VOL 3 • NO 1

ePATIENT

NUCLEAR MEDICINE & MOLECULAR IMAGING

THE FREE NUCLEAR MEDICINE & MOLECULAR IMAGING EDUCATIONAL MAGAZINE AVAILABLE WORLDWIDE

NUCLEAR MEDICINE MADE SIMPLE

MÉDECINE NUCLÉAIRE SIMPLIFIÉE

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PANGEA PROJECT

PANGEA

TECHNEGAS™

FUNCTIONAL LUNG IMAGING

BENEFITS IN USING TECHNEGAS V/Q SPECT/CT

DIAGNOSTIC TOOL

Technegas has the ability to allow the clinician to assess regional airflow and lung function with SPECT or SPECT/CT imaging[1].

It provides a physiological assessment by scintigraphy of alveolar spaces for:

- **Pulmonary embolism**
- **CTEPH**
- **COPD**
- **Asthma**
- **Emphysema**
- **Pre-operative quantification**
- **Radiotherapy treatment planning**

FAST & SIMPLE

A few breaths of Technegas are sufficient to achieve excellent quality images[2]

LOW DOSE BURDEN

V/Q SPECT with Technegas has a low radiation burden as compared with CTPA[3].

QUANTITATIVE TOOL

Advanced quantitative V/Q SPECT/CT with Technegas could be used as a tool for pre-operative evaluation, monitoring disease progression and following-up treatment response[4-5].

> ***" With the advent of SPECT and SPECT/CT technology, significant improvements in ventilation-perfusion imaging have been made not only in our ability to resolve subtle heterogeneity in ventilation and perfusion distributions but also in providing relative quantitation of ventilation and perfusion[1] "***

DIAGNOSTIC ACCURACY

Clinical studies have shown that V/Q SPECT with Technegas has high sensitivity and specificy in diagnosing PE[6] and CTEPH[7] with a very high negative predictive value.

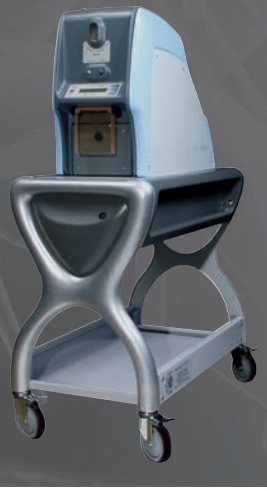
> ***" We consider V/Q SPECT/CT to be superior in most clinical settings with better overall diagnostic performance[6] "***

WHAT IS TECHNEGAS

Technegas is a hydrophobic nanoparticle dispersion of carbon-labelled ^{99m}Technetium[8].

The nanoparticle size and hydrophobic properties of Technegas provide ideal characteristics for gaseous behaviour and alveoli deposition into the lungs[8-9]. This provides for a represention on imaging of peripheral penetration of Technegas to the lungs[9].

According to the Canadian Associaion of Nuclear Medicine (CANM) and the European Association of Nuclear Medicine (EANM) guidelines, Technegas is the preferred ventilation agent for ventilation-perfusion (V/Q) functional lung imaging studies[10-12]. In a few breaths and following SPECT or SPECT/CT, the clinician can produced 3D images providing information on lung function and pulmonary physiology[2,12].



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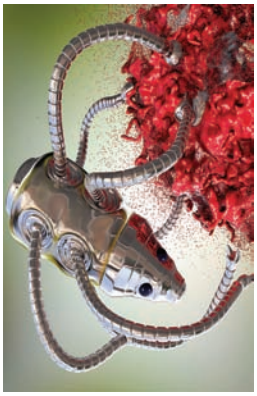
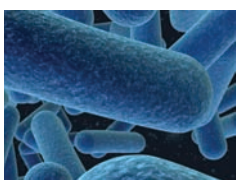
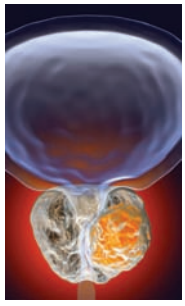
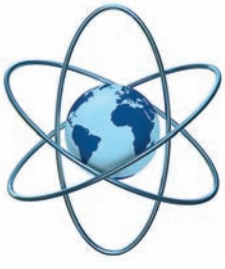
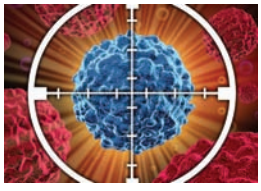
Content











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Don't miss our next issue on Quantification and the second part of Theranostics (neuroendocrine tumors).

EDITORIAL BOARD

Dr. Lamoureux and I are thrilled to introduce our outstanding editorial board members. Through our travel and NM lecturing around the globe, we have met terrific scientists and colleagues. Most, if not all of them, are really passionate about and true advocates for the field of nuclear medicine. They strongly believe in the power, usefulness and safe use of NM diagnostic and therapeutic procedures for the betterment of public healthcare worldwide. We are delighted that the following leaders have embraced the concept of the Pangea-ePatient magazine and accepted to share their invaluable expertise and experience with patients, referring colleagues, health care administrators, government agencies and insurance companies.

Dr. Jean-Luc Urbain

Dr. François Lamoureux,
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INTRODUCTION TO THE FIFTH ISSUE

François Lamoureux
M.D.,M.Sc., FRCPSC
President, CANM

Jean-Luc Urbain
M.D., Ph.D., CPE, FASNC
Past President, CANM

PSMA and the Prostate Cancer Tsunami

On behalf of the editorial board and Dr. François Lamoureux, my co-editor, I would like to welcome you to the fifth issue of your nuclear medicine educational resource magazine ePatient.

Up to a few years ago we would have had some difficulty to share with you a true optimistic message regarding the field of nuclear medicine in North America. The lack of concerted efforts in research and development of new radio-pharmaceuticals in the last part of the last century created a climate of uncertainty about the field of nuclear medicine at the eve of the 21st century.

As the current decade is nearing the end, there are many reasons to express a very optimistic message about the use of medical isotopes for the diagnosis and treatment of diseases. In fact, we are really starting to witness a true renaissance of our specialty. In a very interesting and remarkable turn of events, genomic and phenotypic based radioactive molecular probes and therapies with a level of precision never achieved before have started to populate our radio-pharmacies. Ultrasensitive gamma and positron imaging equipment are also now part of our nuclear medicine armamentarium and they are giving us the ability to detect, image and quantify these specific radioactive probes with a level of accuracy never achieved before. They probes are also given us the ability to treat specifically various forms of tumors like neuroendocrine tumors and metastatic prostate cancers. While in clinical use in Europe for more than a decade and in other parts of the world, the Lu177-Dotatate compound (Lutathera®) was approved by the FDA in January 2018 and more recently by Health Canada. Since 2018, thousands of patients have already benefited from this unique therapy.

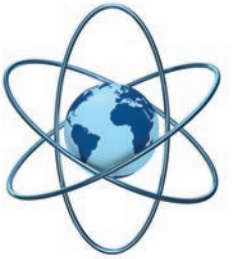
The anticipation of the approval of the Lu177 (PSMA) Prostate Specific Membrane Antigen compound(s) for the molecular treatment of metastatic prostate cancer has generated an enthusiasm among the nuclear medicine community and patients that we have not seen for a few decades in our specialty.

Since 2012, the number of clinical studies using urea-based PSMA ligands has grown exponentially. Among these agents, the Ga68- and 18F-labeled compounds have attracted the most attention, as they can be used for PET/CT imaging. However, the availability of these compound labeled with Iodine 123 or Tc-99m will also allow SPECT/CT imaging in centers without facilities for PET. Based on these studies, the promising uses of imaging with labeled PSMA ligands in the management of prostate carcinoma include: the primary staging of high risk cancer disease, the biochemical recurrence with low PSA levels (as low as 0.2 ng/ml), identification of lesions for biopsy targeting after negative previous biopsy, the monitoring of systemic treatment in metastatic disease, the active surveillance and the treatment monitoring after Lu177-PSMA ligand therapy.

With one of seven men developing prostate cancer, we believe that the regulatory approval of these PSMA molecules will trigger a seismic change in the way we manage patients with prostate cancers. This issue of the ePatient essentially focuses on this upcoming revolution. We should anticipate and be ready for what I called a "Prostate Cancers Tsunami" for nuclear medicine departments in North America and across the globe.

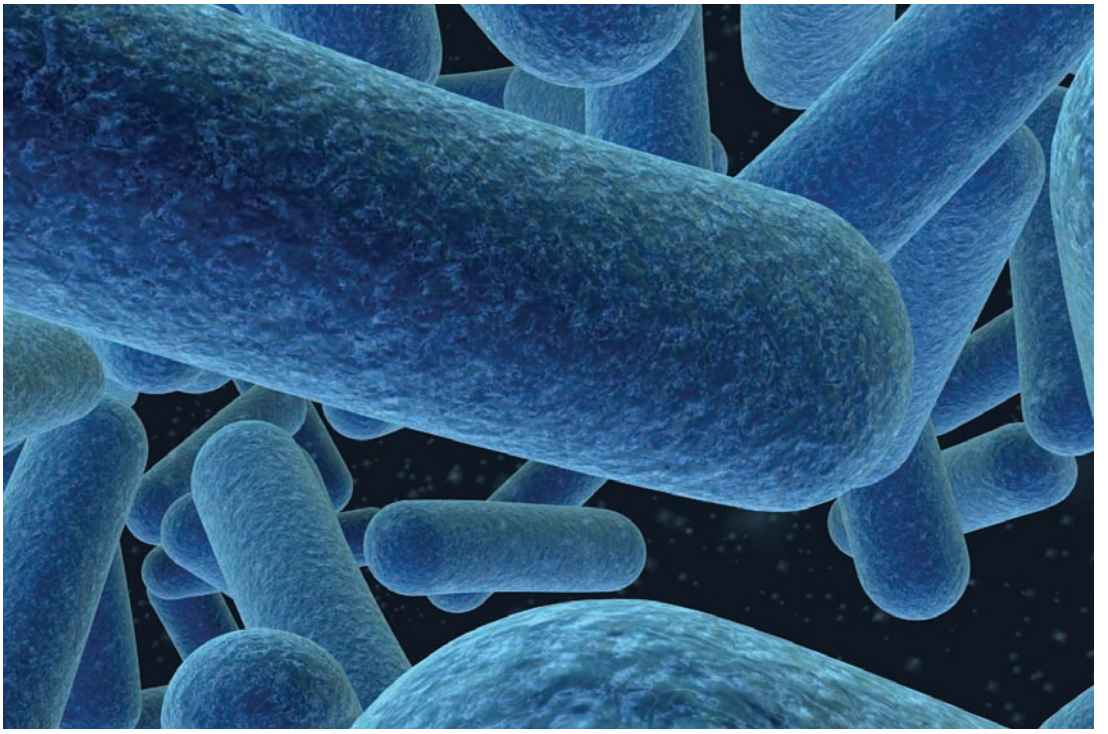
Because of their ability to characterize cellular physiology and dysfunction, the radiopharmaceuticals used in nuclear medicine offer a very unique and specific window on disease that can exploited both for diagnostic and therapeutic purposes. During the past two decades, numerous ligands that bind to specific molecular targets, particularly in cancers, have been identified and characterized. Their labeling with single photon and positron emitters and alpha or beta particles has opened up a new era in nuclear medicine. While still in its infancy, nuclear diagnostic and therapeutic targeting are rapidly becoming a cornerstone of oncology and precision medicine.

Welcome to the very promising world of Nuclear Theranostics!



François Lamoureux
M.D.,M.Sc., FRCPSC
President, CANM

LES AVANCÉES MÉDICO-PHARMACOLOGIQUES



UNE BACTÉRIE SOURNOISE ET QUASI OMNIPRÉSENTE AU NIVEAU PLANÉTAIRE

« Cette bactérie peut donner naissance à des ulcères gastriques et duodénaux, des dyspepsies non ulcéreuses, des métaplasies intestinales, signe d'un état précancéreux et, finalement, à des cancers francs de l'estomac.

L'Helicobacter pylori, une des seules bactéries actuellement connue à pouvoir coloniser l'estomac humain, se retrouve dans plus de 80 % de la population des pays en voie de développement et dans près de 40 % de la population d'Europe et d'Amérique du nord.

Cette bactérie est la première cause des gastrites, une inflammation de la muqueuse de l'estomac. Le patient porteur peut être asymptomatique ou éprouver des douleurs gastriques sous forme de brûlements ou encore de douleurs abdominales chroniques récidivantes. Le système immunitaire humain ne semble pas pouvoir éradiquer ce parasite. Ainsi, une infection à Helicobacter pylori, si non traitée, peut persister toute la vie d'un individu. On croit que l'infection aurait pu se produire par voie fécale-orale ou orale-orale. On a retrouvé de ces bactéries dans les selles, dans l'estomac et sur des plaques dentaires de l'humain.

En plus des gastrites, cette bactérie peut donner naissance à des ulcères gastriques et duodénaux, des dyspepsies non ulcéreuses, des métaplasies intestinales, signe d'un état précancéreux et, finalement, à des cancers francs de l'estomac. Cette évolution survient après plusieurs décennies suite à une série de transformations de la muqueuse gastrique, de l'état précancéreux à un cancer franc de l'estomac.

Deux chercheurs australiens, J. Robin Warren et Barry. J. Marshall, ont d'ailleurs obtenu le prix Nobel de physiologie et médecine en 2005 pour avoir démontré que la plupart des ulcères de l'estomac étaient causés par une infection par Helicobacter pylori et non, par exemple, par le stress ou encore la nourriture épicée.

Cette bactérie gram négatif, qui nécessite peu d'oxygène et tire son énergie de l'hydrogène, est d'aspect hélicoïdal et vit dans l'environnement du pylore, d'où son nom d'Helicobacter pylori. Cette bactérie va s'ancrer aux cellules épithéliales de l'estomac et, grâce à sa capacité de produire une enzyme appelée uréase, elle va transformer l'urée en ammoniac. Cet ammoniac produit va neutraliser en partie l'acide chlorhydrique sécrété par l'estomac, qui sert entre autres à tuer les bactéries.

L'ammoniac produit, ainsi que d'autres irritants sécrétés par cet Helicobacter pylori, vont continuellement enflammer les cellules gastriques et enclencher ces phénomènes de gastrites chroniques, de formation d'ulcères et à la longue chez certains individus, le développement d'un cancer de l'estomac type épithéliale ou lymphomateux.

Chez certains autres patients, on assistera à des troubles de malabsorption de la vitamine B12 ou d'extraits thyroïdiens de remplacement chez les hypothyroïdiens.

C'est une bactérie que l'on ne peut conserver dans notre estomac et que seule une antibiothérapie bien ciblée peut éradiquer.

Nombreux patients, tant enfants qu'adultes, sont encore traités aujourd'hui par des anti-acides ou des inhibiteurs de la pompe à protons sans, au préalable, aucune investigation appropriée de recherche d'Helicobacter pylori. D'autres sont d'emblée soumis à des tests invasifs comme l'endoscopie avec biopsie de la muqueuse gastrique en raison de symptômes de dyspepsie ou de douleurs gastriques.

Il existe un test simple, rapide, non invasif, sans inconfort et facilement disponible dans plusieurs unités de médecine nucléaire qui nous permet de confirmer ou d'infirmer la présence d'une prolifération anormale d'Helicobacter pylori chez un patient. C'est le test respiratoire à l'urée marquée au carbone 14 (*breath test*) dont la sensibilité et la spécificité sont pratiquement de 100 %, phénomène rare en médecine.

Contrairement à d'autres tests moins précis, comme les tests sériques dans le sang ou les selles, on peut également, avec le test respiratoire à l'urée C-14, confirmer en post traitement l'éradication ou non de l'Helicobacter pylori.

Le test se déroule en externe sur une période d'environ 20 minutes. On fait avaler au patient une pilule d'urée marquée au C-14 et, si la bactérie est présente dans l'estomac, l'enzyme uréase que produit la bactérie va hydrolyser l'urée marquée ingérée en gaz carbonique marqué qui sera presque instantanément absorbé dans le sang et, par la suite, expiré dans l'air des poumons du patient. On recueille alors dans un tube l'air marqué au C-14 expiré par le patient et l'on compte le tout dans un compteur bêta. Le résultat est instantané et le coût d'environ 20 dollars canadiens.

En présence d'une prolifération anormale d'Helicobacter pylori, le patient reçoit une trithérapie, soit un inhibiteur de la pompe à protons pour diminuer la sécrétion d'acide chlorhydrique et deux antibiotiques pendant environ 7 jours. Habituellement, le traitement est efficace et tous les symptômes disparaissent. Par la suite on procède à un examen de contrôle du test respiratoire après 4 ou 5 semaines.

Le coût de l'utilisation des anti-acides et des inhibiteurs de la pompe à protons dépasse annuellement les 150 millions de dollars au Québec. Combien de ces patients devraient plutôt être investigués d'abord pour une recherche d'une prolifération anormale d'Helicobacter pylori et, par la suite, traité au besoin par une antibiothérapie, quand on sait maintenant que chez au moins 40 % des gens (Europe - Amérique du nord), l'agent responsable des dyspepsies est une bactérie unique à l'Homme que l'on peut l'éradiquer?

Au Canada, 7 % des consultations chez le médecin de famille concernent un problème des dyspepsie, et ceci tant chez l'enfant que chez l'adulte. Trop d'endoscopies en première intention pour dyspepsie sont encore effectuées. Un test respiratoire à l'urée devrait être la première approche diagnostique chez tout patient, enfant comme adulte, présentant des symptômes de dyspepsie ou de gastrite.

L'endoscopie de première intention devrait être réservée aux patients à risque ou présentant des signes d'alarme comme des vomissements, des saignements, de l'anémie, une masse abdominale ou une perte de poids inexpliquée.

Finalement, en raison des études géniques, un vaccin sera probablement disponible dans le futur et nous permettra de nous protéger contre cet envahisseur sournois et responsable de tant de malaises gastro-intestinaux. ■

« Contrairement à d'autres tests moins précis, comme les tests sériques dans le sang ou les selles, on peut également, avec le test respiratoire à l'urée C-14, confirmer en post traitement l'éradication ou non de l'Helicobacter pylori. »

INTERVIEW WITH:

TOM FRANCKE

PRESIDENT AND CEO OF HERMES MEDICAL SOLUTIONS

Tom, you are the new President and CEO of Hermes Medical Solutions. Can you give us a short resume of your previous involvement in the medical imaging field and give us a short idea of the company? Where is it based and in how many countries it is already involved in?

It is an honour to lead the innovative Hermes team. After three years on the board of directors I know the company rather well. I am trained as associate professor in astroparticle physics specialised in radiation detectors, and have been part of growing medical imaging companies for 22 years in X-ray and ultrasound imaging.

Hermes is one of the pioneering software companies in nuclear medicine and has supplied the medical community with image display and processing software for 44 years. We are proud of focusing on innovation to be the leader of new developments and bring the best applications to the market.

Hermes simplifies the workflow for the clinicians in diagnosis and therapy in nuclear medicine providing excellent viewers and analysis tools.

Hermes software is vendor neutral and accepts DICOM data from all camera manufacturers with consistent results for patient follow up regardless of the camera brand. The multimodality software supports a wide range of imaging procedures with dedicated workflows. Our professional support staff is responsive and match the nuclear medicine expertise of our customers and can discuss in detail the processing algorithms and results.

We have installations in more than 40 countries and are present globally.

Hermes Medical Solutions is a well implanted international company in the Nuclear Medicine Healthcare World. What are the biggest challenges of Hermes Medical Solutions in the immediate future?

The largest challenge, and opportunity, in the near future is to introduce our new revolutionary Affinity suite of products. During EANM 2019 we present a disruptive Viewer, which in the coming months will we followed by new innovative plugin applications in oncology, cardiology, neurology, dosimetry and other nuclear medicine procedures.

The Viewer differs significantly from all other viewers on the market. We have employed expert developers from the gaming industry to revolutionize the performance and usability of the Affinity Viewer to create a completely new experience for clinical software. The workflow and layout are fully configurable down to the smallest detail to simplify and personalize the workflow of each clinicians for maximum efficiency and accuracy. All operations are intuitive reducing the training time to a minimum. The new data loading is instant eliminating all waiting time. The image fusion capabilities are automatic and limitless, where a limitless number of images from any modalities taken by any camera brand at any instant can be fused in any way the user desires. It has large number of image analysis tools to simplify and speed up the workflow. It is designed to handle multiple time points and multiple modality imaging with ease through a powerful simple user interface. The Affinity Viewer introduces a new level of expert reporting in nuclear medicine. It is designed for speed and engineered for quality.

Where is Hermes Medical Solutions going and what will be the impact for the Hermes Medical Solutions users?

The Affinity suite will be the future flagship of Hermes and will set a new gold standard in nuclear medicine procedures. The users will experience more accurate diagnosis capabilities, more diagnostic applications supported and a personalized workflow for high throughput in all clinical scenarios.

We continuously bring new applications to the market based on the latest clinical discoveries. We believe nuclear medicine will be more personalized, move more and more into molecular radiotherapy with strong needs on dosimetry and therapy planning. The number of examinations will increase demanding smoother workflows and instant response. The time for training and learning different systems will be reduced demanding intuitive user interfaces.

How is Hermes Medical Solutions involved in the incontournable contribution of Artificial Intelligence? What will it mean to Hermes Medical Solution's partners?

