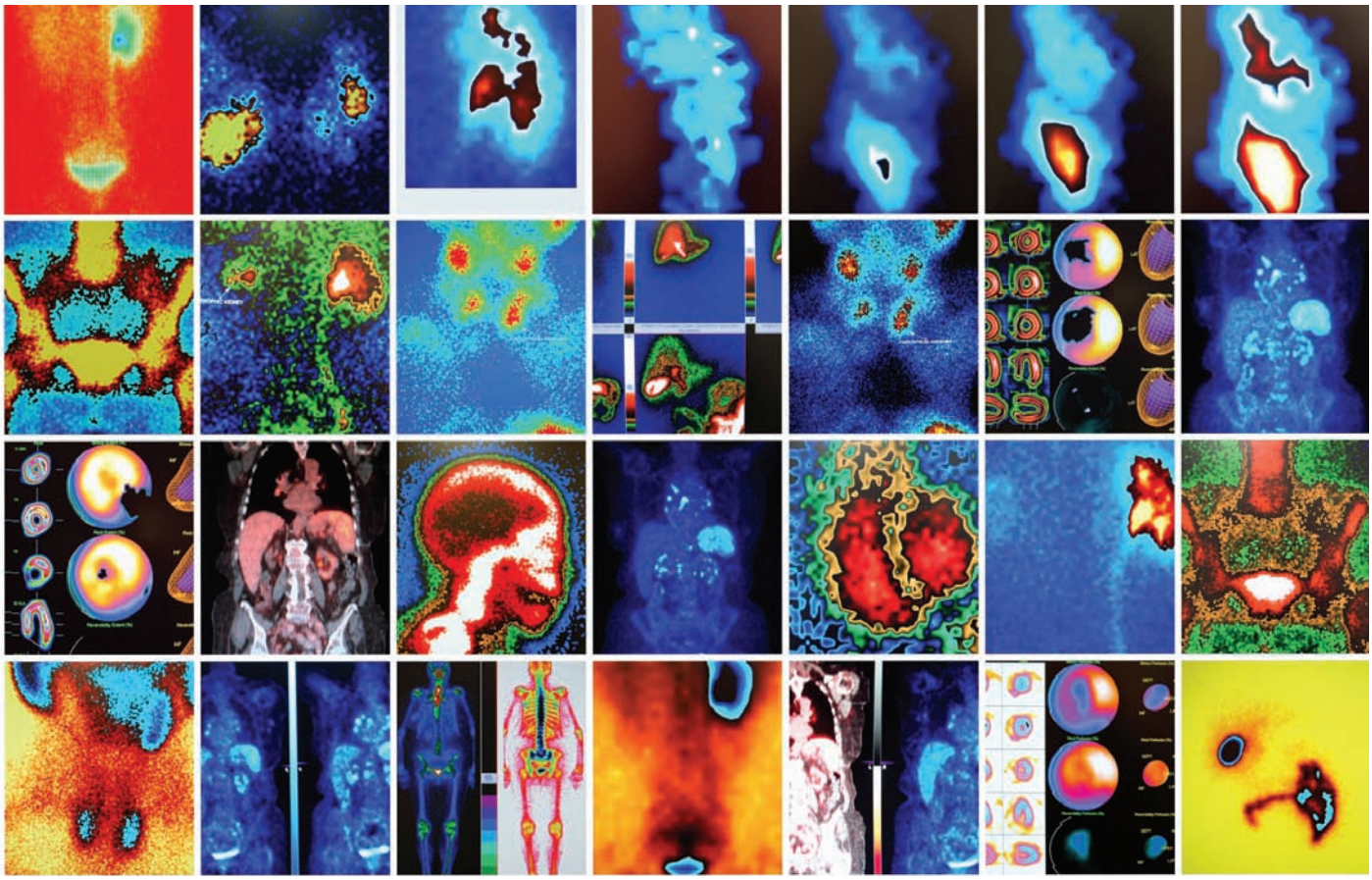
The uses of SSTR imaging include making a diagnosis, defining the extent of the disease (staging), assessing response to therapy or recurrence, and assessing eligibility for SSTR radiopeptide therapy. Patient preparation for SSTR PET is simple and the entire procedure can be performed in a little as 90 minutes.

SSTR Radiopeptide Therapy

The PROMID (2009) and CLARINET (2014) trials showed that most patients with well-differentiated NET will benefit from non-radioactive or "cold" SSA therapy. These non-radioactive SSA molecules mimic somatostatin and yield good symptomatic response by



" The diagnosis of neuroendocrine tumours is often delayed by years, because the symptoms associated with NETs can also be typical for dozens of other diseases and conditions "



anti-secretory effect in secretory tumors, and improve tumoral control by inhibiting tumor growth. Cold SSAs are the appropriate first line of therapy for most unresectable well-differentiated, slow-growing secreting or non-secreting NETs. Additionally, everolimus – another inhibitor of tumor growth - and some chemotherapy agents are used, especially when the tumors are more aggressive.

The NETTER-1 trial was a randomized controlled trial that showed clear benefit of SSTR radiopeptide therapy with ^{177}Lu-DOTATATE for metastatic or unresectable small bowel NETs, compared to a control group receiving high-dose SSAs. Since the mechanism of tumor accumulation is the same as for the imaging agents (e.g. ^{68}Ga-DOTATATE), SSTR radiopeptide therapy is therefore used exclusively in patients with demonstrated high tumor uptake on SSTR imaging. It is indicated for unresectable or metastatic gastroenteropancreatic NETs which progress under cold SSA therapy, and should be considered in progressing SSTR-positive NETs of others origins as well.