Artificial intelligence is the future of all advanced software applications. Hermes is strongly positioned in this development where the R&D team has extensive experience in machine learning and other AI applications. We continuously implement AI in our software development and include many new automatic or semi-automatic applications into the Affinity suite. For the clinician it will simplify and speed up the workflow, enable more accurate diagnosis and make the care provider less dependent on the scarce highly trained resources at the hospitals to increase the throughput of patients.

Finally, what is your greatest wish for Hermes Solutions and its clients?

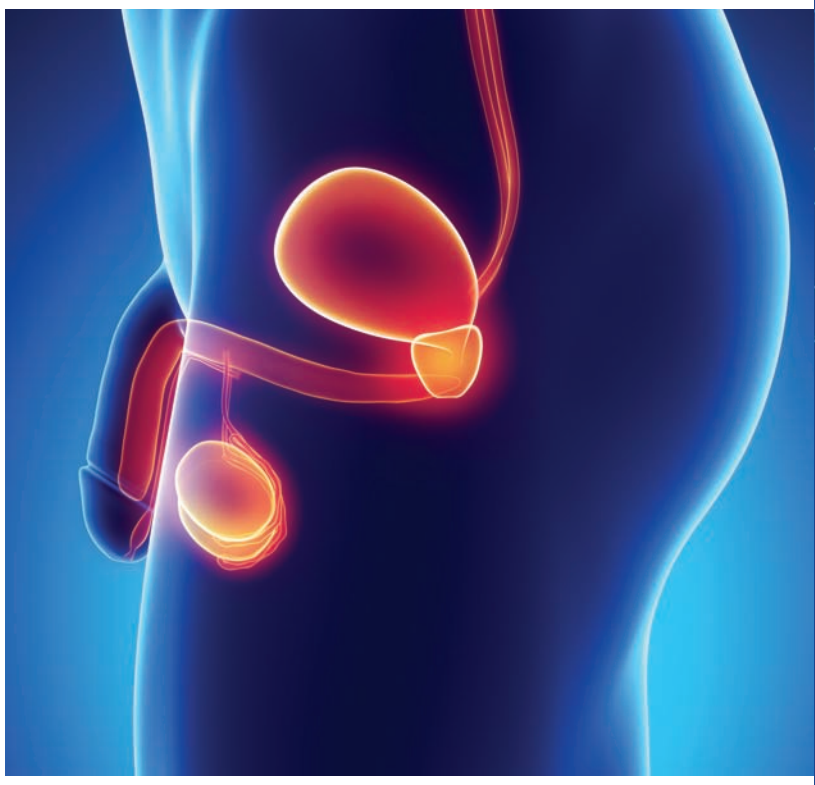
Our customers, and the whole medical community, is our strongest focus. We welcome all the feedback we can get to develop and give back the best possible products the community will need in the future. Let us continue and deepen the fruitful and mutual cooperation we have today. ■

"Hermes is one of the pioneering software companies in nuclear medicine and has supplied the medical community with image display and processing software for 44 years."

"We continuously bring new applications to the market based on the latest clinical discoveries. We believe nuclear medicine will be more personalized, move more and more into molecular radiotherapy with strong needs on dosimetry and therapy planning."

UNE PREMIÈRE MONDIALE POUR LES CANCERS AVANCÉS DE LA PROSTATE

Par Dalila Benhaberou-Brun



DR FRED SAAD, MD FRCS

Professor and Chief of Urologie; Director of GU Oncology; Raymond Garneau Chair in Prostate Cancer; University of Montreal Hospital Centre (CHUM); Director, Prostate Cancer Research; Institut du cancer de Montréal/CRCHUM.

LES STATISTIQUES SONT AFFLIGEANTES : AU CANADA, LE CANCER DE LA PROSTATE TOUCHE QUELQUE 25 000 HOMMES ET UN SUR SIX N'Y SURVIVRA PAS. EN EFFET, 4 300 HOMMES MEURENT CHAQUE ANNÉE DE CETTE MALADIE DANS D'ATROCES DOULEURS. UNE RÉALITÉ QUI ALARME LE DR FRED SAAD, CHIRURGIEN EN UROLOGIE ET CHERCHEUR AU CRCHUM.

CAS DÉSESPÉRÉS

Parmi les cancers de la prostate détectés chaque année, certains évoluent à un stade avancé. Le traitement habituel pour ce type de cancer consiste à donner des hormones. Même si cette prise en charge s'avère efficace dans la majorité des cas, il n'en demeure pas moins qu'une partie des hommes atteints deviendront résistants au traitement et auront des métastases. Dans ces cas, il existe des traitements qui peuvent aider, mais, quand il n'y a pas de métastases, il n'y a aucune thérapie. La seule chose à faire est « d'attendre que les métastases atteignent les os », explique le Dr Saad. Selon les facteurs de risque, les métastases peuvent apparaître dans les 12 à 24 mois et la fin devient vite inéluctable.

DE L'OSTÉOPOROSE VERS LE CANCER

Depuis plusieurs années, toutes les tentatives pour agir sur l'apparition des métastases ont échoué, regrette Fred Saad. Cinq projets majeurs ont été menés dans le monde, mais en vain. Finalement, c'est un médicament qui avait démontré une efficacité pour traiter l'ostéoporose, et aussi les métastases qui s'est révélé être une piste intéressante : le denosumab. Ce médicament avait démontré un effet concluant dans l'ostéoporose, notamment pour prévenir les fractures. « Il nous a semblé évident d'utiliser ses propriétés pour protéger, et même renforcer les os pour les cas de cancers de la prostate qui ne répondent plus au traitement hormonal ».

UN PROTOCOLE NOVATEUR

Quelque 1 432 hommes souffrant de cancer avancé de la prostate ont reçu soit le denosumab à raison d'une injection par mois, soit un placebo. L'objectif était de vérifier si le denosumab pouvait retarder l'apparition des métastases osseuses. Le suivi s'est fait principalement par radiographie.

Et pour la première fois, dans le groupe des hommes qui recevaient le médicament, les métastases ont pu être retardées de façon significative par rapport à l'autre groupe ! « C'est sensationnel qu'on arrive à un tel résultat après tous les échecs passés », déclare Fred Saad, enthousiaste. D'ailleurs, les résultats de cette étude unique au monde seront présentés prochainement dans des congrès internationaux par le Dr Fred Saad et le Dr Matthew Smith, de l'Université Harvard.

DU DÉSESPOIR À L'ESPOIR

Ces résultats auront un impact majeur dans le monde, car ce médicament permet enfin de retarder le moment de l'apparition des métastases osseuses, mais également de maîtriser la douleur intense qui accompagne la maladie. La recherche continue pour cibler les patients à risque de métastases et pour établir la meilleure stratégie d'utilisation de cette nouvelle arme thérapeutique. Le denosumab n'est toutefois pas encore disponible au Canada. Plusieurs étapes devront être franchies et le Dr Saad est heureux de pouvoir redonner une lueur d'espoir à ses patients.

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Kalevi Kairemo

Department of Nuclear Medicine and Molecular Radiotherapy, Docrates Cancer Center, Helsinki, Finland

THERAGNOSTICS: Lu-177-PSMA treatment for metastatic prostate cancer – case examples

Prostate specific membrane antigen (PSMA) is a membrane glycoprotein with enzymatic activity (as explained in vol.1 no.2. by Jean-Luc Urbain). It is highly expressed in high-risk prostate cancer and therefore PSMA could be a basis for theragnostics. ^{177}Lu-PSMA radioligand therapy is mainly used for patients with end-stage prostate cancer, but it can be used earlier. I describe here three patients: one patient with a multiple recurrences and one with extensive metastastic disease during the first visit, and one patient where it was used as first-line treatmen. All these patients demonstrated a major response with ^{177}Lu-PSMA radioligand therapy, i.e. complete response by imaging and substantial reduction of PSA. ^{177}Lu-PSMA radioligand therapy gave only mild adverse effects.

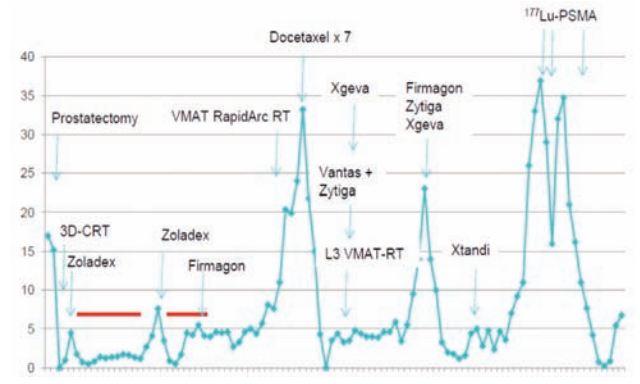
Our first patient had hypertension and diabetes for years. Primarily PSA increased from 4.6 to 17 ng/ml within 6 months. Diagnosis was done based on second round of biopsies 16 years ago when GS 6 (3+3) prostate adenocarcinoma was found in both lobes. Hormonal therapy was started with leuprorelin and bicalutamide. Prostatectomy was performed 6 months later. Tumor was very large and it was infiltrating also to seminal vesicles, consistent with staging pT3b. The full case history including serum PSA behavior is shown schematically in Fig.1, but briefly the case history is as follows.

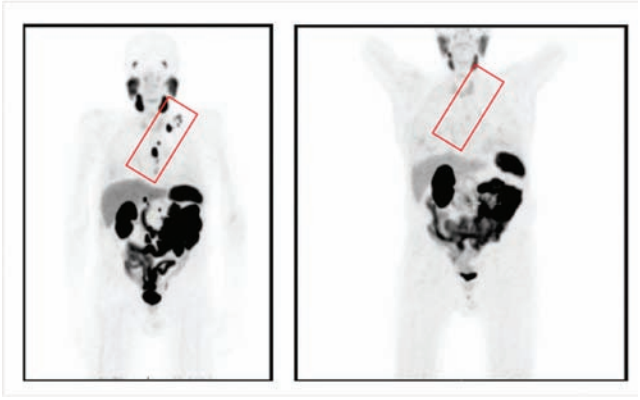
One year later he got external beam radiation therapy to prostate fossa up to 70 Gy, bicalutamide and casodex were used for 3 years, until goserelin was started for 2 years. Bicalutamide was re-started one year later due to PSA increase (up to 4.1 ng/ml). Degarelix was introduced 2 years later for one year. Simultaneously, choline-PET-positive para-iliac and paracaval lymph nodes were irradiated up to 70/2 Gy. However, in PSA continued to increase up to 24 ng/ml and 7 cycles of docetaxel were given with partial response. Four months later, skeletal metastases were found in MRI, and palliative radiotherapy to lumbosarcal region was given. Histrelin acetate device was implanted for castration. Abiraterone and denosumab were started, but they were stopped due to the pain in muscles and joints in four months. The castration implant removed and abiraterone started again for 4 months. Denosumab was also started and continued for more than a year.

Degarelix was restarted, but it was changed to leuprorelin due to local and systemic reaction. He also got radiation therapy to choline positive upper retroperitoneal and mediastinal lymph nodes. Enzalutamide was also started but it had to be stopped in one month due to epileptic seizure. Six month later, dexamethasone combined with cyclophosphamide started to improve immunogenic response, but it had to be stopped due to the diarrhea, swelling and infection. Abiraterone started again, but four months later PSA was 33 ng/ml. On the same day in Ga-68-PSMA-PET-CT at

demonstrated active uptakes in very small lymph nodes on the left side of obturator region, in upper level in para-aortal and in para-caval lymph nodes and in retrocrural region, in the middle of left mediastinum and in supraclavicular region as well. The total volume of the disease estimated to be 20 cm^3.

^{177}Lu-PSMA-617 treatments were given in July, August and October 2016 using 6 week intervals. PSA nadir 0.0 ng/ml was achieved on in March 2017. Complete response was seen in ^{68}Ga-PSMA-11 PET-CT in March 2017 (Fig. 1, lower panel right). The patient is still alive and followed without any specific cancer therapy until January 2018. However, he felt down and broke his femur which was operated. The man is now 82 years.





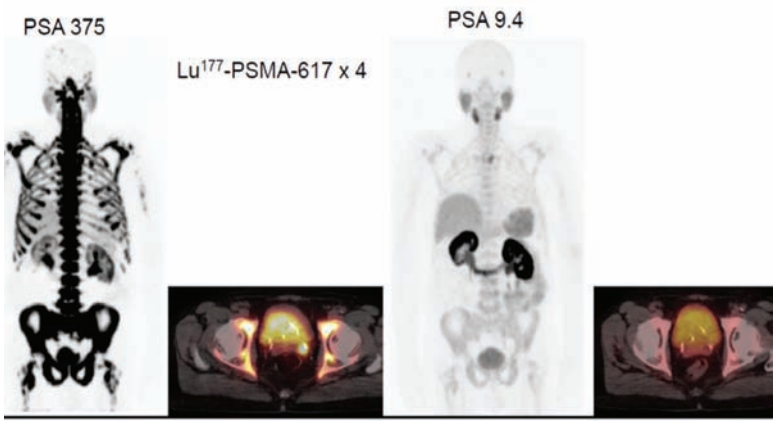
The second patient described here had primarily nocturia, pollacisuria and weak urinary flow resulting in more specific clinical studies four years ago. Initial S-PSA was 216 ng/ml. The biopsies revealed a Gleason Score (GS) 9 (5+4) adenocarcinoma with perineural invasion and extracapsular growth. Clinically the patient was T4, but there were no skeletal metastases in bone scintigraphy. Total androgen blockade (TAB) with leuprorelin plus bicalutamide was started for locally advanced prostate cancer with bilateral hydronephrosis and serum creatinine value 150. After bilateral pyelostomy operations, the patient could also urinate normally twice a day. TAB continued until March 2017. Bone scintigraphy already demostrated a superscan, and CT showed bone metastases with serum PSA value 135 ng/ml, without visceral metastases. At the end of March bicalutamide was stopped and abiraterone was started. Abiraterone was again stopped when ^{177}Lutetium-PSMA started. Patient refused to take any chemotherapy.

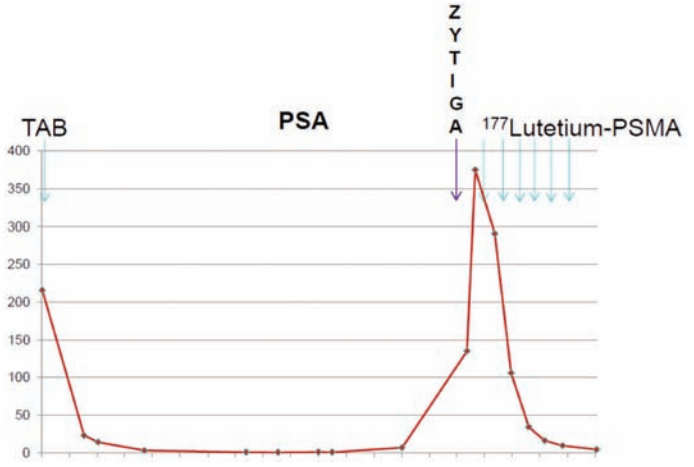
Ga-68-PSMA-PET/CT was performed in April 2017. It revealed an active and aggressive prostate malignancy in the left seminal vesicle region and extensive wide-spread strongly PSMA-positive skeletal disease. The Soloway classification was 3+/3, because extremely high uptakes in lower thoracic spine and sacrum and signs of bone marrow expansion existed. The SUVmax-values were higher than 27, while values higher than 3 are considered pathologic. The serum PSA value was 375 ng/ml.

^{177}Lu-PSMA therapy started in May 2017. It caused tiredness and he had also swelling in foots and ankles, but surgical stockings helped that. The patient had also severe depression and anguish. Following 4th treatment in September 2017 man had nausea and emesis. After 6th treatment he had no nausea and general feeling was also good. This man is now 70 years old.

An interim control Ga-68-PSMA-11-PET/CT was performed at Docrates Cancer Center in late October 2017. The serum value was then 9.4 ng/ml. Fig. 2 demonstrates the Ga-68-PSMA-11-PET/CT-studies performed in late April and late October 2017, i.e. before therapies and 4 weeks after the 4th cycle. In the base line study an extensive skeletal disease can be seen in the MIP-image and also in pelvic fusion image (PET on CT). Normal organs, i.e. salivary and lacrimal glands, liver, spleen hardly visualize in the MIP-image. Additionally, an uptake is seen in the large prostate and in the left seminal vesicle. The interim control PET MIP-image reveals normal organs such as salivary and lacrimal glands, liver, spleen, kidneys and urinary bladder. Very little activity can be observed in the thoracic vertebra (Th 3). In interim control pelvic fusion image (PET on CT) there is no activity in the large prostate nor in the left seminal vesicle.

In control Ga-68-PSMA-PET/CT on in mid-January 2018 at Docrates Cancer Center and 6 weeks after the 6th cycle the active and aggressive prostate malignancy in the left seminal vesicle region had totally disappeared. Similarly, an extensive wide-spread strongly PSMA-positive skeletal disease, original classification probably 3+/3, had responded in all regions. There was only one subtle uptake on the left in Th3 which could be seen as in Fig.2, but the activity could already be considered normal, because the SUVmax value was only 3.8. This was considered as a dramatic response. PSA decreased from 375 ng/ml downto 4.2 ng/ml during the follow-up ^{177}Lu-PSMA therapy. This is shown in Fig. 2.

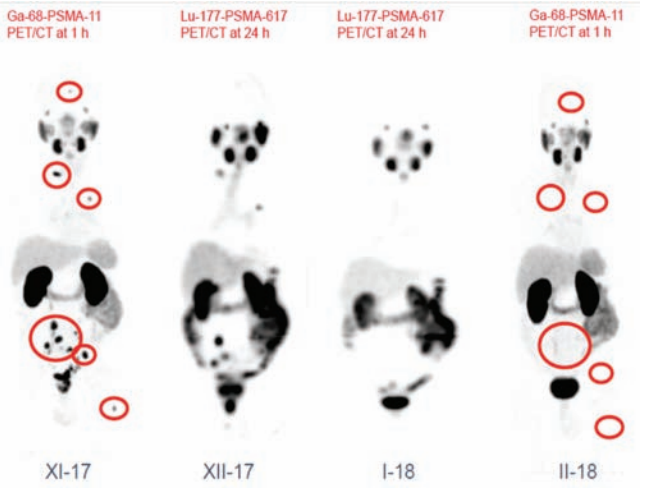


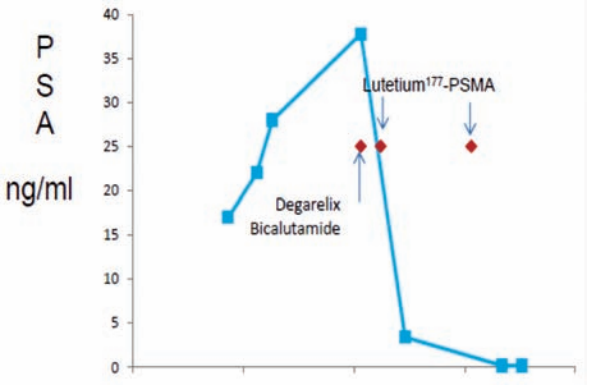


Case 3. Aggressive GS 9 /4+5) prostate cancer in biopsies was found with PSA 28. Man was 59 years. Based on staging 4 by CT and bone scan, man was told that the given therapies according to National and International guidelines are not curative. Therefore he looked second opinion from DCC. Endorectal multiparametric prostate MRI together with NaF- and ^{68}Ga-PSMA-PET-CT confirmed the staging to be T4N1M1. A 9x23 mm lymph node chain and a separate 7 mm node in the mesorectum on the left side, a 3 and a 5 mm suspicious node on the right side, and more cranially in the mesorectum at least two 7 mm nodes, a 9 mm obturator and a 9 mm external iliac node on the left and a 7 mm external iliac node, on the right M1a: 10 mm right common iliac node. In ^{68}Ga-PSMA-PET-CT active and aggressive prostate malignancy was observed mainly in the left lobe with local extension and extensive lymph node disease in the pelvic spaces, the lymph node disease located predominantly on the left with a total volume of 75 cm^3 and it was very active with SUVmax ad 47.

There was lymph node disease in obturator, perirectal, parailiac (ext/int), common iliac, presacral nodes. Wide-spread skeletal disease with low volume (25 cm^3), classification 1/3, but with high uptakes e.g. in lower spine (SUVmax >30); solitary metastases in the skull, spine, thorax and left proximal femur. Since the disease was shown to be aggressive, man was young and very healthy, and the cancer cells appeared to be avid for PSMA we decided to start the therapy using Lutetium^{177}-PSMA together with more traditional hormone treatment. Patient decided to stop smoking also.

In the first early response evaluation PSA went down 37.8 to 0.16 ng/ml and the response was confirmed also by ^{68}Ga-PSMA-PET-CT scanning, demonstrating practically complete response by imaging. Earlier active and aggressive prostate malignancy was not anymore active (SUVmax < 2.7). The local extension and extensive and active lymph node disease in the pelvic and retroperitoneal spaces (obturator, perirectal, parailiac (ext/int), common iliac, presacral nodes) had completely vanished. Similarly, the wide-spread skeletal disease (skull, spine, thorax and left proximal femur) had fully disappeared. The PSMA-positive disease (skeletal 25 cm^3 + lymph nodes 75 cm3) demonstrated a visual metabolic complete response. Quantitative "PERCIST"-response turned out to be -93%.





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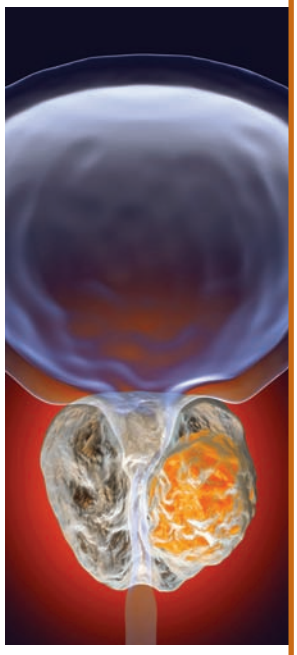
China

前列腺癌



PET/CT 作为当今分子影像最先进的诊断手段之一，在肿瘤早诊、分期、疗效评价及放疗定位等方面发挥着重要作用。新型核素探针的应用更为 PET 技术增加原动力。众多专家提及基于 PET/CT 的新技术、新方法，有望为肿瘤诊疗带来全新的突破，例如用核医学技术治疗泌尿系统肿瘤中的前列腺癌。

前列腺癌是老年男性常见的恶性肿瘤，且前列腺癌的生物学行为差异很大。因此，对于不同前列腺癌患者要进行个体化诊疗。其中，精准的影像学诊断、定位、分期是实现前列腺癌患者个体化诊疗的基石。

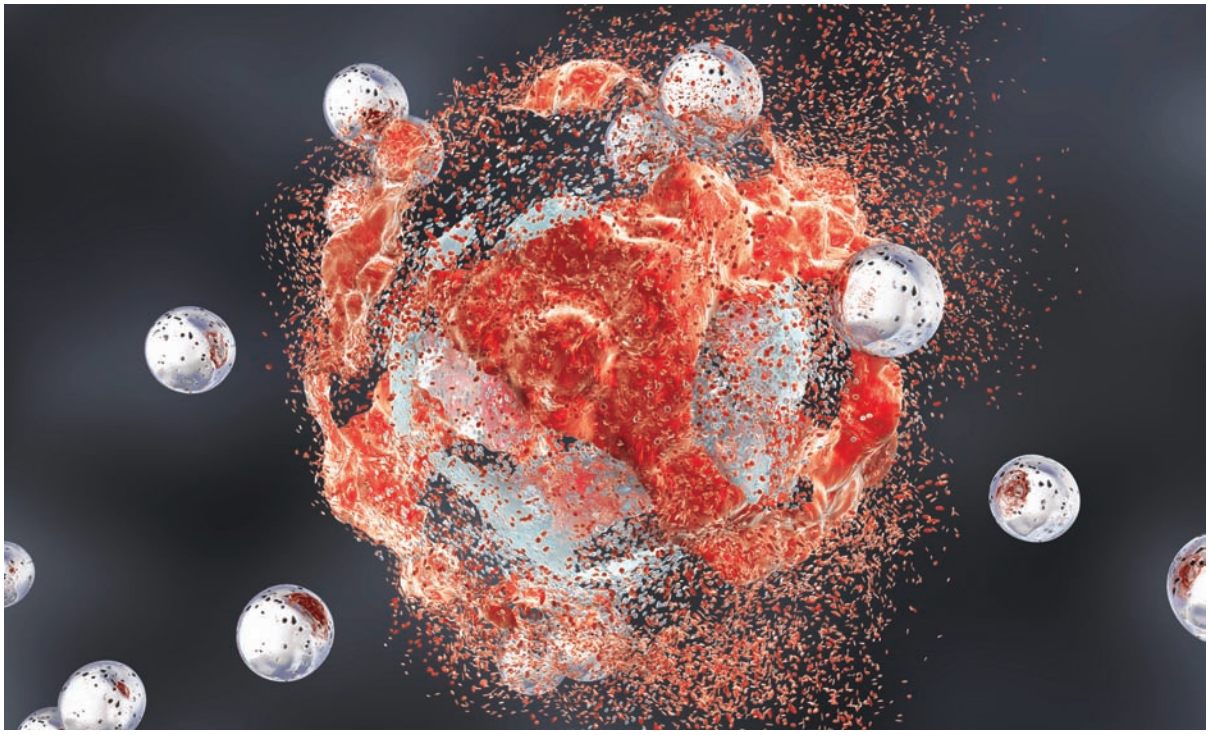
以往对于前列腺癌患者的影像学检查方法主要包括超声、核磁（MRI）以及骨扫描等，但上述检查均存在一定的局限性，例如无法有效地检出前列腺外的病灶，无法早期检出生化复发性前列腺癌患者的病灶等。

随着对前列腺特异性膜抗原（PSMA）研究的深入，研究者发现 PSMA 特异性表达于前列腺上皮细胞，并在前列腺癌组织中高表达，尤其是转移性或去势抵抗性前列腺癌中，表达水平更高，这一特征使得 PSMA 可成为前列腺癌分子影像诊疗一体化的分子靶点。

目前，国际多项临床研究已经证实，PSMA PET/CT 对于诊断前列腺癌、评估病灶范围有重要价值，且在患者生化复发早期，甚至血 PSA 水平很低且其他影像检查手段均无阳性发现时，即可辅助检测出病灶，修正了近40%～60%的患者临床治疗方案的制定。

由于 PSMA PET/CT 显像优异的诊断效能，该检测方法目前已被国内外指南或专家共识所推荐。更重要的是，对于一线化疗失败等去势抵抗性前列腺癌患者，若经 PSMA PET/CT 显像证实其病灶高表达 PSMA，还可通过治疗药物 177Lu-PSMA 进行放射性核素治疗，对前列腺原发及转移病灶进行“精准定向打击”，实现“所治即所见”。

目前，该种核素靶向治疗转移性去势抵抗性前列腺癌患者的有效性以及安全性已得到临床研究充分印证，将有可能成为改善前列腺癌患者预后、延长其生存期的新兴方法和有力“武器”。



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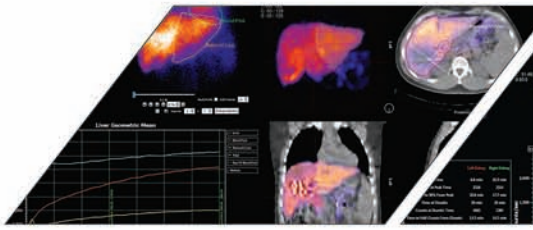

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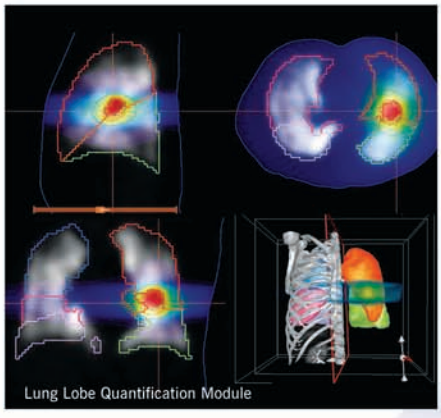

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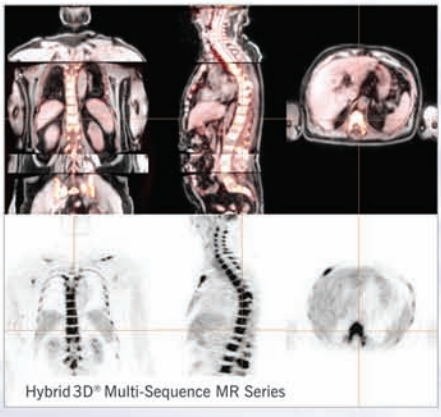

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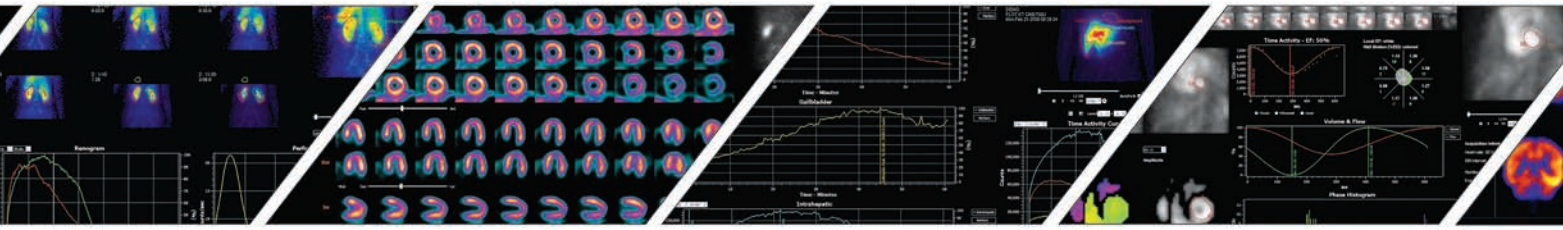

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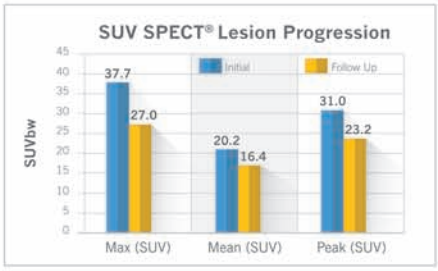

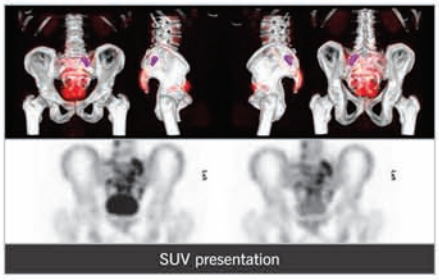

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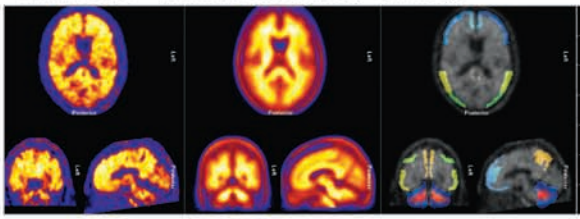

Region Name	SUVr (Z)
Average SUVr	1.65 (2.13)
L Frontal Ctx	1.52 (2.92)
R Frontal Ctx	1.68 (4.24)
L Ant Cingulate	2.15 (5.50)
R Ant Cingulate	2.31 (5.12)
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René Fernández, MD

Médico egresado de la Universidad de Concepción.
Especialista en Medicina Nuclear formado en el Hospital Clínico de la Universidad de Chile.
Encargado de terapias del Centro de Medicina Nuclear y PET/CT PositronMed, Santiago de Chile.
Secretary General - Theranostic World Congress 2021, Santiago de Chile.

AGENTES TERANOSTICOS Y CÁNCER DE PRÓSTATA EN CHILE

El impacto del cáncer de próstata es hoy en día inconmensurable y los números lo avalan, es el segundo cáncer más común y la quinta causa de muerte por cáncer a nivel mundial. Lo anterior ha gatillado desde hace ya varios años a múltiples investigadores en la búsqueda de nuevas opciones de tratamiento que logren controlar la progresión de esta enfermedad y especialmente mejorar la calidad de vida de estos pacientes.

Un grupo de especial preocupación son aquellos pacientes con cáncer de próstata diseminado en los cuales las terapias que reducen las concentraciones de hormonas androgénicas (terapias de privación androgénica o TDA) ya no logran el control de la enfermedad, condición conocida como enfermedad resistente a las hormonas o resistente a la castración.

El año 2004 Docetaxel fue aprobada como primera línea de quimioterapia, desde ahí, varios nuevos tratamientos sistémicos han demostrado prolongar la sobrevida en pacientes con cáncer de próstata que progresan pese al bloqueo hormonal, incluyendo fármacos como la Abiraterona, Enzalutamida, Cabazitaxel y el ^{223}Radio, pero pese a estas terapias se ha observado que la enfermedad continua avanzando, siendo entonces los pacientes referidos a unidades de cuidados paliativos tratando de mejorar su calidad de vida, pero principalmente orientados en lograr un "buen morir".

Investigaciones recientes con agentes teranósticos, es decir moléculas que pueden ser empleadas tanto para una terapia como para el diagnóstico de una enfermedad, han abierto una oportunidad para el manejo de estos casos, apuntando a diversos blancos terapéuticos o al mismo blanco, pero por vías metabólicas distintas.

El radiofármaco ^{177}Lutecio-PSMA-617 es hasta ahora el más prometedor de estos nuevos agentes teranósticos, fue presentado recién el año 2015, introduciendo una renovada alternativa para los pacientes con cáncer de próstata cuya enfermedad progresa bajo la terapia estándar. Este agente fue desarrollado por el Centro Alemán de Investigación Oncológica y el Hospital Universitario de Heidelberg, y ya desde los primeros estudios demostró ser una terapia segura y efectiva en el manejo de esta condición, siendo múltiples los estudios que hoy así lo avalan. El ^{177}Lutecio (^{177}Lu) es un átomo radiactivo que gracias a la emisión de radiación β (electrones) logra administrar una dosis nociva de energía para la célula tumoral. En este caso es unido a una molécula el PSMA-617, la cual se fija específicamente a una glicoproteína llamada antígeno de membrana prostática específica (PSMA, por sus siglas en inglés), que es sobre-expresada 100 a 1000 veces más en la superficie de la célula neoplásica prostática versus el tejido normal. De esta manera, de una forma precisa se logra tratar a la célula enferma, eliminándola una a una.

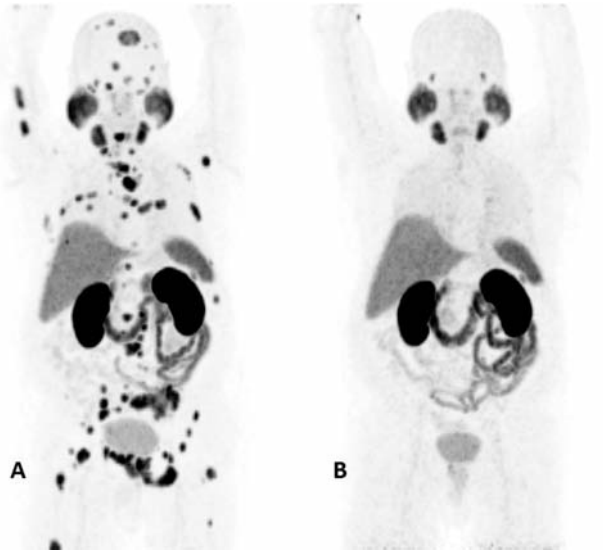


Figura 1: Paciente con antecedentes de cáncer de próstata avanzado resistente a la castración. A) Imagen MIP PET-CT ^{68}Ga-PSMA-11 pre terapia con evidencia de múltiples metástasis óseas y ganglionares del cáncer prostático. B) Imagen MIP PET-CT ^{68}Ga-PSMA-11 tras 8 semanas de la 4ª dosis de ^{177}Lu-PSMA-617, sin identificarse focos de captación que sugirieran viabilidad tumoral.

En Chile, a contar del año 2016 hemos introducido en nuestro centro esta nueva opción terapéutica, a la fecha han sido tratados 22 pacientes con cáncer de próstata con el radiofármaco ^{177}Lu-PSMA-617, hombres que van desde los 51 a los 84 años de edad, quienes han recibido en suma 61 dosis de este agente teranóstico. Al evaluar este grupo de pacientes con un PET-CT con ^{68}Galio-PSMA-11 previo al tratamiento observamos que todos tenían metástasis óseas, dos tercios adicionalmente presentaban compromiso tumoral ganglionar y alrededor de un 20% tenían también compromiso neoplásico en otros órganos. Tal como ya estaba descrito, la gran mayoría no presentaron efectos adversos al tratamiento y si los presentaban eran leves, correspondiente a un descenso en el recuento de leucocitos en sangre y al desarrollo de sequedad bucal, condiciones que no requirieron terapias adicionales, manteniéndose estos casos solo bajo observación. En cuanto a los resultados del tratamiento se logró un descenso mayor al 50% en los niveles de antígeno prostático específico (APE o PSA por sus siglas en inglés) en más de la mitad de los casos tratados y más importante aún, prácticamente en todos hubo mejoría en su calidad de vida, alcanzando inclusive en dos pacientes una respuesta terapéutica completa, es decir ausencia de enfermedad, evaluable por APE indetectable en el seguimiento y un PET-CT post terapia sin evidencias de captación patológica.

Adicional a lo anterior, hemos trabajado en otros tres protocolos clínicos que han sido previamente aprobados por un comité de ética, buscando evaluar la dosimetría, seguridad y eficacia de distintos agentes teranósticos destinados a pacientes con cáncer de próstata que progresan estando en una condición de resistencia a la castración, es así que se ha administrado a 10 pacientes el radiofármaco ^{177}Lutecio-PSMA-ALB-56, molécula derivada del PSMA-617 que contiene un espaciador de nueva generación, lo que permite que se una a la proteína plasmática albúmina, esto permitiría hipotéticamente una mayor disponibilidad y circulación del agente teranóstico, es decir más cantidad del radiofármaco y por más tiempo, mejorando así la fijación y el efecto terapéutico sobre las células neoplásicas. Otros 4 pacientes han recibido ^{177}Lutecio ligado al antagonista sintético del receptor de bombesina (RM2), este receptor se encuentra sobre-expresado en varios tumores, incluyendo hasta en un 50% el cáncer de próstata que progresa bajo TDA, convirtiéndose así en un potencial agente teranóstico alternativo, especialmente para aquellos pacientes que presentan baja expresión de PSMA o potencialmente mayor expresión relativa de RM2. Finalmente, 10 pacientes han recibido el agente ^{177}Lu-DOTAMZOL, este radiofármaco de última generación está basado en la estructura del ácido zolendrónico, medicamento que pertenece a una clase llamada bifosfonatos, fármacos que reducen el recambio óseo que se produce en las metástasis óseas, disminuyendo las complicaciones por ellas generadas como las fracturas y el dolor, condiciones habituales en pacientes con cáncer de próstata avanzado o en fase terminal.

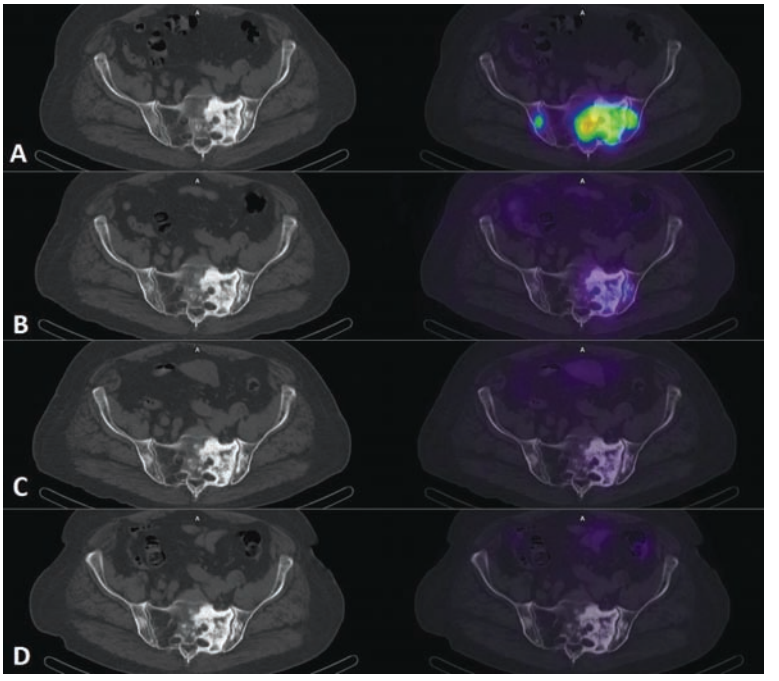


Figura 2: Imágenes SPECT/CT de paciente con cáncer de próstata avanzado bajo tratamiento con ^{177}Lu-PSMA-617. En columna izquierda CT con lesión osteoblástica en sacro y hueso iliaco derecho y en columna derecha imagen fusión SPECT/CT realizadas 24 hrs. post 1ª dosis (A), 2ª dosis (B), 3ª dosis (C) y 4ª dosis (D) respectivamente, con progresiva menor captación del radiofármaco, sugerente de respuesta a terapia.

Creemos que es además importante señalar que estas nuevas opciones terapéuticas han estado disponibles a pacientes no solamente chilenos, sino también a otros provenientes de distintos lugares de Sudamérica, recibiendo en nuestro centro a la fecha a tres pacientes brasileños, uno colombiano y uno boliviano, a quienes hemos tenido el gusto de ofrecer una alternativa de terapia para la delicada condición que les afectaba y cuando ya parecía no existir alguna.

Finalmente, podemos destacar que en lugares aparentemente tan apartados como Chile se tratan y evalúan diversos agentes teranósticos que han demostrado una promisoria actividad anti tumoral, un perfil de toxicidad bajo y más importante aún mejoran la calidad de vida en hombres con cáncer de próstata avanzado y que han progresado luego de tratamientos estándar incluyendo quimioterapia y terapias anti-androgénicas de nueva generación. ■

INTERVIEW WITH:
SAVVAS FRANGOS

Dr. Frangos, the nuclear medicine community knows you quite well through your secretary position at the EANM. They might not know your leadership role in the Cyprus nuclear medicine community. Can you describe the status of nuclear medicine in Cyprus and the activities of the Cyprus Society of Nuclear Medicine?

Nuclear medicine was introduced in Cyprus in 1972 by Dr. Aristides Costeas, who returned to Cyprus in 1968 with a PhD in Biophysics from the Sloan Kettering Institute, Cornell University. Nuclear medicine in Cyprus today, thanks to the tremendous involvement of all those working in the field, is now a well-established specialty. All nuclear medicine examinations and therapies, including PET/CT examinations can be done in Cyprus. Greater interest in nuclear medicine has now begun to develop amongst young physicians.