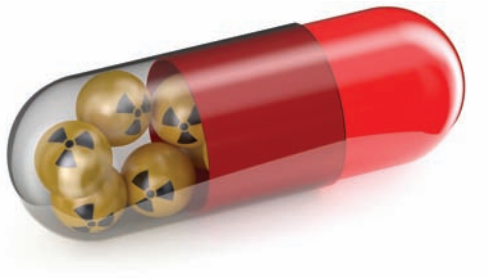
Ongoing Research

Currently, both imaging and therapy techniques are being revisited, this time using somatostatin antagonists. Although imaging studies appear to demonstrate higher tumor uptake and detectability with antagonists, especially in the liver, preliminary therapy results are equivocal with regard to demonstrating superiority over SSTR agonist treatment, with concerns being expressed for higher toxicity, including bone marrow suppression.

As well, radioisotopes more potent than lutetium-177, such as actinium-225 - an alpha emitter - are being investigated with promising results. Alternate routes of administration, including intra-arterial delivery to the liver, also appear to be helpful by delivering most of the dose directly to the location of the largest burden of the disease.

Conclusion

SSTR are highly expressed in neuroendocrine tumors and allow for unmatched detectability using sophisticated PET radiotracers. SSTR radiopeptide therapy has a defined role as a second- or third-line option in progressing well-differentiated metastatic or unresectable NETs with positive SSTR imaging. ■



" Somatostatin transmembrane receptors (SSTR) can be targeted with imaging probes to yield specific imaging techniques to stage and follow neuroendocrine tumors. "

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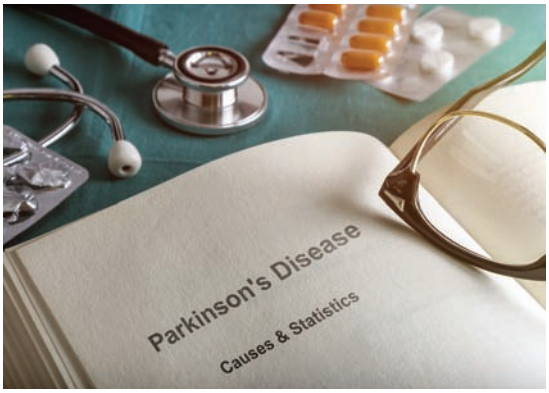
PARKINSON'S DISEASE
CLINICAL FEATURES AND DIAGNOSIS

" The diagnosis of PD is based on accurate history and physical examination, and is predicated on the clinician's ability to recognize the cardinal signs and associated symptoms, especially in the early stages. "

Parkinson's disease (PD) is the second most prevalent neurodegenerative disorder after Alzheimer's disease, and affects between 100 and 200 per 100,000 people in North America. While relatively uncommon in younger populations, the incidence of PD increases rapidly in people over 60 years old, with a mean age at diagnosis of 70 years, and epidemiologic studies suggest that men have a higher risk than women for developing the disease. PD is associated with dopaminergic neuron loss and nigrostriatal degeneration due to the accumulation of proteinaceous deposits that stain positively for alpha-synuclein (also known as *lewy bodies*). While PD is the most common cause, atypical variants also include progressive supranuclear palsy (PSP), multisystem atrophy (MSA) and corticobasilar degeneration (CBD).

The diagnosis of PD is based on accurate history and physical examination, and is predicated on the clinician's ability to recognize the cardinal signs and associated symptoms, especially in the early stages. Collectively referred to as *Parkinsonism*, these include resting tremor, appendicular rigidity, and bradykinesia; while gait changes and diminished postural reflexes usually occur later.



CLINICAL SIGNS OF PARKINSONISM

The canonical motor signs of PD have been recognized since James Parkinson first documented them in his landmark essay in 1917 entitled *The Shaking Palsy* (including the description of resting tremor and its differentiation from action tremor):

> *"Involuntary tremulous motion [...] in parts not in action and even when supported; with a propensity to bend the trunk forwards, and to pass from a walking to a running pace: the senses and intellects being uninjured".*

Though not explicitly highlighted in Parkinson's initial description, bradykinesia is defined as generalized slowness of movement, referring to decreased amount and/or amplitude of movement. Along with rest tremor and rigidity, bradykinesia is one of the core features of motor parkinsonism required for the clinical diagnosis of PD. Moreover, bradykinesia constitutes one of the major causes of disability in the PD population and is often described by patients as "weakness", "incoordination", or "tiredness". In the upper extremities, bradykinesia typically manifests as reduced manual dexterity and fine motor manipulation skills, often impairing dressing tasks (buttons), tying shoelaces, texting or typing. In the lower extremities, bradykinesia will often be referred to as "dragging" of one leg, or shorter (shuffling) steps. Some patients may also describe difficulty standing up from a deep chair or getting out of a car. Later in the disease festination may develop, which James Parkinson described as "an irresistible impulse to take much quicker and shorter steps, and thereby to adopt unwillingly a running pace".

PD tremor is most notable at rest, and typically described as "pill-rolling" based on its specific semiology, with an approximate frequency between 3

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and 6 Hz. Rest tremor in PD can also involve the legs, lips, jaw, and tongue; while anxiety and/or stressful situations can usually exacerbate its appearance. Tremors in other conditions, such as essential tremor (ET) or multiple sclerosis, are typically *action* tremors, in which the tremor occurs when the affected limb is being used, or *postural* tremor, when the limb is maintained in a specific position.

Occurring in up to 90% of PD patients, rigidity refers to increased resistance to passive movement around a joint, and can affect any part of the body. Like tremor and bradykinesia, rigidity usually begins on one side of the body (i.e. unilaterally). The term *cogwheel rigidity* refers to the superposition of increased tone with tremor, and can be appreciated as a ratchet-like sensation when passively manipulating a limb around a joint (most easily detected at the elbow and wrist on clinical examination). 'Cogwheeling' is thus distinct from true rigidity, which is more aptly characterized as a *lead-pipe* sensation of tonic resistance that is consistent throughout the passive movement. Patients will usually refer to "stiffness" and low-level pain when trying to articulate complaints related to rigidity.