The Cyprus Society of Nuclear Medicine was formed in 1999 in Nicosia. Founding members were nuclear medicine specialists, medical physicists, nuclear medicine technicians and other doctors (cardiologists, oncologists) with a special interest in nuclear medicine. I had the honor to be the first president. The society became a member of the European Association of Nuclear Medicine and the World Federation of Nuclear Medicine and Biology. The current president is Dr. Ourania Demetriadou.
The society organized various conferences and seminars including IAEA training courses and also the first International Conference of Radionuclide Therapy (ICRT). This year the society celebrates its 20th birthday and organizes a high-level conference between the 6th and 10th of November 2019. We are thankful to those world class leaders in nuclear medicine who have accepted our invitation to come to Cyprus and share this special time with us.

You have been practicing Nuclear Medicine for a few decades and also travelling the world. In your opinion, which changes have you witnessed in the practice of Nuclear Medicine?

The changes have been dramatic. Both in equipment but also in the way that nuclear medicine specialists are practising. In most countries Nuclear Medicine specialists were seen as 'scan interpreters' and there was a distinction between a clinician and a nuclear medicine specialist. In my opinion, Nuclear Medicine specialists dealing, at first with the therapy of Thyroid Cancer and later with the introduction of other therapies are practising clinical work in the best way possible. They understand better the pathophysiology and in combination with the profound knowledge of radiobiology, nuclear medicine specialists are the most suitable people to treat patients with radionuclides. Also, the introduction of Hybrid Imaging has improved the accuracy of the diagnosis. The description is now based on anatomy. Positron emission is adding value and the discovery of new radiopharmaceuticals for diagnosis and therapy are leading Nuclear Medicine to new heights and wider range of acceptance.

As Past Secretary of the EANM, Past President of the Cyprus SNM and the current treasurer of the World Federation of Nuclear Medicine & Biology, where do you think the field of nuclear medicine will be heading in the upcoming decade?

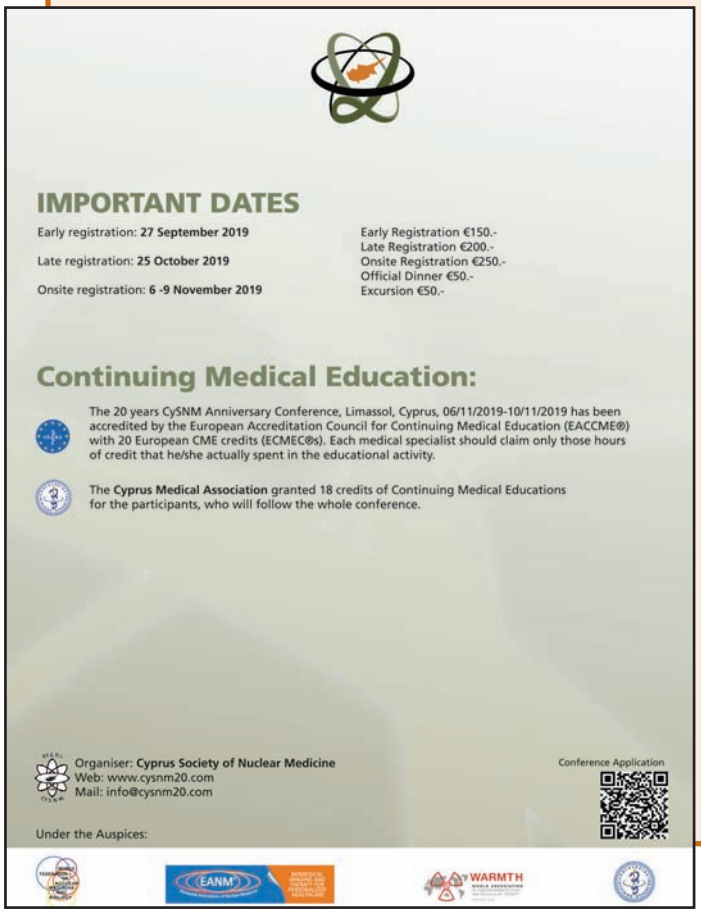
This is an easy question: Therapy will be the main focus of Nuclear Medicine. As I mentioned before the discovery of new radiopharmaceuticals and the use of Theragnostics (treat with knowledge) is the future of nuclear medicine. Also, a great part will be in the evaluation of Therapies, especially in Oncology. The accuracy of PET/CT with specific radiopharmaceuticals including labelling of Oncology therapeutically agent can either predict the success of the therapy or evaluate the therapy. If the therapy shows failure then it could be interrupted and switched to another therapy. Made to measure therapies could be achieved.

The education of the young generation of nuclear medicine professionals is a subject close to your heart. Which advice/recommendation can you give to the young physicians that are considering a career in nuclear medicine?

I am a member of the executive committee of the section Nuclear Medicine of The European Union of Medical Specialists (UEMS) which is dealing also with the education on Nuclear Medicine. European Standards in Medical Training regarding Nuclear Medicine are established and published. More details can be found at: https://www.uems.eu/__data/assets/pdf_file/0017/43523/UEMS-European-Training-Requirements-NUCMED-final.pdf Even though the Standards are not compulsory, many European but also non-European countries are following those recommendations. The advice to young physicians is to join the Nuclear Medicine world. It is a fascinating way of practicing medicine. It is a combination of basic knowledge and clinical work and they can work closely with other specialties for the best benefit of the patient.

Dear Friends,

The Cyprus Society of Nuclear Medicine (CySNM) is looking forward to celebrating its 20th birthday with all those friends and colleagues who have contributed to the society's success. We strongly believe that the best way to achieve that is through the organization of an "Anniversary Conference". The conference will be held between 6 and 10 November 2019 at Atlantica Miramare Hotel Limassol Cyprus. This would not just be a standard nuclear medicine conference. Though Cyprus is a small country we have had a big impact in the world of nuclear medicine and we wish to share our birthday with all our good friends worldwide. We are thankful to those world class leaders in nuclear medicine who have accepted our invitation and come here to Cyprus to share this special time with us. We will structure the meeting such that there will not only be exciting and learned lectures but there will be plenty of time for interaction and discussion including lively debates on controversies concerning nuclear medicine and its application.



For detailed information please visit
our web page at

www.cysnm20.com

Rena Demetriadou
President CySNM & Chair Organising Committee
Savvas Frangos
Chair Scientific Committee
info@cysnm20.com
www.cysnm20.com

Spotlight on:
Society of Nuclear Medicine and Molecular Imaging

The Society of Nuclear Medicine and Molecular Imaging (SNMMI) is a nonprofit scientific and professional organization representing more than 16,000 nuclear medicine professionals worldwide. The Society's Outreach Committee works to help patients and the medical community—including referring specialists, as well as nurses, technologists, and other healthcare providers—understand the value and appropriate uses of nuclear medicine. Through the Committee and its Working Groups, the Society offers a variety of practical resources for both healthcare providers and patients.

For Healthcare Providers

SNMMI Roadshows
The Society offers healthcare providers education on nuclear medicine topics through a variety of roadshow symposiums throughout the United States. Roadshows currently ongoing or under development provide education on neuroendocrine tumor therapies, DaT SPECT scan reading and interpretation, and lymph node mapping. For a current listing of roadshows and to register for events in your area, visit www.snmmi.org/outreach.

Speakers
SNMMI regularly provides speakers on nuclear medicine topics for national, regional, and state medical society meetings as well as institutional grand rounds and other events. If your organization would like to have an expert speaker on a nuclear medicine and molecular imaging topic, please email outreach@snmmi.org for more information.

PET PROS Documents
SNMMI offers numerous resources for physicians ordering PET/CT imaging, including:

- The SNMMI Coding Corner, offering answers to a variety of nuclear medicine coding questions
- *Elements of PET/CT Reporting*, a comprehensive guide to help physicians create accurate, useful patient reports (includes sample reports)
- Educational brochures on diagnosis and treatment plans
- Charts and diagrams for use in physician offices on the topics of liver segments, neck nodes, and small lung nodules

For more information, visit www.snmmi.org/PETPROSResources.

Appropriate Use Criteria

The SNMMI, working with numerous medical societies including the American Society of Clinical Oncology, the North American Neuroendocrine Tumor Society, the Society for Pediatric Radiology, the Society of Thoracic Surgeons, the Society of Interventional Oncology, the European Association of Nuclear Medicine, and others, is developing a series of Appropriate Use Criteria (AUCs) to describe when, and how often, certain diagnostic procedures should be performed.

These criteria are developed using a systematic review of evidence followed by a process that includes identification of relevant clinical scenarios, a systematic synthesis of available evidence, individual and group ratings of the scenarios using a formal consensus process, and document drafting based on final group ratings and discussions.

To date, AUCs have been published on the following topics:

- Somatostatin Receptor PET Imaging in Neuroendocrine Tumors
- FDG PET/CT Restaging and Response Assessment of Malignant Disease
- Hepatobiliary Scintigraphy in Abdominal Pain
- Ventilation/Perfusion Imaging in Pulmonary Embolism
- Bone Scintigraphy in Prostate and Breast Cancer
- Amyloid Imaging

AUCs are currently under development for the following topics:

- Gastrointestinal Tract Imaging
- Infection Imaging
- PET-Myocardial Perfusion Imaging
- Prostate Cancer
- Differentiated Thyroid Cancer

The AUCs, including charts offering ratings-at-a-glance, can be found at www.snmmi.org/auc.Factsheets offering overviews of the AUCs a well as the charts are available for physician office use; to learn more, email outreach@snmmi.org.

For Patients

www.DiscoverMI.org
This website, created specifically to meet the needs of patients, offers videos, factsheets, and information on a variety of diseases and conditions as well as nuclear medicine procedures.

Patient Factsheets
SNMMI offers dozens of patient factsheets on various diseases and procedures as well as the general information factsheets on "What is Nuclear Medicine and Molecular Imaging?" "What is PET?" "Optical Imaging" and "Nuclear Medicine and Radiation Safety." Many factsheets are available both in English and Spanish. To view and download, visit www.snmmi.org/factsheets.

Patient Education Day
Each year, the SNMMI and its Patient Advocacy Advisory Board offer a Patient Education Day in conjunction with the SNMMI Annual Meeting. This full-day program includes general session presentations on topics such as an introduction to nuclear medicine, radiation safety and clinical trials; breakout sessions on specific disease areas; a tour of relevant technologies in the SNMMI exhibit hall; and a networking lunch and reception.

The 2019 SNMMI Patient Education Day will be held June 23 at the Anaheim Convention Center and Arena in Anaheim, California. The program for this free event will be available in spring 2019 at www.discovermi.org.

SNMMI Patient Advocacy Advisory Board

The SNMMI works closely with a Patient Advocacy Advisory Board (PAAB) to keep its members informed of the patient perspective with regard to nuclear medicine; to advocate for legislative, policy and insurance coverage decisions that promote quality patient care; and to educate patients and caregivers on nuclear medicine diagnostic and therapy procedures.

Organizations currently represented on the SNMMI's PAAB include:

- Alzheimer's Association
- Colon Cancer Alliance
- FORCE: Facing Our Risk of Cancer Empowered
- Lung Cancer Alliance
- Lymphoma Research Foundation
- Men's Health Network
- NorCal CarciNET Community
- Susan G. Komen Foundation
- ThyCa: Thyroid Cancer Survivors' Association
- WomenHeart: The National Coalition for Women with Heart Disease
- ZERO: The End of Prostate Cancer

Patient advocacy groups interested in applying for representation on the PAAB should email outreach@snmmi.org.

PAAB members Theresa Wickerham (ThyCa), Josh Mailman (NorCal CarciNET), Stephen Schwartz (LRF), Rosemary Ciotti (FORCE), and Jeri Francoeur (Susan G. Komen) participated in a 2018 U.S. Capitol Hill Day to educate legislators on issues regarding patient access to diagnostic radiopharmaceuticals.

Photo courtesy of Josh Mailman

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CANM ACMN

The Canadian Association of Nuclear Medicine
Association canadienne de médecine nucléaire

The Canadian Association of Nuclear Medicine (CANM) is in the process of establishing national guidelines for the performance and interpretation of Nuclear Medicine procedures in Canada with the aim to support the Nuclear Medicine specialists of Canada with readily accessible information as well as the hope of standardizing procedures across Canada as much as possible.

Our first initiative was a review of V/P SPECT Lung Scanning for Pulmonary Embolism. A subcommittee of four Nuclear Medicine specialists who have extensive experience in Lung Scanning was established. This group did a review of guidelines and approaches and quickly determined that the EANM guidelines from 2009 were ideal for Canada, and we quickly endorsed these guidelines.

Our group, however, felt that it was important to review some more up to date literature and to establish an executive summary and a short review for quick and easy reference for both the Nuclear Medicine specialist and the referring Physician.

Our committee hopes that readers find our approach useful. **(View page 44)**

Christopher O'Brien,
MDCM FRCPC
Medical Director,
Nuclear Medicine
Brantford General Hospital,
Brantford Ontario
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COMMITTEE MEMBERS

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DR. MICHEL TESSIER

DR.GLENN OLLENBERGER

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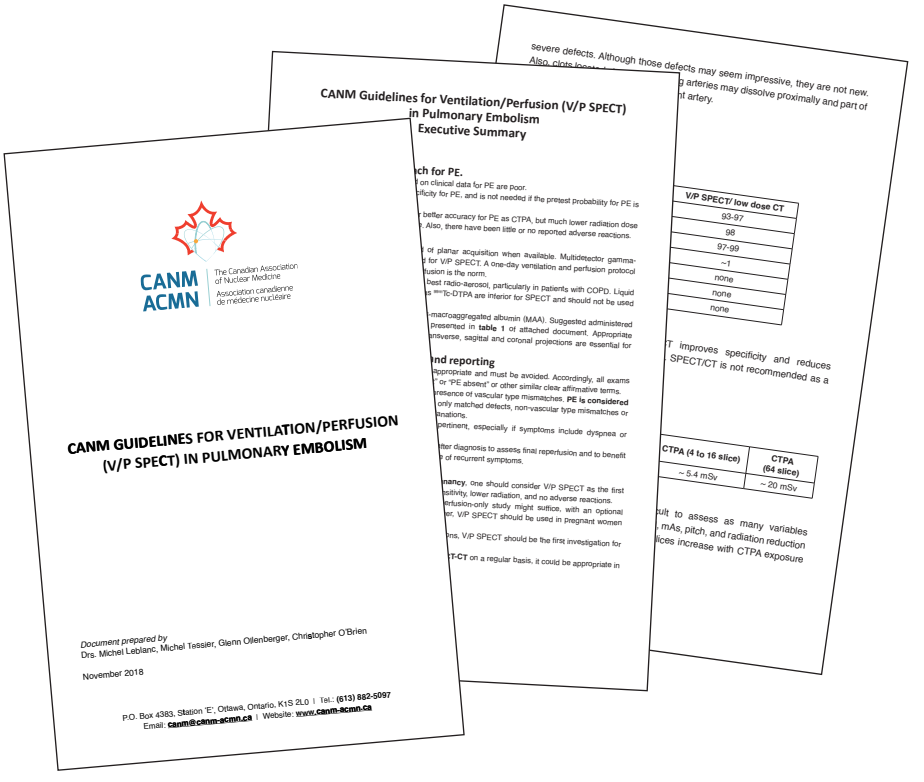

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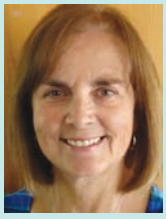

Hélène Samson

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President Canadian Association of Nuclear Medicine

The Canadian Association of Nuclear Medicine is more than honored to work closely with the International Associations or Societies of Nuclear medicine in the World. It is with all of us sharing our expertise that we will succeed in providing to our patients the best of what Nuclear Medicine can offer.

The future of Nuclear Medicine is so bright either in the diagnostic field as in the treatments that our biggest challenge at the moment is to train enough nuclear medicine specialists and technologists.

Nuclear Medicine is on a supersonic development.

The Canadian Association of Nuclear Medicine also believes that all of us should do more to make known the plus value of Nuclear Medicine to patients, to our governments and to the doctors as much to the specialists as to the general practitioners.

CANM is sincerely committed to this vision and his collaboration to the magazines LePatient or the Epatient are one of the examples of our implication.

www.lepatient.ca
www.nmpangea.com

EANM Barcelona Spain 12-16 October 2019
ALASBINM Lima Peru 13-16 November 2019
CANM Ottawa Canada 23-25 April 2020
SNMMI New Orleans USA 13-16 June 2020
EANM Vienna Austria 17-21 October 2020
WFNMB Kyoto Japan 7-11 September 2022

SISTER ORGANIZATIONS

SNMMI Society of Nuclear Medicine and Molecular Imaging
EANM European Association of Nuclear Medicine — Biomedical Imaging and Therapy for Personalized Healthcare
World Federation of Nuclear Medicine and Biology
AIPES
ARCENM
ASNC
AFNMB Asia Oceania Federation of Nuclear Medicine and Biology
IAEA International Atomic Energy Agency
alasbimn Asociación Latinoamericana de Sociedades de Biología y Medicina Nuclear
SFMN Société Française de Médecine Nucléaire et imagerie moléculaire
ARSNM Arab Society of Nuclear Medicine
South African Society of Nuclear Medicine

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Wake Forest University / Baptist Medical Center

PSMA – THE FUTURE OF PRECISION THERAPY FOR PROSTATE CANCER? AN OVERVIEW

The buzz word "Theranostics" refers to the use a radioactive targeting molecule for both therapy and diagnosis. This is a concept dating back to 1946 when the first treatment of radioiodine Theranostics for thyroid disease was performed. Since then, multiple advancements in molecular imaging have paved way to an exciting future for targeted treatments. As doctors we understand that every patient is different from the other, then why should every patient be 'mass treated' with standard therapy for a disease that behaves differently in each patient? The allure of Theranostics is that it opens up a pathway for precision medicine by presenting the possibility of precise therapies for each patient.

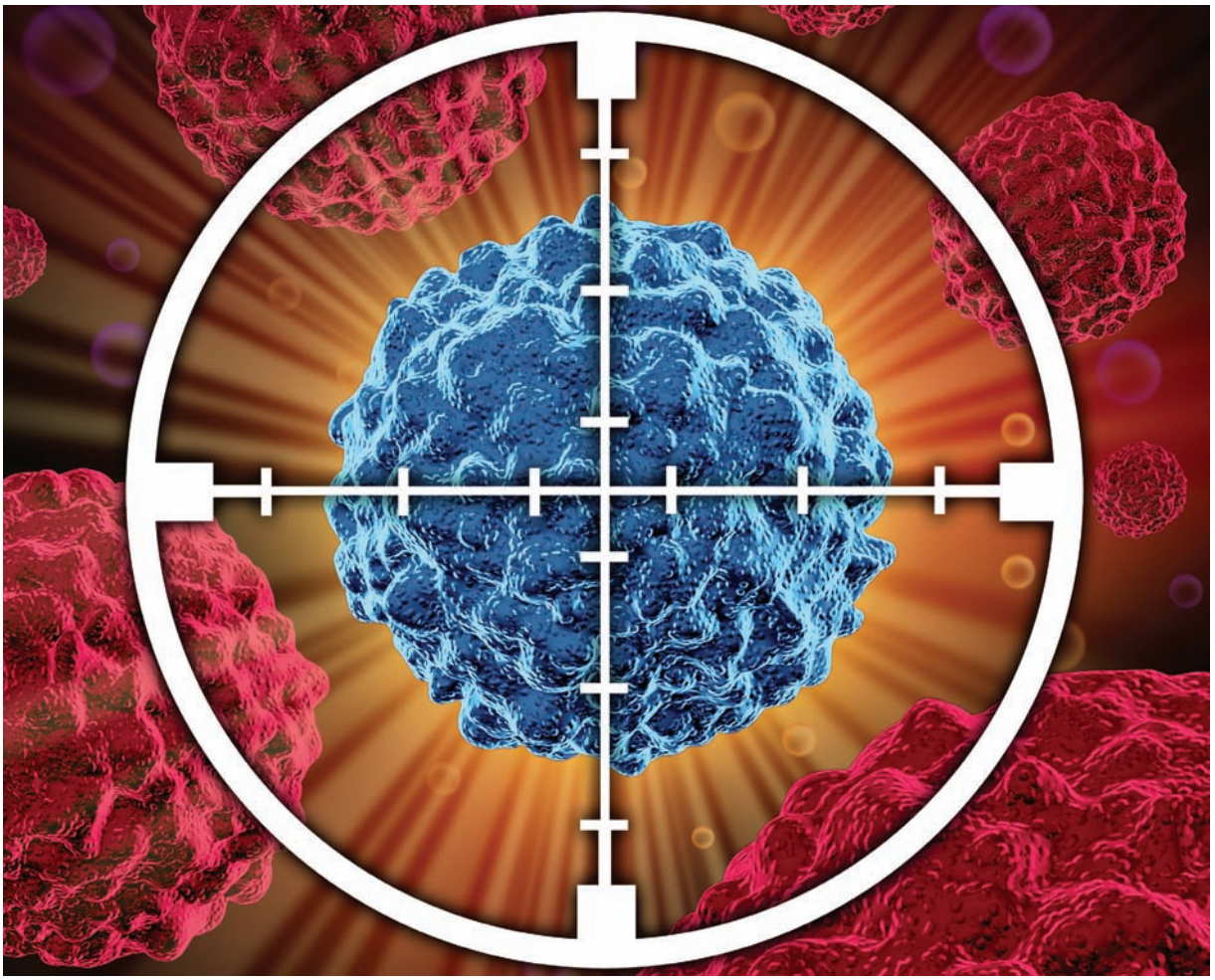
As the United States eagerly awaits FDA approval of PSMA PET imaging probes, it will be interesting to see how PSMA will evolve in the coming years. As for those who are not familiar with the compound, this article will hopefully shed some basic light on current practices and internationally reported experiences.