Finally, postural instability denotes an impairment of centrally mediated postural reflexes that can often result in a sense of imbalance or precariousness that increases vulnerability to falls. Postural instability is tested clinically using the *pull test*, where the examiner applies a retropulsive force which the patient is meant to withstand in less than a few steps. Postural instability leading to falls usually does not appear until later in the course of PD, and serves as a red flag when patients with parkinsonism fall early in the course of the illness. In these situations, the presence of early and repeated falls backwards or forwards may hail another parkinsonian syndrome such as PSP or MSA, respectively.

While PD has traditionally been considered a motor system disorder, it is now generally recognized to affect almost all body systems. As such, it can involve a panoply of diverse neuropsychiatric and nonmotor manifestations in addition to the aforementioned motor signs. These include cognitive dysfunction and dementia, mood disorders, sleep disturbances, autonomic dysregulation, psychosis, impaired olfaction, and gastrointestinal issues.

" In cases where the clinical diagnosis is unclear, striatal dopamine transporter imaging using 123I-FP-CIT single-photon emission computed tomography (DaTscan™) is a useful tool in the clinician's repository. "

DIAGNOSIS AND INVESTIGATIONS

PD is a clinical diagnosis, and there are no physiologic, radiologic, or blood tests that may substitute an accurate clinical evaluation. Neurodiagnostic testing is almost always unhelpful in the work-up of suspected PD, and is not necessary in a patient with a classic presentation of PD who does not have any other neurologic signs, and who has a good response to levodopa therapy.

While neuroimaging is usually non-diagnostic in initial evaluation, magnetic resonance imaging (MRI) may have a role in excluding rare, unexpected mimics of PD, such as stroke, tumour, or hydrocephalus. Other conditions that do not involve nigrostriatal degeneration make up the extensive differential diagnosis of PD. Primary etiologies include atypical Parkinsonian syndromes, ET, psychogenic parkinsonism, normal aging, and dystonic tremor. Neurodegenerative diseases such as Alzheimer's, Huntington's, and Frontotemporal dementia should also be considered, while secondary causes include drug-induced parkinsonism, vascular parkinsonism, infectious causes (e.g. CJD), and toxic parkinsonism (e.g. carbon monoxide).

In cases where the clinical diagnosis is unclear, striatal dopamine transporter imaging using 123I-FP-CIT single-photon emission computed tomography (DaTscan™) is a useful tool in the clinician's repository. Specifically, DaTscan may be helpful in distinguishing patients with PD or other parkinsonian syndromes associated with nigrostriatal degeneration (e.g. MSA, PSP, or CBD) from controls or patients with ET. As such, DaTscan may be a useful tool in situations where a patient has longstanding ET and develops subtle Parkinsonism over time, but who does not respond to Levodopa therapy. Importantly, DaTscan cannot differentiate PD and the other parkinsonian syndromes from each another, and would be normal in cases of drug-induced parkinsonism.

SUMMARY

Parkinson's disease is a neurodegenerative disorder associated with loss of dopaminergic neurons and nigrostriatal degeneration. The cardinal features of PD are tremor, bradykinesia, and rigidity, and the diagnosis is based on clinical history and neurologic examination. As such, there are no diagnostic tests for PD. The differential diagnosis of PD is extensive, and striatal dopamine transporter imaging (DaTscan) or neuroimaging may be useful for patients in whom the clinical diagnosis is unclear, or to rule out unexpected mimics that have a lesional basis. Despite their utility in specific situations however, the available evidence suggests that DaTscan and related ancillary testing for parkinsonian syndromes is no substitute for a carefully obtained history and physical examination. ■

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Marc Hickeson, MD and

Anthony Ciarallo, MD
Nuclear Medicine, McGill University Health Center, Glen Campus, Montreal, Canada.

" Infection is defined by the invasion and multiplication of microorganisms such as bacteria, viruses, and parasites that are not normally present within the body. "

DEFINITION AND PATHOPHYSIOLOGY OF INFECTION

Infection is defined by the invasion and multiplication of microorganisms such as bacteria, viruses, and parasites that are not normally present within the body. In acute infection, damaged tissues lead to the release of large quantities of prostaglandins, histamines and bradykinins. This results in an increase in blood flow and vascular permeability leading to an increase of vascular fluids and proteins to leak into actively inflamed tissues, producing localized swelling, redness and pain.

Initially, inflammation involves the infiltration of neutrophils that begins as early as 30 minutes and reaches a maximum by 24 hours. Afterwards, macrophages gradually accumulate at the infected sites. Chronic infection differs from acute infection by the predominant presence of macrophages and less intensely increased blood flow and neutrophils accumulation.

GALLIUM IMAGING

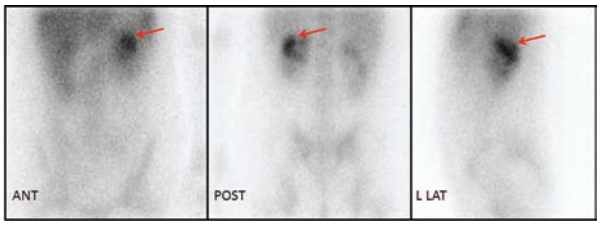
Gallium imaging is a nuclear medicine imaging procedure using Ga-67 for the detection of infection. Imaging usually is performed 24–72 h after injection of Ga-67. Specific applications include the search of a focus of infection in a patient with fever of unknown origin and the evaluation of osteomyelitis.