What is PSMA?

Prostate specific membrane antigen or glutamate carboxypeptidase II is a 750-amino acid type II transmembrane glycoprotein.

Why PSMA?

While PSMA is not unique to prostate cancer (PC); it is also expressed in other normal tissues and neoplastic tissues. However it is upregulated and overexpressed in PC, increasing in poorly differentiated, hormone-refractory and metastatic PC. This feature enables PSMA to become increasingly expressed in malignant tissues compared to benign prostatic tissue and non-targeted normal tissues



making it an ideal molecule for both diagnostic and therapeutic purposes of PC.

What are PSMA ligands?

They are small peptide targeting agents that are highly PSMA-specific which bind to the extracellular structure of PSMA and subsequently undergo cell internalization or endocytosis by the PSMA receptor. They contain 3 components – a binding motif, a radiolabel bearing moiety such as a chelator or prosthetic group and a linker molecule which connects both binding motif and radiolabel bearing moiety. Their small size enables them to have rapid plasma clearance, thereby reducing stagnant background irradiation to normal tissues.

Isotopes

The development of F-18 labelled PSMA ligands seems practical as it would allow for commercial distribution in larger areas compared to the required on-site production of Ga-68. Although, currently 68Ga-PSMA-11 conjugated with chelator HBED-CC is being used for diagnostics, whereas 177Lu-PSMA mAb J591 and 177Lu-PSMA-617 are used for therapeutic applications. Lutetium-177 is a beta emitter with a half-life of 6.7 days and a maximal penetration of 2 mm. This short path length of emitted beta particles is beneficial in minimising side effects as it travels a short distance within tissues. On decay, Lu-177 emits gamma-rays that enable image acquisition and dosimetry determination using SPECT or planar imaging following treatment.

Safety

Overall the PSMA ligands have demonstrated a favourable safety profile with multiple studies reporting low toxicity and good antitumor activity. Widely reported toxicity with Lu177-PMSA ligands includes hematotoxicity (anemia, leukopenia and thrombocytopenia), xerostomia, nausea, fatigue and low grade renal toxicity.

Example of a Therapy protocol

Indications for RLT - include patients with PSMA-positive metastatic disease, progressive disease despite newer hormonal therapies or chemotherapy, patients not suitable for chemotherapy, patients not suitable for 223-Ra-dichloride therapy due to visceral metastasis or diffuse osseous metastases.

Imaging prior to the RLT- include imaging with PSMA-PET or SPECT imaging to verify PSMA positive lesions and renal scintigraphy to rule out obstructive dysfunction. Renal dysfunction must be treated prior to therapy.

Lab prerequisites – WBC > 2,000/microliter, Hb>8g/dl, Platelets > 75,000/microliter, creatinine <2mg/dl.

Proposed therapy protocol: 4-6 cycles of therapy 177Lu-PSMA given every 6-8 weeks with external cooling of the salivary glands with icepacks 30 minutes prior therapy to 4 hours post therapy to reduce risk of radiation damage through vasoconstriction, reduced blood flow and decrease PSMA uptake in salivary glands.

Follow up: PSMA-PET or SPECT imaging before first cycle and after the last cycle to assess efficacy, lab monitoring with blood counts, renal and liver panels every 2 weeks after therapy.

Efficacy

Multiple studies have demonstrated a significant decline in PSA, statistically significant difference in overall survival, positive response on imaging and reduction of symptoms following radioligand therapy with PSMA. Radionuclide therapy with PSMA has shown improved survival outcomes when compared to chemotherapy or second-generation antiandrogen hormonal therapy.

Studies have indicated low efficacy of PSMA in the presence of negative indicators such as second line chemotherapy and visceral metastasis.

Developments and future directions for RLT with PSMA

Developing new ligands - Modifications in the linker region of the ligand can alter the effects of the characteristics of the ligands and help in making new ligands.

Intraoperative tumour localisation - by dual-labelling a PSMA ligand with a radionuclide and a fluorophore.

Alpha-emitting radioisotopes such as 225-Actinium are being studied as they have shorter path lengths of 40 micrometers when compared to 2 millimeters seen with beta particles, reducing toxicity, particularly to the bone marrow.

Use of combination therapies – additional use of cytotoxic and radio-sensitizing drugs which inhibit DNA repair mechanisms may increase efficacy of RLT.

Synergistic therapeutic effect of androgen deprivation and PSMA-based radionuclide therapy must be studied since the androgen deprivation is known to upregulate PSMA expression.

PSMA-targeted drug delivery and PSMA-targeted photodynamic therapy are other potential Theranostics applications.

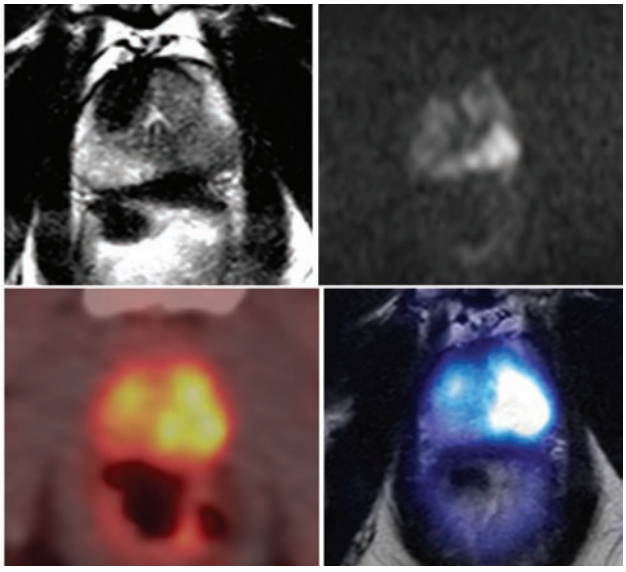
Emerging multimodal probes are being developed for PET-MR and SPECT-MR for precision diagnosis which will dictate research directions in molecular imaging.

Hybrid imaging and prostate cancer

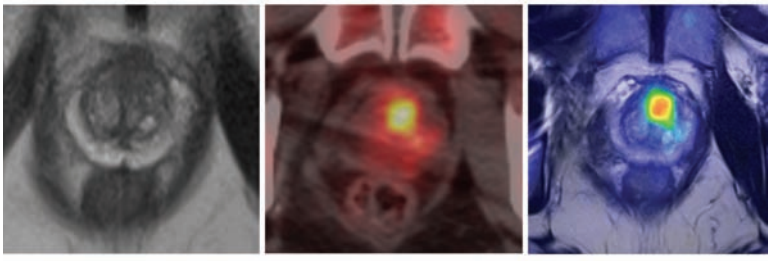
In theory, PET-MRI is the perfect imaging tool to provide simultaneous structural and functional information. MRI is now being widely used for the grading of prostate cancer owing to its excellent tissue characterization and high spatial resolution. With the advent of PSMA ligands labelled with positron emitting isotopes, PET/MRI shows great

promise by providing a synergistic combination of micrometric anatomic resolution and phenotypic tissue characterization.

At our centre, F18-Fluciclovine-PET is routinely being performed for the staging of prostate cancer and we have observed an excellent correlation between areas of abnormal and increased tracer uptake on PET with contemporaneous MRI lesions. This is nicely illustrated in the following sets of images.



60y/m with biopsy proven prostate cancer. Top left image: T2 weighted MRI image demonstrating a T2 hypointense lesion in the left posterior peripheral zone; top right image: same lesion demonstrating restriction on DWI; bottom left picture: F18-Fluciclovine-PET demonstrating avidity in the left hemi prostate; bottom right image: fused images of PET-MRI shows reliable registration of the lesion between the two image sets.



76y/m with suspicion of prostate cancer. Left frame:T2 weighted MRI image with poor delineation of the lesion due to tissue heterogeneity; middle frame: Focal tracer uptake on the F18-Fluciclovine-PET; right frame: fused images of PET-MRI depicting excellent registration of the lesion.

It will be exciting to see how PSMA based imaging and hybrid imaging will fare in the coming future as we are ready to replace PET-CT and MRI as individual modalities with PET-MRI as standard imaging for different types of cancer.

The implementation of PET/MRI in routine clinical imaging practice and patient management will require a concerted effort in the part of the stakeholders to address, among other challenges, the regulatory requirements, education and training of technologists, radiologists and nuclear medicine physicians, reimbursement, cost effectiveness and optimization of clinical workflow.

Conclusion

We have come a long way since the inception of the treatment of thyroid cancer with radioiodine. The few available nuclear Theranostics compounds of the 21st century have already triggered a true renaissance of the field of nuclear medicine.

Radio-labeled PSMA ligands are poised to become the new blockbuster radiopharmaceuticals that we have hoped for a long time. In combination with sophisticated hybrid imaging equipment such as PET/MRI, we anticipate that it will become a major disruptive paradigm in the management of prostate cancer. Their meaningful use in clinical practice will require a high level of collaboration among all stakeholders that could ultimately significantly benefit patient care. ■

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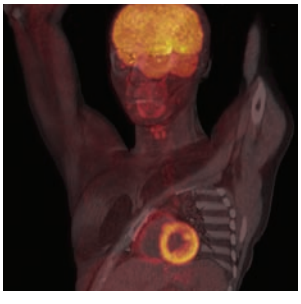
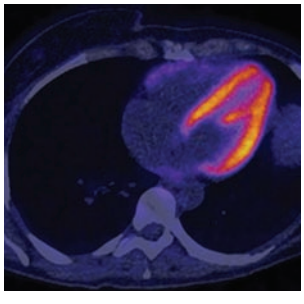
The healthcare market operates in a constant state of flux, which can be challenging as you strive for better clinical outcomes, faster workflow, and consistent quality of results.

What if you were able to visualize smaller lesions, get information for more accurate staging and patient risk stratification, and manage operational inefficiencies to facilitate the most appropriate treatment strategy[1]?





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3.2 mm LSO crystals[1]
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Accuracy to reveal the bigger picture.
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Reproducibility to understand disease progression.

[1]Based on internal measurements (resolution and time of flight) compared to current systems. Data on file.

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POSITRON EMISSION TOMOGRAPHY (PET)

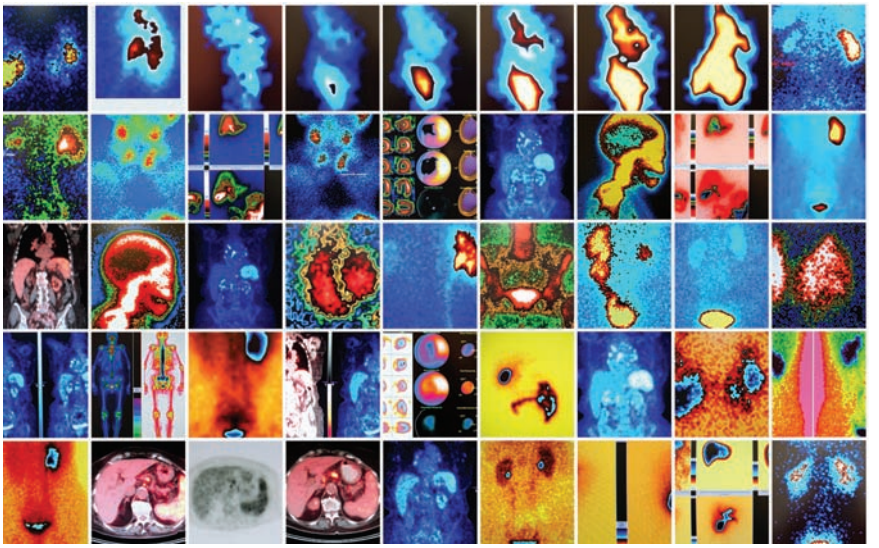
Positron Emission Tomography (PET) is a cutting edge, non-invasive, diagnostic imaging technique which allows the measurement of biochemical processes or the expression of cellular receptors by the use of positron-emitting radioactive tracers. The imaging tracers most often contain atoms naturally found in organic molecules, but in the form of radioactive analogues of Oxygen (^{15}O), Nitrogen (^{13}N), Carbon (^{11}C) or Fluorine (^{18}F) atoms.

Developed during the 70s to study the normal and pathological brain function, in the 90s, PET became an important clinical tool for oncological imaging following the demonstration of its usefulness in the detection of several cancer types.

Initially confined to research centers, PET has spread rapidly since 1998 to the vast majority of important oncologic centers in industrialized countries. Since 2001, PET has been paired to axial computed tomography (CT) (Figure 1) in order to better locate lesions by relation to the anatomical structures. It also facilitates the interpretation of results by improving the specificity and, furthermore, combined PET/CT data allows the planning of radiation therapy treatment. PET/CT images also have a considerable advantage for planning the surgical approach, since an accurate anatomical localization may be established. It is also possible to merge any PET study to any three-dimensional imaging including MRI and SPECT tomography, even if they have been obtained on different devices or at different times (Figure 2).

Gradually, the price of PET/CT devices has dropped by half and now can be purchased for 1.2M$. The scanner allows the accomplishment of a full study from the neck to the pelvis in less than 25 minutes, thus improving considerably the productivity of PET and helping to reduce the cost of each exam (throughput of 15-20 exams per scanner per 8 hours). Since 2005, PET/CT technology deployed quickly in the public and the private health systems across Canada. However, in 2014, access to PET is very different from east to west provinces and Canada is still behind many developed countries. Quebec is by far the province providing the best access to this technology. Quebec is also the first province which has deployed the latest generation of PET/CT devices to regional hospitals away from academic and research centers.

As with the studies performed in conventional nuclear medicine (bone or thyroid scan, myocardial perfusion, etc.), PET/CT is performed after the intravenous injection of a radioactive substance called radiotracer. Over the past few years, several radiotracers have been developed for the detection of cancer and the most important is the fluorine-18 Fluorodeoxyglucose (^{18}F-FDG). The fluorine-18, with a half-life of 110 minutes, is the isotope of choice for cancer imaging. This isotope can easily be distributed to multiple institutions and its long half-life allows it to accumulate at levels that are sufficient for imaging with adequate contrast for tumor detection. The molecule of ^{18}F-FDG is an analogue of glucose obtained by substituting a hydroxyl (-OH) group of a glucose molecule by a radioactive fluorine atom with a nucleus that contains more protons than neutrons. This atypical ratio of protons/neutrons makes the atom unstable and the latter must expel a positive charge in the form of



a positron to regain its stability. The PET devices are conceived to detect radioactive emissions induced by these positrons, and to precisely locate this emission inside the body. At the cellular level, the ^{18}F-FDG uses the same transmembrane carriers as glucose, and its passage is transporter – and insulin – dependent. After its entry into the cell, the ^{18}F-FDG is phosphorylated by the hexokinase, but it rapidly stops advancing into the glycolysis cascade. It thus becomes sequestered in the cell where it accumulates. The ^{18}F-FDG permits to obtain cellular information relative to the cell viability and metabolism based on the metabolic rate of the cellular glucose.

The excretion of ^{18}F-FDG is mainly through the urinary tract, regardless of if the patient is diabetic or not, because the ^{18}F-FDG molecule is not completely reabsorbed by the renal tubules, unlike glucose. There is also a certain proportion, very variable from one individual to another, which is excreted by the intestines. Figure 3 (left) shows a normal biodistribution of ^{18}F-FDG compared to the image on the right which illustrates the important consumption of ^{18}F-FDG by striated muscle due to a non-respected fasting/ glucose-free procedure. Figure 3 (right) is considered non-diagnostic. Consequently, the exam must be repeated at a later date.

The ^{18}F-FDG PET is aimed at four main fields of clinical application: oncology, cardiology (Figure 4), neurology (Figure 5) and infection/ inflammation (Figure 6). Overall, in a general hospital, more than 95 per cent of the examinations currently carried out are for oncologic indications. The rationale behind the use of ^{18}F-FDG PET in oncology is based on the increased use of glucose by the neoplastic cells, a phenomenon closely linked to the neoplastic transformation. A rapidly growing neoplasia is also ischemic in its center, hence favoring the metabolic pathway of lactic acid, which greatly increases the demand for glucose. A non-negligible proportion of the uptake also comes from the inflammatory cells surrounding the tumor. It should be noted, however, that these phenomena vary significantly depending on the type of neoplasia.

Although PET is excellent to detect neoplastic lesions, it has limitations. Some cancers have slower growth and do not substantially increase their ^{18}F-FDG accumulation and may remain undetectable (false negative). The activated neutrophils and macrophages can consume a lot of glucose and the highly inflammatory lesions can also incorporate this radiotracer (false positive). In particular, active granulomatous inflammation (tuberculosis, sarcoidosis) as well as abscesses can cause false positive results (Figure 7). Conversely, some well-differentiated cancers, such as prostate cancer, high mucinous content tumours, well differentiated neuroendocrine tumors, and certain lobular breast cancers may have a low uptake. Others, such as the hepatocarcinoma, possess phosphorylases, which allow cells to quickly eliminate the ^{18}F-FDG. A list of clinical indications for oncology PET with ^{18}F-FDG is detailed in Tables 1 and 2. Taken together, lung cancer (Figure 8) and lymphoma indications represent about 50% of the available imaging time on a PET scanner.

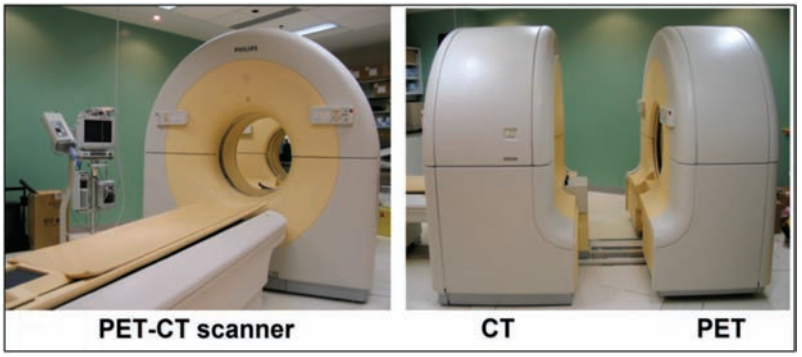


Figure 1:
PET/CT scanner allowing to sequentially obtain an axial tomography (CT) and a positron emission tomography (PET) during a same medical visit.

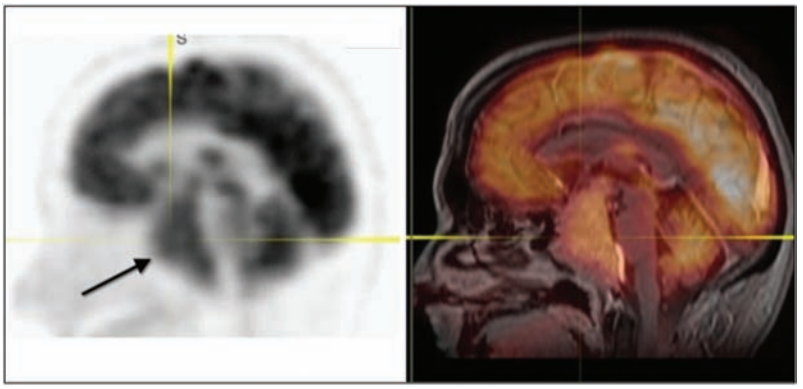


Figure 2:
Current software which enables the merging of PET not only with the CT, but with all 3D imaging modalities, including MRI. PET-MRI fusion allows better localization and characterization of the neoplastic cerebral lesions (the arrow shows a voluminous pituitary prolactinoma).

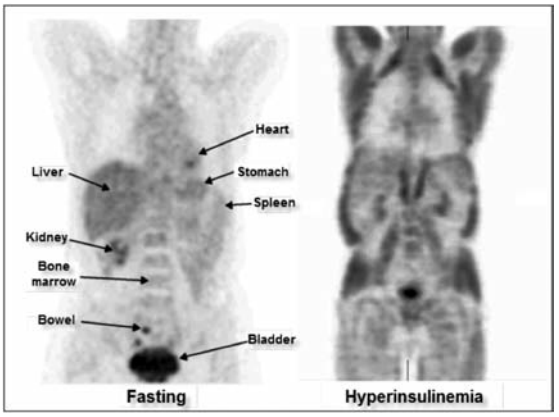


Figure 3:
PET studies performed in two different patients. The image on the left illustrates a normal biodistribution of FDG in a patient having observed the fasting procedure. The image on the right has been obtained in a patient with dextrose solute (diffuse muscle uptake induced by hyperinsulinemia).

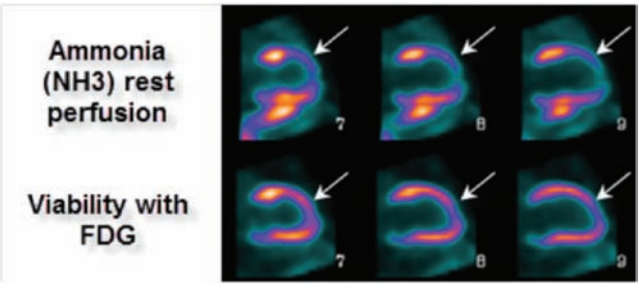


Figure 4:
This PET exam uses ammonium to assess myocardial perfusion at rest and FDG for viability. This exam is more sensitive than Thallium for the demonstration of severely ischemic regions at rest or hibernating myocardium in order to orient the therapeutic approach (to increase the ejection fraction and decrease morbidity). The example illustrates severe hypoperfusion at rest (rest ischemia) in the region of the descending anterior, completely viable on the FDG study. The study therefore suggests that this wall will resume a normal kinetic after revascularisation that will result in gain of ejection fraction.