FEVER OF UNKNOWN ORIGIN

The definition of fever of unknown origin (FUO) was first derived by Petersdorf and Beeson in 1961. It is defined as fever of greater than 38.3 **º**C (101 **º**F) for at least 3 weeks with the failure to establish a diagnosis after 3 days of in-patient investigations or in 3 out-patient visits. Possible causes of FUO are infections, such as abscesses; tumor, particularly lymphoma; collagen disorders; inflammatory diseases and drug reactions, especially antibiotics.

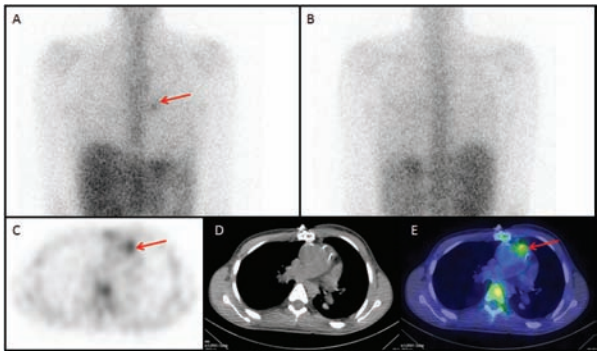
The most common cause of fever of unknown origin is infection. Investigations of FUO include a comprehensive history, physical examination, and appropriate laboratory testing, including blood cultures and sensitivities. The presence of bacteria in the blood is known as bacteremia. The risk of mortality is significantly increased in patients with bacteremia of unknown origin as compared to those with identified sources.

Figure 1



This 28-year-old female presented with fever and low back pain. Gallium images demonstrated focal gallium accumulation in the superior pole of the left kidney (arrow). The diagnosis of the scan was pyelonephritis. Subsequent urine culture was positive for E. Coli.

Figure 2



This 34-year-old male with a prosthetic pulmonary valve presented with bacteremia. Gallium scan of the whole body was ordered to localize the site of infection. Planar images of the chest in the anterior (A) and posterior (B) projections with tomography with gallium(C), CT (D) and SPECT/CT (E) demonstrated a focus of gallium activity in the prosthetic pulmonary valve (arrow).The diagnosis of infected pulmonary valve was confirmed by a transthoracic echocardiogram showing bacterial vegetation in the region of the pulmonary valve.

OSTEOMYELITIS

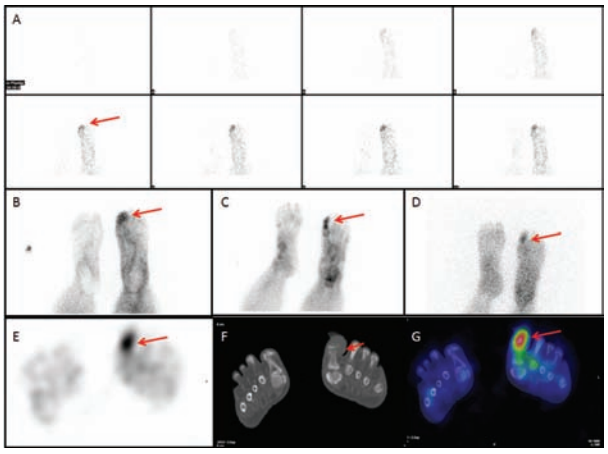
Osteomyelitis is an infection of the bone, a potentially serious condition. Bones can become infected either by the blood stream or by direct extension. In adults, direct extension is the most common mode of spread

into the bones. Osteomyelitis, once considered incurable with amputation as the only effective treatment, can currently be treated with prolonged regimen of antibiotics. Thus, the infected bone can be saved, and the spread of infection can be prevented in most patients with osteomyelitis. Risk factors for osteomyelitis include diabetes, decubitus ulcers, compound fractures (fractures in which a fragment of the bone pierces the skin), severe periodontal disease and infection of the spine.

Patients suffering from diabetes are particularly susceptible to have osteomyelitis, most often affecting the foot. Foot infections are common in patients with diabetes are associated with a high morbidity and risk of lower extremity amputation. Diabetic foot infections range in severity from being confined to the skin known as cellulitis to involving the bone known as osteomyelitis. The treatment of osteomyelitis is much more difficult than cellulitis and involves prolonged treatments with intravenous antibiotics and surgical debridement. Osteomyelitis due to diabetic foot infection is the most common cause of non-traumatic lower extremity amputation.

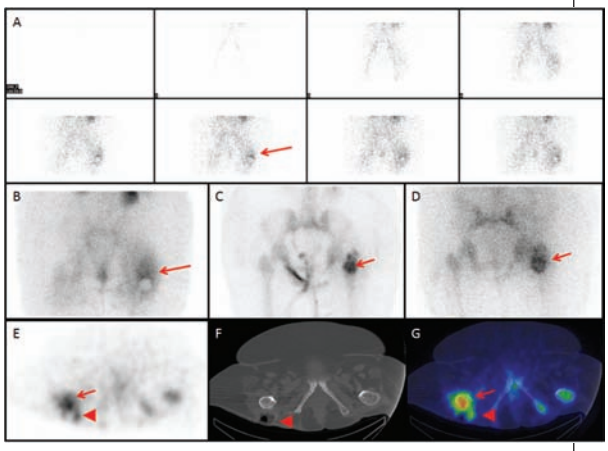
The three-phase bone and gallium scan is commonly used for the evaluation of osteomyelitis. The bone scan findings in osteomyelitis are recognized earlier than with radiographs. Early treatment of diabetic foot infections is paramount to prevent extension of the infection and to minimize the need of amputation. On the three phases bone and gallium scan, osteomyelitis is associated with increased blood flow, increased focal activity on blood pool images and intense focal uptake on delayed bone tracer images in the affected bone. Gallium imaging is used to improve the specificity to differentiate osteomyelitis from trauma. Gallium uptake is increased at the affected site with more intense uptake or non-congruent uptake as compared to on the bone scan.

Figure 3

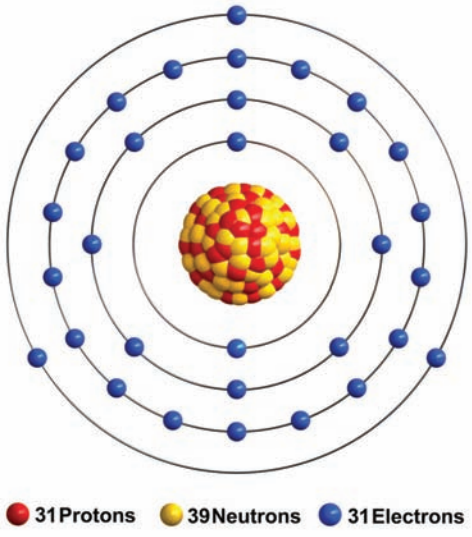


This 75-year-old male presented with a wound in the left first toe. The three-phase bone and gallium scan of the feet was positive for osteomyelitis. It demonstrated increased perfusion (long arrow) on the flow study (A), increased focal activity (long arrow) on the blood pool image (B), increased uptake (long arrow) on the delayed bone tracer images (C) and non-congruent increased activity (long arrow) in the left first toe on gallium images (D). Tomographic gallium (E), CT (F) and SPECT/CT (G) images demonstrated increased gallium activity (long arrow) associated with destruction of the proximal and distal phalanges of the left first toe (short arrow).

Figure 4



The three-phase bone and gallium scan of the pelvis and hips shown in the posterior projection was positive for osteomyelitis of the right proximal femur. It demonstrated increased perfusion (long arrow) on the flow study (A) and increased focal activity (long arrow) on the blood pool image (B) in the region of the right hip as well as increased uptake (short arrow) on the delayed bone tracer images (C) and increased activity (short arrow) in the left first toe on gallium images (D). Tomographic gallium (E), CT (F) and SPECT/CT (G) images demonstrated increased gallium activity in the intertrochanteric region of the left femur (short arrow) and overlying soft tissues posteriorly (arrowhead) associated with skin ulcer. ■



" Gallium imaging is a nuclear medicine imaging procedure using Ga-67 for the detection of infection. Imaging usually is performed 24–72 h after injection of Ga-67. Specific applications include the search of a focus of infection in a patient with fever of unknown origin and the evaluation of osteomyelitis. "

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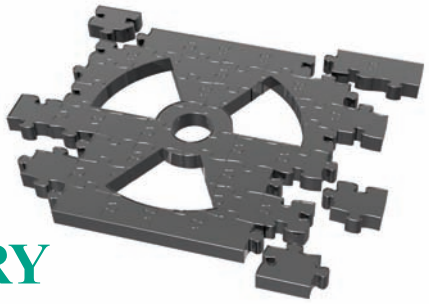
THERANOSTICS AND THE IMPORTANCE OF PERSONAL DOSIMETRY IN NUCLEAR MEDICINE



" The first steps towards dosimetry for MRT is to make better use of the quantitative nature of Nuclear Medicine imaging.

ExRT is delivered using high energy X-ray beams that are precision guided from the radiotherapy machine onto a target tumour in the patient. These X-ray beams can be turned on and off via control switch with beams being shaped to ensure optimal coverage of the target tumour whilst minimising radiation dose to adjacent radiosensitive organs known as organs at risk (OAR). In Brachytherapy sealed radioactive sources are placed into body cavities or directly into tissues, the effect of the radiation on the adjacent tissue is predicted using planning software to maximise damage to tumour tissues. Sealed radioactive sources are positioned in planned, fixed places and can be removed once the desired therapeutic dose has been delivered. Molecular radiotherapy (MRT), by comparison, is more complex; radiopharmaceuticals can be delivered systemically making use of biological processes to ensure radiation is only delivered directly into tumour cells. Alternatively radiation can be selectively delivered to specifically targeted tumours in the liver by making use of the blood vessels directly supplying tumours. There is no on/off switch for the radiation associated with MRT. Planning and then evaluation of dose delivery requires consideration of the biological and physical half-life of the radiopharmaceutical used; the method of uptake by the tumour cells; excretion pathways of excess radiopharmaceutical not taken up in tumours; residence time of that radiopharmaceutical in different organs; and its proximity to other radiosensitive organs. These added complexities compared to ExRT and Brachytherapy mean the development of planning and treatment delivery evaluation for MRT lags as much as 30 years behind ExRT and Brachytherapy.

During the phase I and II trials of new MRT radiopharmaceuticals dose escalation is carried out to determine a treatment regime that provides benefit without toxicity becoming too high. Dosimetry may be carried out in a small cohort of trial patients; however this is not common place for whole trial populations and is insufficient to establish dose-response curves for MRT. Dose limits for OAR are initially adopted from ExRT experiences however the radiobiology of MRT is completely different. The response of a tumour to an external high energy X-ray beam versus internalised alpha or beta radiation will be different; these differences need to be better understood.