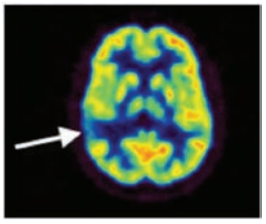


Figure 5:
Brain FDG PET in search of inter-ictal epilepsy foyers. Right temporal hypometabolism testifies to an epileptic foyer (arrow).

Table 1:

- Characterization of a mass: benign versus malignant
- Evaluation of the extension of the disease (staging and restaging)
- Orientation toward the most accessible biopsy site
- Detection of occult primary tumor site in patients with metastatic disease
- Detection of residual disease after chemotherapy/ radiotherapy or surgery
- Radiotherapy planning (delineation of gross-tumor-volume)
- Differentiation between relapse and post-surgical/ post-radiotherapy changes
- Biochemical evidence of relapse (elevated markers) without clinical signs or radiological evidences
- Follow-up or surveillance when conventional studies are equivocal or suspicious

PET should be an accessible exam to be considered by a specialist as well as the family physician. However, for a better management of the resource, it is important to recognize the strengths and weaknesses of the technique in order to ensure that the examination can answer the clinical and therapeutic dilemma. The following guiding points are to be considered if a PET/CT exam is to be requested:

Does the patient need to be fasting? Is fasting mandatory for all patients? What about diabetic patients?

Patients arriving for their exam must obey the fasting procedure (sugar-free) for at least 6 hours prior to the exam. Diabetic patients can take their oral hypoglycemic agents and their slow onset insulin dose in the morning of the examination day. However, special attention should be paid to metformin because this medication is responsible for a very intense bowel uptake (Figure 9). Thus, metformin should be stopped at least two days prior to PET if an intestinal lesion is suspected.

All sources of glucose (including lozenges, mints, gums, glucose in solution) must be strictly avoided so as to maintain circulating insulin at the basal level. If there is any doubt about the patient's glucose intake in the last six hours, the study should be deferred in order to observe fasting procedure for at least six hours (Figure 3). It is also required that the capillary blood glucose level at the time of injection is less than 10 mmol/L. If the result is higher than 10 mmol/L, one to two doses of rapid i.v. insulin can be injected in order to normalize the blood glucose level. An additional waiting period of 60 minutes is necessary to allow the exogenous insulin to be metabolized. The exam will be postponed to a later date if it is not possible to normalize the blood glucose level. It is therefore important to ensure that the diabetes is well controlled and that the glucose level is normalized (or almost) and stable before requesting an ^{18}F-FDG study.

Is there a reasonable doubt of neoplasia in respect to the clinical and para-clinical evaluation?

The prescription of an oncology PET study should ideally be limited to patients with proven or strongly suspected neoplasia. A clear clinical question should be included in the request form for the exam. It is the responsibility of the requesting physician to be as clear as possible.

What is the location of the neoplasia?

The degree of metabolism of a tumor must be put in relationship with the basal metabolism of the organ in which the tumor is sought (Figures 2 and 3). In some cases, this can cause interpretation problems and can limit the sensitivity of the examination. The bladder comes in at the first place of hypermetabolic organs due to the physiological urinary excretion. Fortunately, it is easy to significantly decrease the physiological activity in urinary bladder by diluting its activity through the i.v. administration of furosemide. This

protocol allows therefore to image high grade bladder cancer and to make the assessment of its extension (Figure 10). In contrast, since this is not a procedure carried out on all patients, it is important to specify in the request for examination if there is a suspicion of bladder neoplasia, lesion to the outer wall (implant of a gynecological neoplasia) or at the edge of the bladder (metastatic lymph node). The brain comes in second place of hypermetabolic organs. Unlike the bladder, there is no easy method to decrease brain activity other than by sedation. It is therefore difficult to locate brain metastases in this physiologically very active organ. MRI remains the imaging of choice in the assessment of neoplastic cerebral lesions, but PET is the imaging of choice for monitoring post radiotherapy response.

What is the size of the lesion under evaluation?

The sensitivity and resolution of PET equipment is increasing from year to year. In the optimal conditions, the technology currently available can detect lesions in the vicinity of 4.5 mm. Unfortunately, these perfect conditions are almost impossible to obtain in the human body, and a reasonable estimate of the camera resolution would be at about 6 mm. If the anomaly to be imaged is sought in a mobile organ, the sensitivity decreases as a function of the amplitude of the movement. It is therefore difficult to identify a nodule of 6 mm located at the base of the lung or an infra- centimeter hepatic metastasis juxtaposed to the diaphragmatic dome. To overcome this limit, imaging techniques synchronized with the respiratory rate are now available (respiratory gating).

What is the histological type of the initial tumor and its grade in a context of staging, restaging or when evaluating treatment response?

The higher or more undifferentiated histological the grade is, the more it will accumulate ^{18}F-FDG. Because of their low glucose metabolism, some histological types do not uptake any or will accumulate very little of ^{18}F-FDG so that the role of PET with FDG is limited for these types of tumors: well differentiated prostate cancer, some hypernephroma, small lymphocytic lymphoma (chronic lymphoid leukemia), marginal zone lymphoma, lymphoplasmocytary lymphoma (Waldenstrom), leukemia, well differentiated hepatocellular carcinoma, minimally invasive lung carcinoma (bronchiolo-alveolar), any tumors with high mucin component, low grade neuroendocrine tumor, low grade sarcomas (particularly liposarcoma), teratoma, and some well differentiated breast cancer (particularly the lobular carcinoma).

How much time should we wait between a PET study and the last surgery, radiotherapy or chemotherapy?

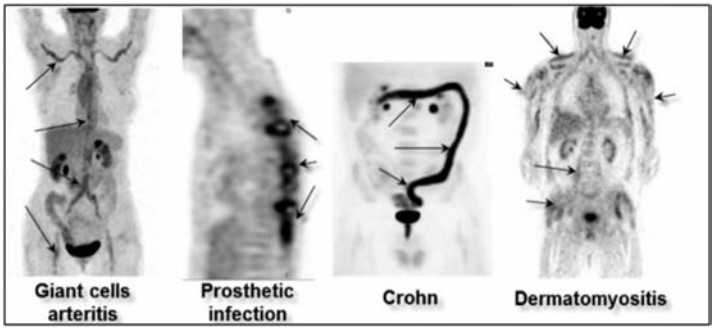


Figure 6:
PET FDG is not only useful in oncology. It can be used for the diagnosis and monitoring of giant cell arteritis, the search for infectious foyers (ex: infection of orthopaedic materials), the diagnosis of myositis/dermatomyositis and even in the assessment of inflammatory intestinal diseases.

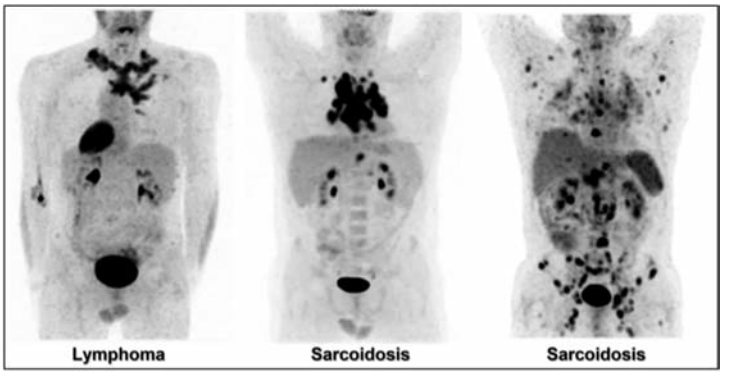


Figure 7:
Active chronic inflammatory granulomatosis conditions, like sarcoidosis, can resemble a lymphoma (center), or even a plurimetastatic disease (right). Some criteria, including the symmetric hilum distribution, the disproportion between the size of lymph nodes and their activity, the presence of lymph nodes and splenic calcifications, are elements in favor of a granulomatous disease. In cases where presentation is more atypical (image on the right), only a biopsy can differentiate between the two entities.

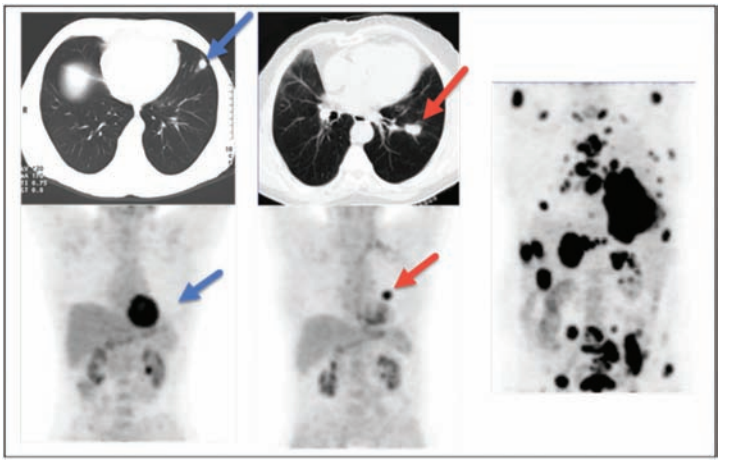


Figure 8:
Evaluation of an undetermined lung nodule. Left Images (CT and PET): Lung nodule to the lingula presenting no significant metabolic activity, compatible with a benign/inflammatory nodule (blue arrows). Center Images (CT and PET): Lung Nodule near the left hilum presenting very significant metabolic activity that is compatible with primary pulmonary malignancy (red arrows). Right Image (PET alone): Plurimetastatic disease (bone, lymph nodes, adrenal glands) from the left lung.

Table 2:

Brain:
- Relapse versus radionecrosis of high-grade gliomas post-radiotherapy
- Primary brain tumor versus metastasis: primary site search

Head and neck:
- Search for a primary site explaining metastatic cervical adenopathy
- Initial staging in suspected advanced stage
- Residual disease assessment post-treatment

Thyroid:
- Thyroid cancer when thyroglobulin level is elevated and radioiodine scan is negative
- Staging and restaging of poorly differentiated thyroid cancer, Hurthle carcinomas, or medullary thyroid carcinomas

Lungs:
- Classification of an undetermined lung nodule
- Pre-operative staging assessment
- Radiotherapy planning in case of significant lung atelectasis
- Relapse versus scar tissue formation post-surgery or post-radiation
- Lower sensitivity for the bronchiolar-alveolar adenocarcinomas

Breast:
- Initial staging and follow-up of locally advanced or metastatic cancer when conventional imaging studies are equivocal or suspicious
- More accurate in triple negative cancers or HER-2 overexpression
- Less sensitive if lobular or well differentiated (hormonosensitive breast cancer)

Oesophagus:
- Initial staging to assess respectability
- Restaging after an induction chemotherapy and/or radiation
- Response to treatment
- Radiotherapy planning

Stomach:
- Useless in the detection of a primary
- Only useful in metastatic assessment

Liver:
- Differentiate between benign or malignant lesions when conventional studies are equivocal or suspicious
- Search for liver metastases
- Cholangiocarcinoma (other than tubular or mucinous)
- Less useful for the well differentiated hepatocellular carcinoma

Pancreas:
- Pre-operative metastatic assessment
- Less useful in the characterization of a mass

Colorectal:
- Local Recurrence versus scar tissue
- Unexplained markers elevation (CEA) in post-therapy context
- Pre-surgical evaluation of a single liver lesion
- Pre-operative adenopathy assessment and search for metastases
- Treatment response
- Less sensitive in the presence of significant mucinous component

Melanoma:
- Search for metastases (Breslow > 1.5 mm), Stages II and III
- Restaging in patients with recurrent disease following therapy
- Less useful in Stage I, because the metastatic risk is < 5 %

- Hodgkin and non-Hodgkin lymphoma:
- Routine pre-treatment staging
- Measure treatment response, chemotherapy and radiotherapy
- Evaluation of relapse
- Restaging before bone marrow graft
- Guide biopsy to the most accessible site

Gynaecologic (cervix):
- Preoperative staging assessment
- Detection of residual disease after treatment
- Restaging at relapse
- Could be of interest for radiotherapy planning

Testicular:
- Search for metastases
- Chemotherapy / Radiotherapy response evaluation
- Teratoma content may cause false positive and false negative studies
- Residual mass assessment/surveillance

Bladder (with iv Lasix, voided bladder):
- Preoperative staging
- Search for metastases in the context of relapse
- Treatment response evaluation

Prostate:
- Should not be used if well differentiated histology and Gleason < 8
- Staging if histologically undifferentiated

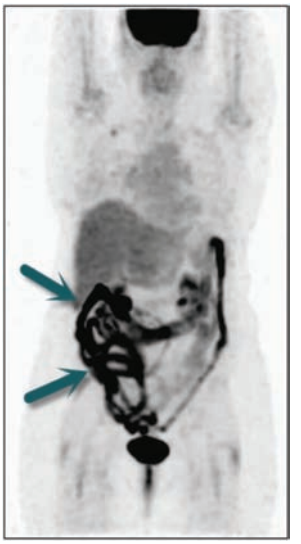
Sarcoma:
- More sensitive in high grade sarcomas
- Low grade tumors are frequently false negative

Especially for the evaluation of a local recurrence or that of a treatment response, it is recommended to wait four weeks between the PET study and surgery or chemotherapy, or to wait three months after the last radiation treatment, since the local residual inflammation could cause false positive results. If performed too soon post-treatment, the evaluation may be associated, depending on the case, to a higher rate of false positives or false negatives. It is also important to mention that if the patient is under hormonal therapy, this medication can also affect PET results, same as chemotherapy.

Is there an infection near the site under evaluation? Is the patient known for a non-neoplastic disease that naturally uptakes ^{18}F-FDG?

FDG PET does not provide a way to differentiate between a neoplastic lesion and an active infectious or inflammatory process (Figure 6), since the two latter will avidly capture the ^{18}F-FDG. It is therefore difficult, for example, to differentiate active tuberculosis foyer from a primary pulmonary malignancy or an abdominal abscess of a colonic neoplasia from a lymphoma. Some benign pathologies, like sarcoidosis, active Wegener, tuberculosis, uterine fibroid, thyroiditis, stomach ulcers, acute or chronic cholecystitis and many others may capture FDG. Without biopsy of the lymph node, it is often difficult to differentiate by PET a sarcoidosis from a metastasis or a lymphoma (Figure 7), a uterine fibroid tumor from a sarcoma or yet, the histiocytosis from a multifocal bone metastasis.

Figure 9:
FDG PET performed while taking metformin. Metformin modulates a highly intense FDG accumulation in the bowel (blue arrows) which makes it impossible to detect bowel lesions. Metformin should be stopped at least two days before FDG PET.



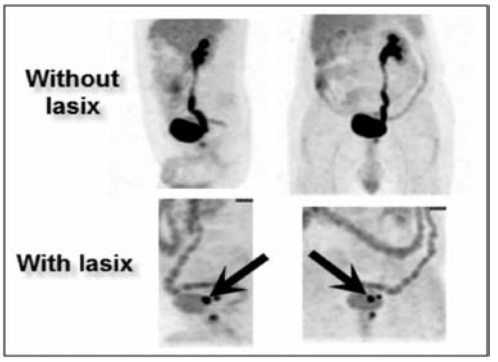


Figure 10:
In the physiologically hypermetabolic organs, some maneuvers may be attempted in order to decrease the basal metabolism and to allow visualization of the tumor. Bladder cancer is the typical example of how the use of a diuretic helps the bladder to drain quickly so that the tumor can be easily set apart (black arrows).

In other words, FDG may accumulate in places with active inflammation, be it acute, chronic, infectious or granulomatous. The distribution of the radiotracer and the appearance of lesions can sometimes allow the nuclear medicine specialist to distinguish between an infection, an inflammatory process or a neoplastic lesion, but it is important to remember that these conditions represent the most frequent cause of false-positive results.

FDG PET is now the oncology standard for several types of cancers. This very powerful diagnostic tool is only in its early stages in Canada and will be called upon even more in the coming years. Even if FDG is an excellent radiotracer for tumors and metastases localization, some cancers cannot be easily assessed with this radiotracer. Consequently, there is a need for new clinical tracers to increase the diagnostic accuracy of PET for cancers where FDG is less efficient. Sodium fluoride is one of the new tracers in clinic which allow earlier detection of the bone metastases (Figure 11). ^{18}F-MFES, an oestrogen derivative under clinical trial in BC and Quebec, is one of the most promising tracers for the detection and staging of hormonosensitive breast cancer (Figure 12).

Since there are multiple factors to consider in a FDG PET study, it is crucial to provide maximal clinical information to the nuclear medicine specialist who will be interpreting the imaging results (pathology reports, summary of surgical procedures, radiology results, blood biochemistry) in order to give a more precise answer to the clinical question. And, for more complex cases, a discussion with the nuclear medicine specialist may be relevant before prescribing the exam. ■

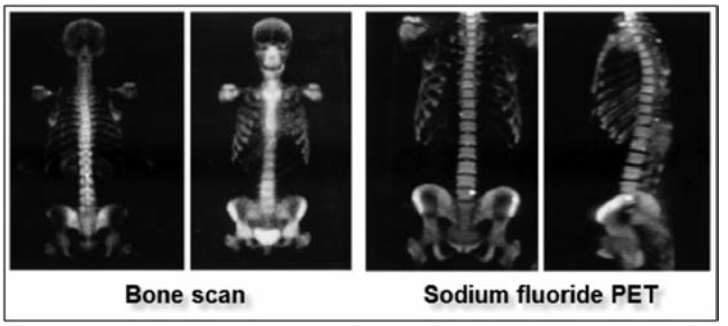


Figure 11:
The future of the PET lays within the development of new radiotracers enabling sensitivity increase of already existing exams and/or newer indications. The development of sodium fluoride PET (NaF PET) as a replacement for the conventional bone scan is an example. This study is carried out 30 to 45 minutes after the injection of the radiotracer and the acquisition of the images only lasts for 35 minutes (compared to a waiting time of 4 hours and 40 minutes imaging, on average, for a regular bone scan). With NaF PET, which is more sensitive and faster, it is possible to locate metastases as small as 5 mm.

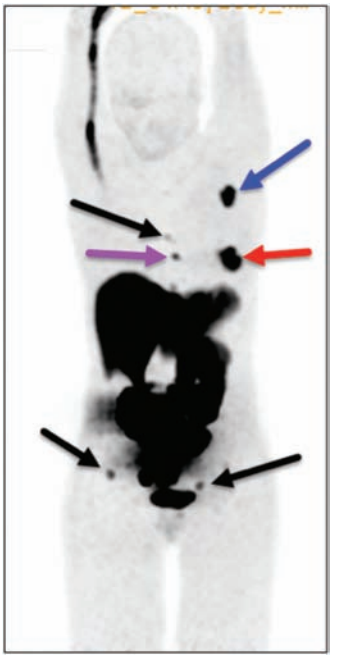
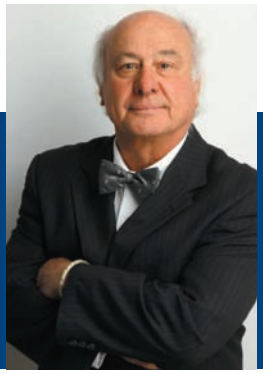


Figure 12 :
PET performed with ^{18}F-MFES, an oestrogen derivative highly sensitive to detect hormonosensitive breast cancer and metastasis. Clinical trials, funded by the Canadian Breast Cancer Foundation, are underway in Quebec and in the initial phase in BC. Red arrow: Primary breast cancer. Blue arrow: axillary metastasis. Purple arrow: internal mammary metastatic lymph node. Black arrows: Bone metastasis.

ANTIMATTER AT THE SERVICE OF NUCLEAR MEDICINE



François Lamoureux
M.D.,M.Sc., FRCPSC
President, CANM

We can now measure and visualize the metabolic activity of an organ in a human being and detect its functioning and integrity. This is positron emission tomography (PET) or, expressed another way, the functional imaging of cell metabolism.

Using PET, we can detect certain pathologies, such as cancer, which initially alter the normal physiology of cells.

In order to live, function and reproduce, the organism's normal cells need energy in the form of glucose (a sugar that can be metabolized by the organism.) This energy source is indispensable to all the living cells of the organism, and this sugar is found naturally in the blood. The more active a cell is, the more sugar it consumes.

A cancer cell that has lost all control over its unbridled multiplication must constantly consume large quantities of energy in the form of glucose (sugar).

In nuclear medicine, a glucose analog, deoxyglucose, is used as a decoy: it mimics glucose by entering cells but in a form that cannot be used as an energy source by the cancer cell.

To detect intracellular deoxyglucose, the molecule is radioactively labelled beforehand with a positron (antimatter) in the form of fluoride-18 (F-18).

As it accumulates in cancer cells, the positive electrons (e+) of F-18 come almost immediately in contact with the cell's negative electrons (e-). This produces a disappearance of the injected matter and antimatter, an annihilation reaction in which two photons are emitted at 180 degrees in the form of external radiation.