In the case of Lu-177 DOTATE for the treatment of neuroendocrine tumours (NETs) a regime of 4 treatment cycles at 8-12 week intervals with 7.4GBq of Lu-177 DOTATATE delivered at each cycle was deemed to be effective from early trials. This has been rolled out internationally with little or no dose planning or evaluation being carried out for patients. In the Phase III NETTER-1 trial; Lu-177 DOTATATE delivered in 4 cycles of 7.4GBq at 12 week intervals was compared to treatment with Octreotide LAR in

Figure 1 A

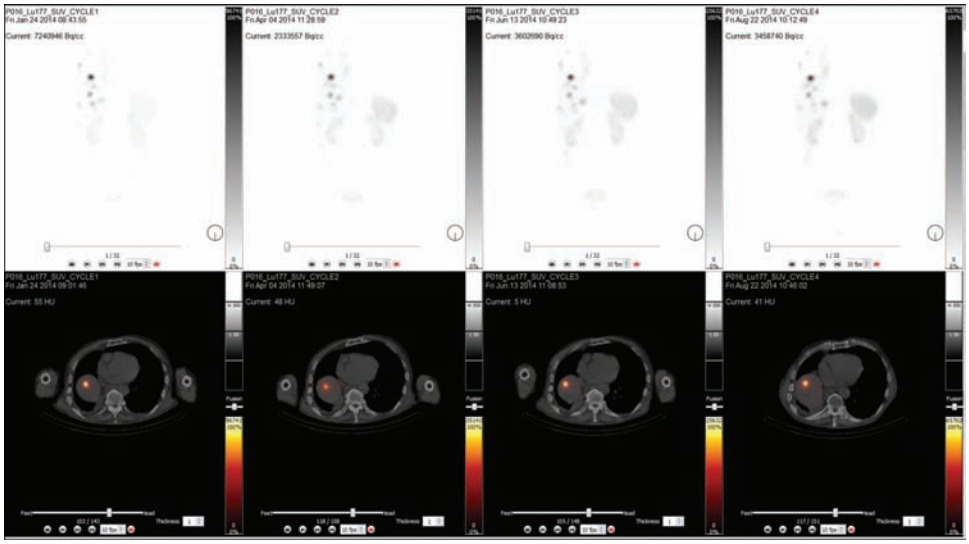


Figure 1 B

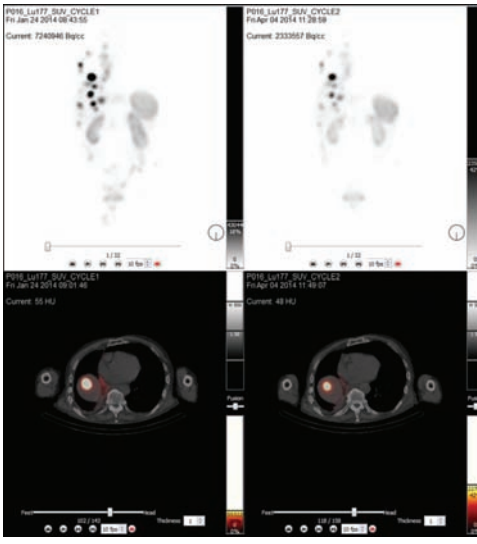
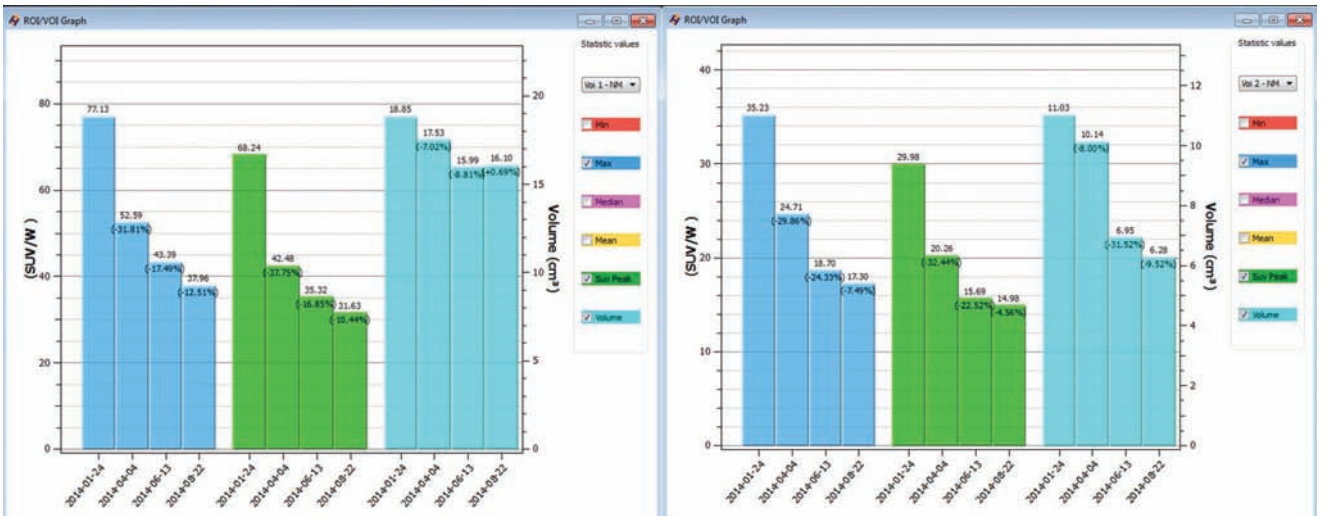


Figure 2



231 patients, dosimetry was only carried out in a subset of 20 patients. This was a missed opportunity to gather dose-response data from Imaging and tie in imaging response to clinical response.

Fixed dosing regimens in the era of patient specific treatment also need to be revised. MRT is used to treat widespread metastatic disease, not all patients will have the same overall tumour burden, and they may require more or less radiation than the current fixed dose regime prescribed. Without knowing what dose thresholds must be reached in order to achieve a positive clinical response in tumours for each different type of MRT; we are not using MRT effectively and could be doing better for our patients.