The cell becomes radioactive and the emitted rays are captured by an external PET camera. Powerful computers interfacing with the PET camera identify abnormal areas of radiation emission, a sign of the abnormal accumulation of F-18 FDG in the cancerous tissue.

The cancer tumour is detected and its activity is measured. Then a 3-D reconstruction is done, in multiple slices and dynamically. The result is an exploratory metabolic autopsy of the patient *in vivo* that is non-invasive.

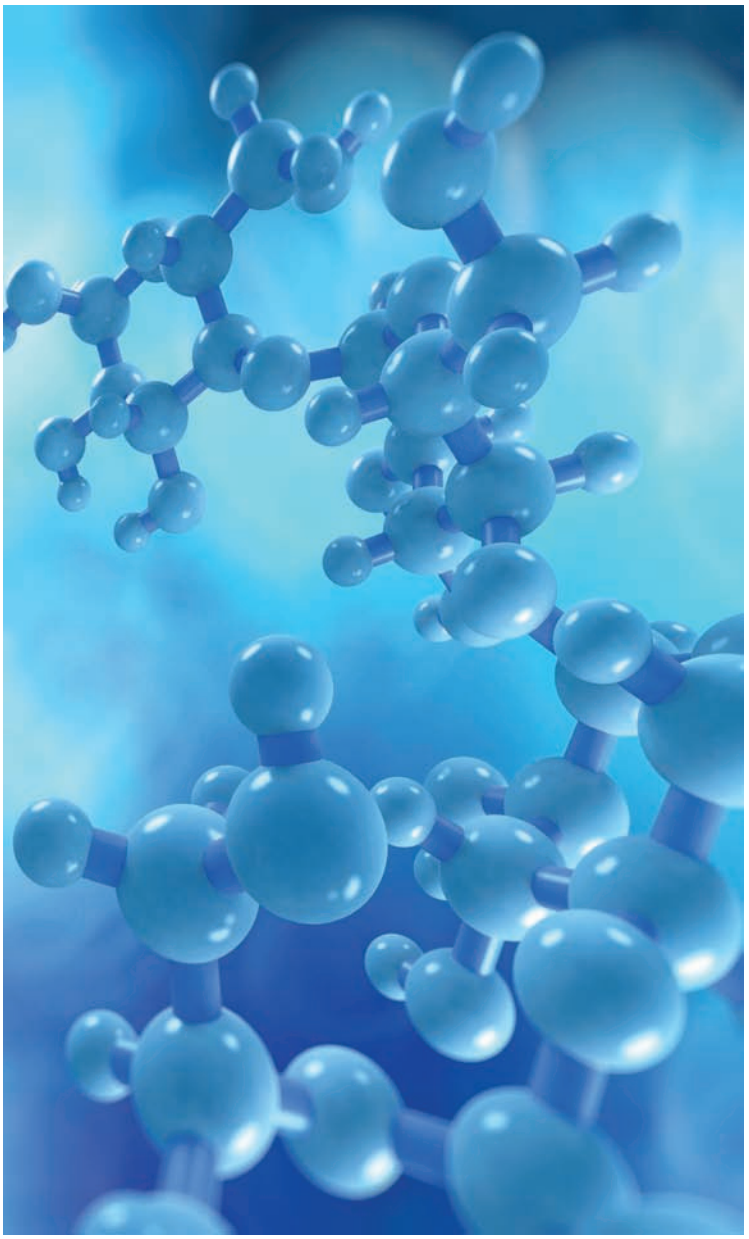
The external shape of the PET camera's detector resembles a tomodensitometer or magnetic resonance imaging device, but its function is completely different. The other two devices produce mainly anatomical images of the organs of the human body.

Moreover, today PET cameras are being teamed up with tomodensitometry detectors and, in the near future, will also be paired with magnetic resonance imaging devices in order to better localize the site of pathological processes.

With a simple intravenous injection of F-18 FDG that is painless and without identifiable side effects, we are pushing the diagnostic limits ever further and tracking down cancer cells in their very last cellular bastions.

While F-18 FDG is currently the most commonly used radioactive tracer, it is not the only one. Carbon-11, oxygen-15 and nitrogen-13, for example, can also be used to conduct neurological, cardiac or pulmonary exams.

In Quebec, PET technology is currently available in some nuclear medicine units. In mid-2008, thanks to new facilities in such places as Montréal, Quebec City, Chicoutimi, Gatineau, Rimouski and Trois-Rivières, this newly deployed technology enabled patients in centres that were not equipped with these cameras to have access to PET scans within a reasonable timeframe.



There are no inter-hospital charges or costs for either hospitalized patients or outpatients. The cost of each PET scan performed in a hospital centre is individually, directly and completely covered by the Government of Quebec. PET scans are prioritized based on a patient's clinical condition, whatever and wherever that may be, and not on the patient's physical location or the physical location of the PET camera.

Considering that PET technology has been applied as a just and universal social measure for all patients in Quebec, this is a success story and an example to follow. ■

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PSMA Theranostics for Prostate Cancer

Prostate Cancer and PSMA

Prostate cancer is the most common cancer and the second most common cause of cancer death in North American men. Prostate specific membrane antigen (PSMA, also known as folate hydrolase I or glutamate carboxypeptidase II) is expressed by greater than 90% of prostate cancers and its expression is further increased in poorly differentiated, metastatic and hormone-refractory prostate cancers, rendering it a useful diagnostic and therapeutic target in these patients.

Theranostics, a portmanteau of therapeutics and diagnostics, is a field of medicine which combines targeted therapy based on similarly-targeted diagnostic tests. Radiopharmaceuticals which are targeted to PSMA can be labeled with a positron-emitter to create in vivo whole-body scans with positron emission tomography (PET). In addition to PSMA PET imaging tracers, very similar radiopharmaceuticals can be created to release high-energy beta-minus particles for radioligand therapy (RLT) of prostate cancer. The lock-and-key principle in PSMA PET and PSMA RLT is identical – the only change is the nuclide, which can be swapped to allow for imaging or treatment, as needed.

These highly promising novel urea-based small molecule PSMA radiopharmaceuticals are rapidly making their way from the research setting to the clinic, both in the form of PSMA PET for early stage disease and PSMA RLT for metastatic prostate cancer.

PSMA Positron Emission Tomography

For reasons only partly understood, PET with ^{18}F-fludeoxyglucose (FDG) never showed adequate diagnostic performance in the prostate cancer indications where it mattered most – effectively shutting out these patients from the most advanced oncologic imaging in current clinical practice. PSMA-based imaging is finally unlocking the potential of PET for prostate cancer patients.

Early antibody-based attempts to image PSMA suffered from many drawbacks such as low count rates due to indium-111 labelling, less precise SPECT imaging, slow blood clearance and very poor target-to-background ratios – needless to say these were clinical failure. All of the new PSMA PET agents do not suffer from these drawbacks and are finally fulfilling the promise identified by earlier research.

To date, the most studied PSMA PET molecule has been ^{68}Ga-PSMA-11. However, more recently, much progress has been made with fluorine-18 (^{18}F) alternatives such as ^{18}F-DCFPyL. In comparison with 18F, gallium-68 (^{68}Ga) has a shorter physical half-life of 68 min, which can cause logistical problems when attempting to ship the tracer from central radiopharmacies. In addition, ^{68}Ga is produced by a generator and can only be eluted 3 times per day, with each elution only producing enough activity for 1 to 3 patient doses, depending on the generator strength and the synthesis time. This is limited in comparison with the number of doses that can be produced with ^{18}F, which is produced in much larger amounts by a cyclotron. Commercialization and widespread use of PSMA PET will most likely be with the ^{18}F-based tracers.

For the major prostate cancer body imaging indications, PSMA PET widely exceeds the sensitivity, specificity and accuracy of conventional imaging modalities such as CT & bone scan and significantly outperforms the prior gold-standard ^{18}F-fluorocholine PET.

PSMA PET for Staging of High-Risk Prostate Cancer

In the setting of high-risk prostate cancer, such as those with Gleason scores of 8 or more, high serum PSA at diagnosis or advanced clinical T-stages, up to 10–20% have extra-prostatic disease not detected by conventional imaging. Additionally, conventional imaging is sometimes inconclusive or equivocal, hampering doctors from making fully-informed treatment decisions. In patients with nodal disease amenable to surgical excision or pelvic radiation, PSMA PET allows physicians to adapt and personalize local therapy. Patients upstaged with PSMA PET-detected widespread metastases are offered systemic therapy and spared

invasive surgery or the side effects of radiation which would not be beneficial to their disease.

As PSMA PET gains wider acceptance, there is also a new-found realization that conventional imaging suffers not uncommonly from false-positives. Not every lymph node with a short axis of 1 cm or more harbors metastatic cancer, and not every scintigraphic lesion on bone scan is a metastasis. PSMA PET can, in certain cases, downstage patients while identifying a conventional imaging false-positive, allowing doctors to proceed with potentially-curative local therapy.

PSMA PET for Restaging of Biochemically Recurrent Prostate Cancer

Anywhere from 20–40% of patients undergoing radical prostatectomy and 30–50% of patients undergoing radiation therapy will experience biochemical recurrence, also known as PSA relapse, within 10 years. Because conventional imaging such as CT & bone scan are almost invariably negative in early biochemical recurrence, local therapies depending on disease localization were rarely possible, however PSMA PET promises to change this paradigm.

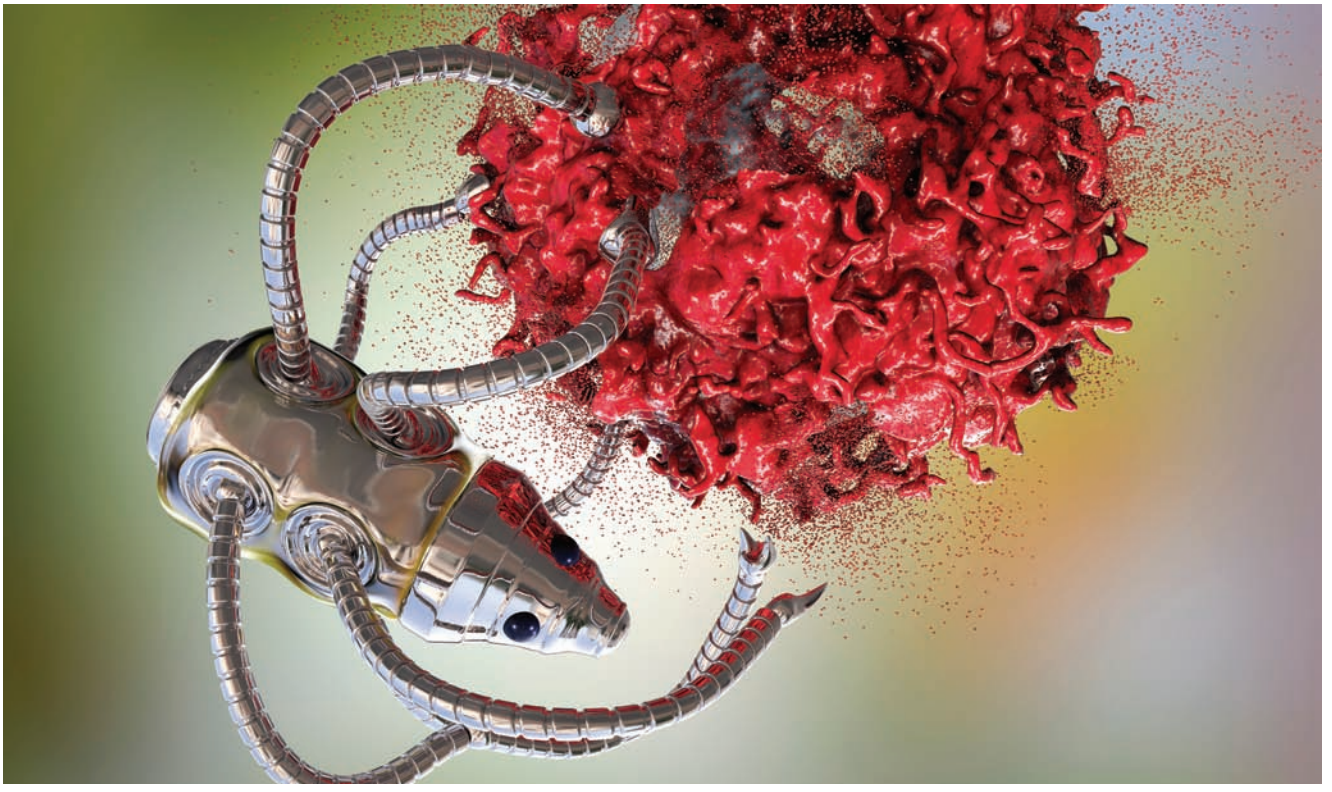
The advantage of PSMA PET is especially evident in patients with ultra-low PSA biochemical recurrence; detection rates of almost 60% have been reported in biochemical recurrence after radical prostatectomy in a PSA-range 0.2–0.5 ng/ml. In such early stages of recurrence, curative-intent salvage procedures such as secondary lymphadenectomy and targeted radiation therapy become a reality.

PSMA PET has shown great promise in radiation therapy planning in low-PSA biochemical recurrence, giving doctors a precise map of the disease locations so as to focus their treatment, giving additional radiation where the tumors are – and sparing the surrounding cancer-free normal structures. A number of randomized clinical trials are currently assessing the clinical impact of PSMA PET as a radiation therapy planning tool.

PSMA Radioligand Therapy for Metastatic Prostate Cancer

Metastatic disease is the final cause of prostate cancer related death. Initial management with hormonal therapy via chemical or surgical castration, plus or minus chemotherapy, is effective for patient with metastatic disease, however most patients will progress to a castration-resistant phase within 2-3 years. Recently, novel androgen axis drugs (NAADs) such as abiraterone, enzalutamide have shown significant survival benefit in a number of different clinical settings, however eventually patients also cease to be responsive to NAADs and will continue to progress.

Radioligand therapy (RLT) using PSMA-targeted small molecules attached to beta-emitters has demonstrated promising results. These molecules bind the extracellular domain of PSMA selectively with high affinity, and are internalized thus



allowing absorption of the intense energy emitted and resulting in cancer cell death. Hofman and his group in Australia published results from a single-arm, single-center phase II trial showing that treatment with ^{177}Lu-PSMA-617 RLT has high response rates, low toxic effects and reduction of pain in men with metastatic castration-resistant prostate (mCRPC) who have progressed after conventional treatments. Patients with mCRPC underwent a screening PSMA PET/CT confirm high PSMA-expression and of those treated, 57% achieved best PSA decline of 50% or more. Best responses in this trial are illustrated in Figure 1.

Recently, phase-II trials with another PSMA targeted small molecule, ^{131}I-PSMA-1095 have begun and interest is mounting in PSMA RLT with alpha-emitters such as actinium-225, which can theoretically deliver ever higher doses of radiation to metastatic lesions than ^{177}Lu.

PSMA PET and PSMA RLT Landscape

Despite very promising results, none of the above molecules are currently FDA nor Health Canada approved, however the PET agents are available under research protocol at a number of centers in both the US and Canada. Approval of ^{18}F-DCFPyL is expected in 2020 or 2021 and widespread adoption should not be far behind. ^{68}Ga-PSMA-11 does not have patent protection, but companies are looking to gain regulatory approval to commercialize labelling kits in the near future.

The phase-III registration trial, known as VISION, which should lead to regulatory approval and widespread availability of 177Lu-PSMA-617 RLT is currently enrolling at over 70 sites world-wide including the Jewish General Hospital and CHUM in Montreal, Hotel Dieu Hospital in Quebec City, Odette Cancer Centre in Toronto and BC Cancer in Vancouver. Enrollment has been brisk and should be completed by the end of 2019, owing to the enthusiastic responses to PSMA RLT both from physicians and patients. The final results of the VISION trial will probably be available in 2021.

Conclusion

The discovery of PSMA PET and PSMA RLT have brought the age of theranostics and molecular personalized medicine upon us. Nuclear medicine physicians, urologists and medical oncologists have powerful new tools at their disposal to detect and fight prostate cancer. Although much work remains to be done to bring these discoveries to all prostate cancer patients who might benefit, the future is promising. ■

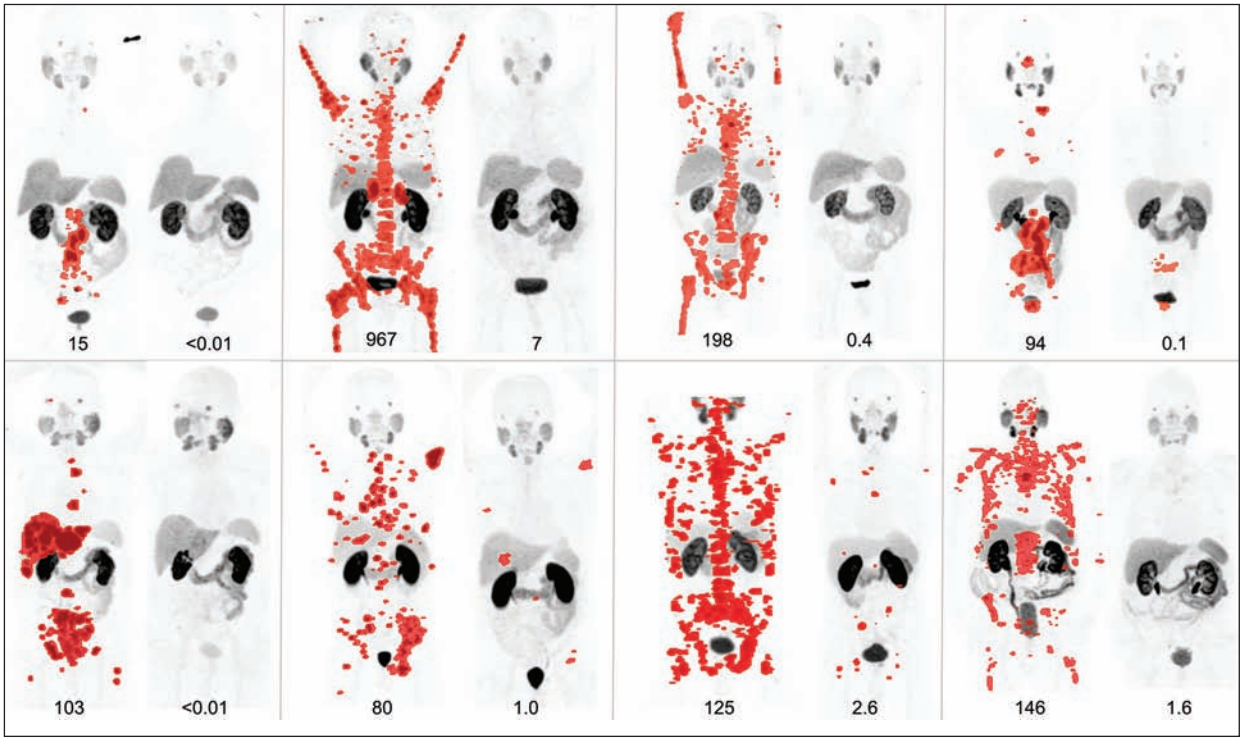


Figure 1. SNMMI Image of the Year, ^{68}Ga-PSMA-11 PET maximum intensity projection (MIP) images at baseline and 3 months after ^{177}Lu-PSMA-617 in 8 patients with PSA decline ≥ 98 percent in a prospective phase II study. Any disease with SUV over 3 is in red. Credit: Michael Hofman, John Violet, Shahneen Sandhu, Justin Ferdinandus, Amir Iravani, Grace Kong, Aravind Ravi Kumar, Tim Akhurst, Sue Ping Thang, Price Jackson, Mark Scalzo, Scott Williams and Rodney Hicks, Peter MacCallum Cancer Centre, Melbourne, Australia.

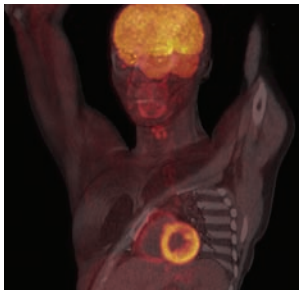
Biograph Vision

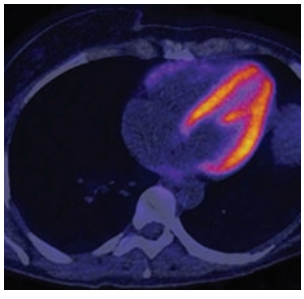
Profiter d'une toute nouvelle précision

Contribuer au développement de la médecine de précision.

Le marché des soins de santé évolue constamment, ce qui peut être difficile alors que vous vous efforcez d'obtenir de meilleurs résultats cliniques, un flux de travail plus rapide et une qualité des résultats uniforme.

Et si vous pouviez visualiser de plus petites lésions, obtenir de l'information pour préciser davantage la stadification et la stratification du risque du patient ainsi que gérer les inefficacités opérationnelles afin de faciliter la stratégie de traitement la plus appropriée[1]?





La clarté impressionnante et la délimitation remarquable caractérisent les images du Biograph Vision. Données acquises selon le protocole approuvé par le comité d'éthique indépendant.

Cristaux LSO de 3,2 mm[1]
Temps de vol rapide de 214 ps[1]
Haute sensibilité efficace de 84 cps/kBq[1]
Couverture totale du capteur[1]

Précision offrant une meilleure vue d'ensemble.
Performance pour maximiser l'efficacité.
Reproductibilité pour comprendre l'évolution de la maladie.

[1]Selon les mesures prises à l'interne (résolution et temps de vol) par rapport aux systèmes actuels. Données consignées.