The first steps towards dosimetry for MRT is to make better use of the quantitative nature of Nuclear Medicine imaging. When using PET; there is no question about using quantitative imaging techniques that allow Physicians and Radiologists to monitor the activity taken up by tumour using Standardised Uptake Values (SUVs). Conventional SPECT CT images can be made quantitative (QSPECT CT) by following a calibration process and using dedicated software to display images such as Hermes SUV SPECT®. For Lu-177 DOTATATE MRT post therapy imaging using QSPECT CT and display using Hermes SUV SPECT® allows the Radiologist to evaluate MRT uptake and treatment response. SUV scaled images provide instant comparison between follow up scans, the need for the radiologist to subjectively threshold each image prior to starting their comparison is removed. Figure 1 shows a patient who has received four cycles of Lu-177 DOTATATE, in figure 1A the 4 post treatment cycle images are scaled using absolute counts, no thresholding has been applied. In figure 1B the same 4 SPECT CT scans are displayed using absolute counts however thresholding has been applied to give the spleen the same appearance in all images to allow the radiologist to compare response. Figure 1C shows the same 4 SPECT CT scan displayed using

" When using PET; there is no question about using quantitative imaging techniques that allow Physicians and Radiologists to monitor the activity taken up by tumour using Standardised Uptake Values (SUVs). "

Figure 1 C

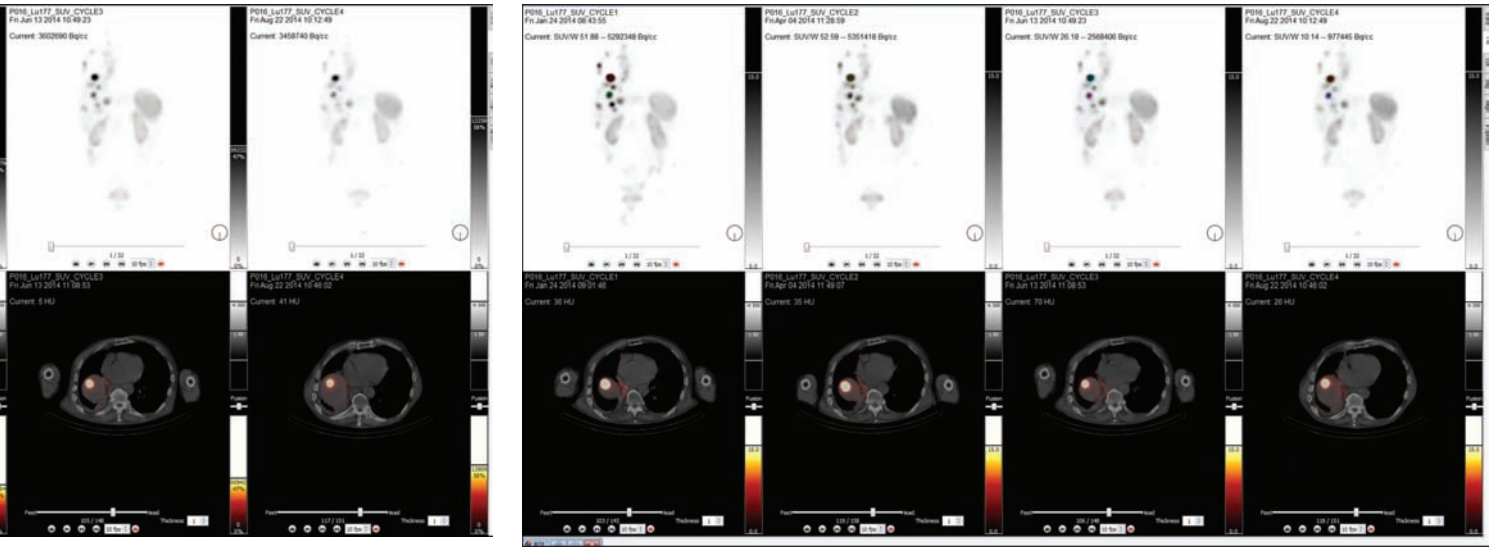
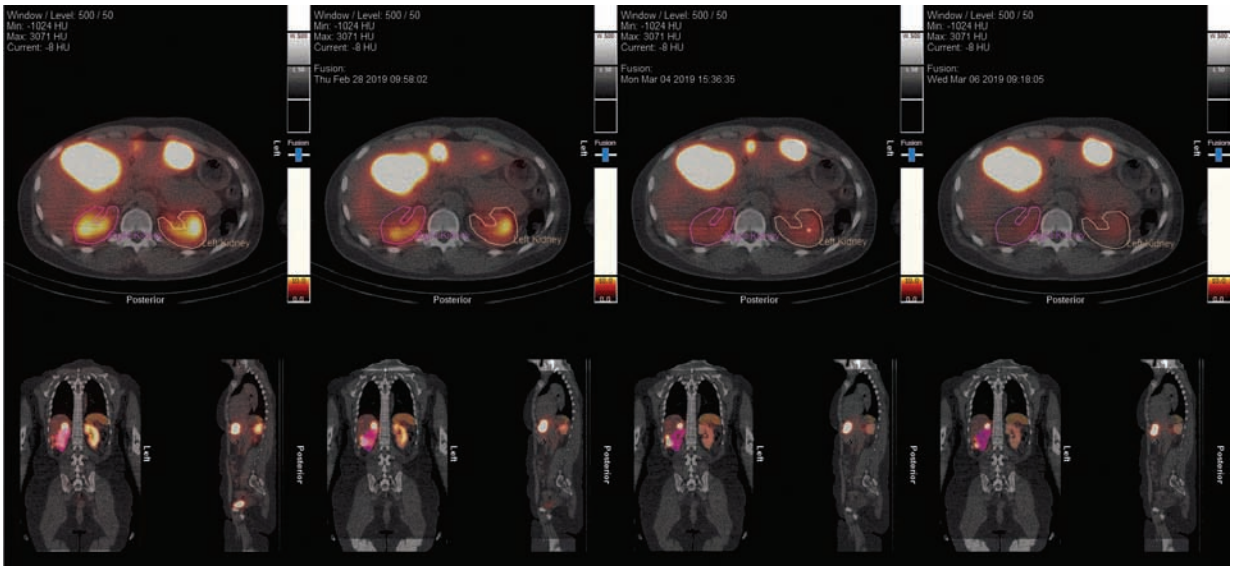


Figure 3



SUV thresholding. Figure 2 shows the data that can be pulled out of SUV SPECT images, the change in SUVmax, SUVpeak, and tumour volume is displayed for two distinct tumours in the liver over 4 treatment cycles.

A further benefit to using QSPECT CT and SUV software is that QPSECT CT images can be read into dosimetry software without the need for further image reconstruction. Dosimetry software such as Hermes Hybrid Dosimetry® or Hermes Voxel Dosimetry® can be used to determine the dose delivered to tumour volumes and OAR. Figure 3 shows post therapy images for four cycles of Lu-177 DOTATATE therapy; images are displayed using SUV thresholding with kidney regions drawn to obtain dosimetry values. Figure 4 shows the dose volume histogram for the kidneys and spleen. Figure 5 shows the calculated dose to the kidneys.

Evaluating the dose delivered to patients receiving the fixed treatment regime of 4 cycles of 7.4GBq Lu-177 DOTATATE MRT, would be the starting point for building a dose-response curve and determining MRT specific dose limits for OAR. Comparing the dose delivered to tumours and OAR to the patient's response measured on imaging and via clinical markers would require a multi-disciplinary approach involving Physicists, Radiologists and Physicians. In the future QSPECT CT combined with dosimetry, dose-response data and MRT specific OAR dose limits would allow patient specific planning of the next Lu-177 DOTATATE treatment cycle. Activity would be prescribed on an individual patient basis rather than a standardised regime.

In comparison to external beam Radiotherapy (ExRT) and Brachytherapy; the field of personalised dosimetry in Molecular Radiotherapy (MRT) is in its infancy. Nuclear Medicine is a quantitative imaging modality, the software is available to carry out dosimetry and evaluate treatment response. A multi-disciplinary team approach is required to establish dosimetry protocols in Nuclear Medicine and move towards patient specific treatment prescription for MRT.

Figure 4

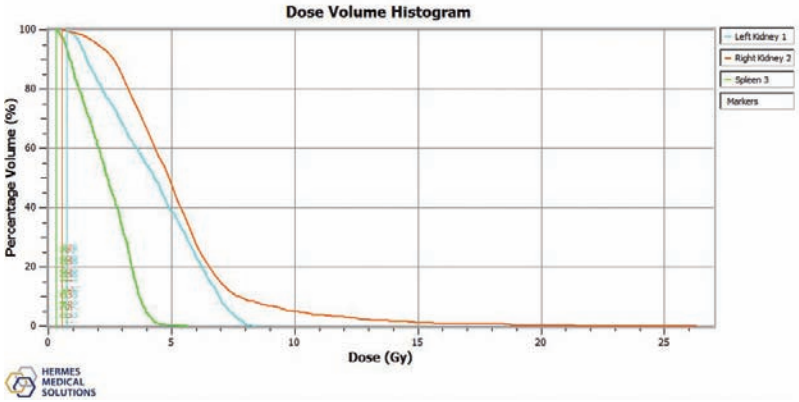


Figure 5

Name	Min (Gy)	Max (Gy)	Mean (Gy)	std Dev (Gy)	D95% (Gy)	D90% (Gy)	D2% (Gy)	volume (ml)
Left Kidney 1	0.76	8.35	4.26	1.97	1.30	1.53	7.82	140030.89
Right Kidney 2	0.56	26.27	5.23	2.71	2.12	2.64	13.29	128343.28
Spleen 3	0.34	5.63	2.36	1.06	0.66	0.87	4.24	115773.57

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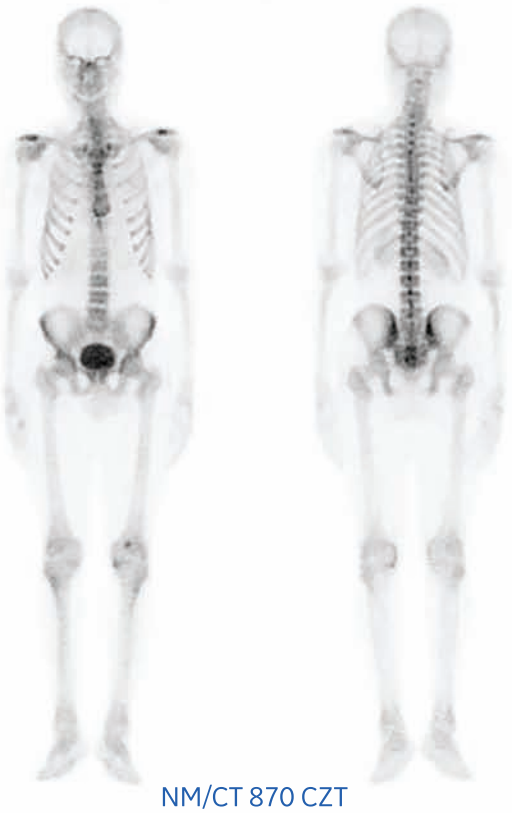

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References:
1 Together with Clarity 2D and Evolution6 and compared to Discovery NM/CT 670 Pro/ES/DR without Clarity 2D and Evolution6. As demonstrated in phantom testing using a bone scan protocol, and the NEMA IEC Body Phantom. The actual time/dose reduction depends on the clinical task, patient size, anatomical location and clinical practice.
2 Demonstrated in phantom testing using NEMA IEC Body Phantom at 50% scan times with Evolution6. Compared to Discovery NM/CT 670 Pro/ES/DR.
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