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CANM ACMN
The Canadian Association of Nuclear Medicine
Association canadienne de médecine nucléaire

CANM GUIDELINES FOR VENTILATION/PERFUSION (V/P SPECT) IN PULMONARY EMBOLISM

Executive Summary

Document prepared by
Drs. Michel Leblanc, Michel Tessier, Glenn Ollenberger, Christopher O'Brien

November 2018

1. Diagnostic approach for PE.
Generally, predictive models based on clinical data for PE are poor.

D-dimer has high NPV but low specificity for PE, and is not needed if the pretest probability for PE is other than low.

V/P SPECT has at least the same or better accuracy for PE as CTPA, but much lower radiation dose especially regarding breast exposure. Also, there have been little or no reported adverse reactions.

2. Methodology
V/P SPECT should be used instead of planar acquisition when available. Multidetector gamma-cameras with large FOV are preferred for V/P SPECT. A one-day ventilation and perfusion protocol where the ventilation precedes the perfusion is the norm.

For ventilation, ^{99m}Tc-Technegas is the best radio-aerosol, particularly in patients with COPD. Liquid aerosols produced in nebulizers such as ^{99m}Tc-DTPA are inferior for SPECT and should not be used unless Technegas is not available.

Lung perfusion is performed using ^{99m}Tc-macroaggregated albumin (MAA). Suggested administered doses and acquisition parameters are presented in **table 1** of attached document. Appropriate iterative reconstruction and display of transverse, sagittal and coronal projections are essential for interpretation.

3. Interpretation criteria and reporting
Interpretation in probabilistic terms is not appropriate and must be avoided. Accordingly, all exams should be interpreted as either "PE present" or "PE absent" or other similar clear affirmative terms.

Affirmative diagnosis of PE requires the presence of vascular type mismatches. **PE is considered excluded** if perfusion is normal, if there are only matched defects, non-vascular type mismatches or reverse mismatches. See document for explanations.

Findings other than PE may be clinically pertinent, especially if symptoms include dyspnea or desaturation.

All PEs should have a final control 3 months after diagnosis to assess final reperfusion and to benefit from the availability of a baseline exam in case of recurrent symptoms.

4. Other considerations
In the **pediatric population and during pregnancy**, one should consider V/P SPECT as the first investigation for suspected PE due to better sensitivity, lower radiation, and no adverse reactions.

As ventilation co-morbidities are unlikely, a perfusion-only study might suffice, with an optional ventilation study the next day if needed. However, V/P SPECT should be used in pregnant women with co-morbidities or a history of smoking.

Due to a higher sensitivity and no adverse reactions, V/P SPECT should be the first investigation for the assessment of **Chronic PE**.

Although we do not recommend performing **SPECT-CT** on a regular basis, it could be appropriate in more challenging and selected cases.

CANM Endorsement of the 2009 EANM Guidelines for Ventilation / Perfusion Scintigraphy

1) Diagnostic approach to pulmonary embolism (PE)

Key Points:

1. **Predictive models for PE are generally inaccurate**
2. **D-dimer has high sensitivity but low specificity for PE**
3. **Negative D-dimer has a high NPV**
4. **High quantitative value of D-Dimer increases likelihood for PE**
5. **D-dimer is not needed if pretest probability for PE other than low**
6. **V/P SPECT has at least the same or better accuracy for PE as MDCT**
7. **Availability is the main determinant of use for MDCT vs V/P SPECT**
8. **Fetal dose is roughly equivalent for both V/P SPECT and MD-CTPA**
9. **Breast dose is much higher with MD-CTPA as compared to V/P SPECT**
10. **V/P SPECT carries less risk of allergic reaction associated with contrast agent injection**
11. **99% of patients referred for V/P can undergo the exam.**

Referral criteria and assessment of clinical probability

For the diagnosis of PE the patient's clinical factors are non-specific. The clinical probability of PE can be accomplished empirically or by means of a prediction rule. Wells model is most frequently used. PISA model may be a more precise predictor of PE. Combining clinical probability with objective testing for PE can rule in or out PE. The measurement of D-dimer is widely used in the investigative work-up of patients with suspected venous thromboembolism. D-dimer features a low specificity (40%). Accordingly, a negative quantitative D-dimer test has a high negative predictive value for venous thromboembolism. High quantitative value of D-Dimer increases likelihood for PE

CANM endorses Fig. 1 and 2 - **Clinical algorithms for investigation of patients with suspected PE** as published in *Eur J Nucl Med Mol Imaging* (2009) 36:1528–1538.

Imaging studies in PE

The diagnosis of PE relies upon imaging tests, notably V/P scan and MDCT. In many clinical studies, including recent ones, comparisons between V/P scan and MDCT have been based upon obsolete scintigraphic techniques and interpretation criteria. The lack of a satisfactory gold standard for the diagnosis of PE poses difficulties for the assessment of sensitivity, specificity and accuracy of all diagnostic methods for PE. V/P SPECT has at least the same or equal accuracy for PE as MDCT. Additional diagnoses found on V/P SPECT include COPD, left heart failure and pneumonia. MDCT provides valuable information about diagnoses other than PE, such as aortic aneurysm, tumour, pleural effusion and pneumonia. A high number of patients are ineligible for MDCT due to kidney failure, allergy, ventilator support, recent MI and critical illness. 99% of patients referred for V/P can undergo the exam. CTPA is more readily available on a 24/7 basis and thus may be used more often.

Radiation Doses

The effective radiation dose from V/P SPECT is 1.2–2 mSv. The absorbed dose to the female breast is estimated as 0.8 mGy. During the first trimester, the estimated dose for perfusion study (50 MBq) gives a fetal absorbed dose of 0.1–0.2 mGy [47].

For MDCT during the first trimester the absorbed fetal dose was estimated as 0.24–0.66 mGy and significantly higher later during gestation. Recent studies have shown that MDCT is often technically suboptimal during pregnancy. The rate of nondiagnostic MDCT studies was 27.5% during pregnancy, versus 7.5% in nonpregnant women.

Based upon data from ICRP reports, the effective dose for V/P SPECT with the recommended protocol is about 35–40% of the dose from MDCT. The dose to the female breast for V/P SPECT is only 4% of the dose from MDCT. During the first trimester of pregnancy the fetal dose from MDCT is greater than or equivalent to that of V/P SCAN. The advantage of V/P SPECT increases after the first trimester.

Follow-up

V/P SPECT is ideally suited for use in the follow-up of PE because small and large emboli are recognized so that regression or progression of thrombotic disease can be studied in detail. Furthermore, the low radiation exposure allows repeated studies. It can be applied **in all patients**. Using the same method for diagnosis and for follow-up has great advantages. Perfusion-only scintigraphy may be chosen for control during the initial phase of treatment

CANM endorses Fig. 3 - **Algorithms for diagnostic imaging for acute PE suspected** as published in *Eur J Nucl Med Mol Imaging* (2009) 36:1528–1538.

2) Methodology

Introduction

Planar ventilation/perfusion technique with probabilistic interpretation suffered disrepute since the PIOPED I study showed that 65% of scans were nondiagnostic for PE. Consequently, it has become an inferior technique for most clinicians and should be replaced by more advanced nuclear medicine imaging using SPECT acquisition whenever available. The following recommendations regarding the choice of radiopharmaceuticals and imaging strategies for V/P studies are based on the 2009 EANM guidelines, updated with the more recent literature.

Radiopharmaceuticals

Ventilation

^{81m}Kr (krypton) is currently the only gas appropriate for V/P SPECT. However, because of high costs and limited distribution, it is not readily available in Canada. The best widely available agent for ventilation is ^{99m}Tc-Technegas, an aerosol of carbon nanoparticles (5-200 nm) generated in a high temperature furnace (Technegas Generator, Cyclomedica). Because of the very small particle size, this agent is distributed in the lungs almost like a gas and deposited in alveoli by diffusion, where they remain stable, thus providing the best possible images for ventilation SPECT. In practice, between 400-900 MBq (1025 mCi) of $^{99m}TcO_4$ in 0.15ml NS is vaporized in a graphite crucible at 2750 °C in an argon atmosphere. The resulting ^{99m}Tc-Technegas is inhaled as soon as possible (<5 minutes) by the patient in a supine position, over the course of 2 to 5 inspirations. Activity over the lungs should be monitored, and administered activity should be around 30-50 MBq (0.8-1.4 mCi).

Liquid aerosols produced in nebulizers, such as ^{99m}Tc-DTPA, are inferior for SPECT, and should not be used unless technegas is not available. Overall, technegas remains the best radio-aerosol, particularly in patients with obstructive lung disease. Another advantage is that only a few breaths are sufficient to achieve an adequate amount of activity in the lungs, reducing time and personnel exposure to radiation.

Perfusion

Lung perfusion is performed using ^{99m}Tc-macroaggregated albumin (MAA). These albumin particles average 10–90 um in size, which allows them to lodge in the pulmonary capillaries and properly define lung perfusion. Normally, about 400,000 particles are injected, but a reduction to between 100,000 and 200,000 is recommended in patients with severe pulmonary hypertension or after a single lung transplantation. A minimum of 60,000 particles is needed to obtain a uniform distribution.

The suspension containing ^{99m}Tc-MAA should be gently shaken immediately before use and then administered by slow i.v. bolus injection over several respiratory cycles while the supine patient breathes at normal tidal volumes. Withdrawal of blood into the syringe must be avoided to prevent aggregation artefacts. The administered dose is typically between 120–240 MBq (3-6 mCi) but actually depends on the count rate of the ventilation agent. The activity ratio between perfusion and ventilation should be at least 4:1. The EANM guidelines recommend doses at the low end of the range to keep radiation exposure low (< 2.5 mSv).

Equipment and imaging protocols

A one-day ventilation and perfusion protocol where the ventilation precedes the perfusion is the norm. Ventilation is essential to maximize specificity and may help recognize alternate pathologies. A perfusion only protocol might be considered during pregnancy (with an optional day-after ventilation study if needed) or in the context of massive PE.

Planar acquisition should not be used anymore, unless SPECT is not feasible for some reason. In this case, six to eight projections are recommended for both ventilation and perfusion. The recommended matrix size is 256x256 in combination with a LEHR collimator, and acquisition time should be long enough to yield 500–1,000 kcounts per view.

Multidetector dual or triple head γ-cameras with large FOV are preferred for V/P SPECT. LEHR parallel collimators with 128 x 128 matrix size represents a good combination, but LEAP collimators with a 64 x 64 matrix are also adequate especially if one aims for lower doses and/or shorter acquisition times. It is important that the patient remains in the

same supine position, carefully maintained between ventilation and perfusion acquisitions. A total acquisition time of 20–30 minutes (excluding dead time) is usually sufficient to complete both the ventilation and the perfusion SPECT scans. Ranges of acceptable doses and acquisition parameters are shown in Table 1 below. Ultimately the doses to be administered should be determined by each institution on the basis of the image quality obtained in a reasonable time, which is influenced by factors such as camera sensitivity, collimator choice, acquisition matrix size, processing parameters and local radiation protection guidelines. The added benefit of SPECT-CT is still debated, but the SPECT part acquisition parameters are similar, if there is a need to acquire CT data in selected cases.

Table 1: Suggested doses and acquisition parameters for V/P SPECT

Parameter	Value range
Administered dose Ventilation	30 - 50 MBq
Administered dose Perfusion	120 - 240 MBq
Collimator and Matrix size	LEHR (128 x 128), LEAP (64 x 64)
# steps / 360°	64 - 128 (32 - 64 / detector)
Step time for Ventilation	10 - 25 seconds
Step time for Perfusion	5 - 15 seconds
P/V activity (count rate) ratio	at least 4:1

Reconstruction and display

Transverse, sagittal and coronal projections are generated using an OSEM (ordered-subset expectation maximization) or equivalent iterative reconstruction algorithm. The number of iterations, subsets and other parameters may vary according to the manufacturer's software used to this end, but overly noisy images should be avoided as they do not promote reproducible interpretations. A 3D post reconstruction filter is usually applied, and the final images can be reviewed in each of the orthogonal planes, preferably on a workstation with dedicated software. Pseudo-planar images can be generated using an angular summing technique and other methods. More advanced data processing can also be performed. Defect contrast on perfusion SPECT can be further enhanced by subtracting the background activity remaining from the preceding ventilation scan. Further, by examining the pixelbased V/P ratio, quotient images can be generated from the SPECT data. These parametric images can facilitate reporting and improve the demonstration of defect location and extent.

3) Interpretation criteria and reporting

- **Basic criteria**
- **Affirmative or negative w/r to PE**
- **Other possible diagnoses**
- **Follow-up recommendations**

Interpretation

Interpretation in probabilistic terms is not appropriate with VQ SPECT and should be abandoned. All images should be interpreted as either "PE present" or "PE absent" or other similar clear affirmative terms. A small number of "non-diagnostic or equivocal studies" is inevitable for various reasons but should not exceed 5% of the case load.

Affirmative diagnosis of PE requires the presence of vascular type mismatches. Vascular type perfusion defects have the following characteristics: moderate to severe defects, with clear borders, which are pleural based, wider at pleura than centrally, with an orientation compatible with pulmonary vascular anatomy. At the sub-segmental level, the shape is usually triangular.

PE present: PE is diagnosed if there is at least one lobar or segmental vascular type mismatched defect (perfusion defect with preserved ventilation), or two sub-segmental vascular mismatches, regardless of other findings.

PE absent: PE is considered excluded if perfusion is normal, if there are only matched defects (regardless of morphology), non-vascular type mismatches or reverse mismatches (perfusion preserved but ventilation absent).

A frequent cause of non-vascular mismatches is physiologically compressed lung. Typical locations are posterior para-mediastinal lung, costophrenic angles, the top of the great fissures and shallow posterior lung surfaces in cases of gravity dependant atelectasis. Other causes include penetration of ventilation agent in emphysema bullae or cystic space in severe fibrosis.

False positives interpretation may occur mainly in extrinsic vascular compression, pulmonary vein stenosis and rare cases of vasculitis.

The interpretation of an isolated vascular-type defect that is matched on ventilation and congruent with a radiographic opacity of similar size remains controversial because an isolated pulmonary infarct is a possibility (albeit not a frequent one). If symptoms are not acute (more than a few days), partial reperfusion of embolic disease can give atypical perfusion patterns. In difficult cases, consultation with the clinician is suggested.

Other diagnoses

Other findings than PE may be clinically pertinent, especially if symptoms include dyspnea or desaturation.

- Cardiac failure: redistribution of perfusion to superior and anterior portions of the lungs (inversion of the normal gradient) associated with preserved normal ventilation gradient is highly suggestive of early cardiac failure and can be observed earlier than on chest X-ray. This redistribution of perfusion is often lost with more advanced failure and typical X-ray change of edema.

- COPD: The magnitude of changes observed on VQ SPECT correlates with COPD severity, which can be underestimated clinically. Changes are typically more severe on ventilation, which include varying degrees of heterogeneity, ventilation defects and aerosol deposition at various bronchi levels indicating turbulence.

- Reverse mismatch: indicates failure of the physiological pulmonary vasoconstriction in the presence of a ventilation defect. May contribute to hypoxemia because of right-to-left shunt effect. Frequent association with pneumonia and may also be seen in atelectasis, mucous plug or other causes of bronchi obstruction.

Follow up

All PEs should have a final control 3 months after diagnosis to assess final reperfusion and benefit from the availability of a baseline exam in case of recurrent symptoms. Once a diagnosis of PE is made, a follow up exam is necessary to evaluate the degree of reperfusion. This has 2 purposes. First, incomplete reperfusion of a moderate to extensive PE is associated with the development of chronic pulmonary hypertension. Second, if there is a suspicion of new PE on follow up, it may be impossible to distinguish new PE from unresolved prior PE.

If PE is extensive, routine early control 7-10 days after diagnosis is advisable since a substantial part of reperfusion may occur in the first week. If there is early suspicion of new PE, this early control may be invaluable for correct diagnosis in this group.

Interpretation of new defects on control VQ SPECT has some known pitfalls. Sometimes, a partially occluding proximal defect may dissolve in several distal severe defects. Although those defects may seem impressive, they are not new. Also, clots located close to branching arteries may dissolve proximally and part of the clot may be drawn in the adjacent artery.

4) Additional considerations

CHART 1: ACUTE PE

	V/P SPECT	V/P SPECT/ low dose CT
SENS	93-97	93-97
SPEC	91-96	98
NPV	97-99	97-99
Inconclusive	1-3	~1
Nephrotoxicity	none	none
Mortality	none	none
Allergy	none	none

COMMENT: low dose non-contrast CT improves specificity and reduces inconclusive findings in selected patients. SPECT/CT is not recommended as a routine procedure in the diagnosis of PE.

CHART 2: RADIATION EXPOSURE

V/P SPECT	V/P SPECT/ low dose CT	CTPA (4 to 16 slice)	CTPA (64 slice)
~ 2.1 mSv	~ 3.1 mSv	~ 5.4 mSv	~ 20 mSv

COMMENT: exposure from CTPA is difficult to assess as many variables influence exposure: these include patient BMI, mAs, pitch, and radiation reduction protocols to name a few. As the number of slices increase with CTPA exposure does increase.

CHART 3: CHRONIC PE

	SENS	SPEC
CTPA	51	
V/P SPECT	93-97	90

CHART 4: PREGNANCY

	CTPA	V/P SPECT
Breast Exposure	10-70 mGy	less than 1.5 mGy
Fetal Exposure	less than 1.0 mGy	less than 1.0 mGy
Adverse reactions	Possible	None

Conclusions

In situations of Acute PE, Chronic PE, Pregnancy, Pediatrics, and the COPD population one can consider V/P SPECT, with or without low dose CT, as a first line investigation due to high sensitivity and specificity, low radiation, and no adverse reactions.

In situations of Pregnancy and Pediatrics due to the low likelihood of ventilation co-morbidities one could consider Perfusion only SPECT as a first line investigation. If co-morbidities exist then a full V/P SPECT should be performed. Also, V/P SPECT is not influenced by vascular volume changes during pregnancy as is CTPA.

In situations of COPD up to 31% of patients may have PE and up to 10% may die. Even those patients who have abnormal Chest X ray can still undergo V/P SPECT and in selected patients, V/P SPECT with low dose non-contrast CT could be considered. Technegas is considered the agent of choice in this population as there is less central airway deposition, better peripheral penetration, and it does not wash out as quickly as traditional aerosols.

List of Acronyms Used In The Present Document

COPD	Chronic Obstructive Pulmonary Disease
EANM	European Association of Nuclear Medicine
FOV	Field of View
ICRP	International Commission on Radiological Protection
LEAP	Low Energy All-Purpose
LEHR	Low Energy High Resolution
MDCT	Multi-Detector Computed Tomography
MD-CTPA	Multirow-Detector Computed Tomographic Pulmonary Angiography
OSEM	Ordered-Subset Expectation Maximization
PE	Pulmonary Embolism
PIOPED	Prospective Investigation of Pulmonary Embolism Diagnosis
SPECT	Single Photon Emission Computed Tomography
SPECT-CT	Single Photon Emission Computed Tomography—X-ray Computed Tomography
V/P SPECT	Ventilation/Perfusion Single Photon Emission Computed Tomography

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LINKS TO EANM 2009 GUIDELINES FOR VENTILATION/PERFUSION SCINTIGRAPHY

https://eanm.org/publications/guidelines/gl_pulm_embolism_part1.pdf

https://eanm.org/publications/guidelines/gl_pulm_embolism_part2.pdf

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BARCELONE

Texte : Anik Messier

La Catalogne et Barcelone sont devenues l'une des premières destinations touristiques d'Espagne, elles ont tout pour plaire à la majorité des visiteurs : une histoire parmi les plus anciennes d'Europe, une capitale, Barcelone, qui ne dort jamais et un arrière-pays plein de charme, mais aussi, les belles plages de la Costa Brava, sans compter la variété des trésors artistiques, les églises romanes et les grands noms de l'art et de l'architecture moderne, Dali, Gaudi, Miro, Picasso...

Barcelone, située entre mer et montagne, a trouvé un formidable équilibre : un pied dans le traditionalisme et l'autre dans l'avant-garde. Barcelone a la réputation d'être la ville la plus cosmopolite, moderne et avant-gardiste d'Espagne. Elle s'est renouvelée pour les Jeux olympiques de 1992.

Que faire à Barcelone en 1, 2, 3 ou 4 jours?

Barcelone est une ville passionnante à visiter car elle possède une immense richesse culturelle et touristique. En toute honnêteté, même si vous êtes très curieux et en même temps très bien organisé, une bonne partie de cette ville vous échappera. C'est ce qui la rend si attrayante et inspire le désir irrésistible d'y retourner.

Comme vous êtes habitué de voyager, vous avez certainement réservé votre hôtel au centre de Barcelone. Donc, vous êtes déjà au cœur de la question. Si vous n'avez pas eu cette chance, ce n'est pas un problème, les moyens de transport sont nombreux et beaucoup plus économiques que dans les autres capitales européennes. Sautez dans un bus en direction de la Plaza Catalunya (Place de Catalogne) autour de laquelle rayonne toute la ville historique.

Que faire à Barcelone en un jour?

Une seule journée à Barcelone ? Donc, vous êtes en « mode combat », levez-vous tôt! Il est suggéré d'associer l'exploration de la ville à pied, à vélo ou en bus touristique et faire la visite d'au moins un monument ou un musée. L'accent sera donc mis sur les quartiers historiques de Barcelone, dans la soi-disant Ciutat Vella – la vieille ville, et sur les quartiers comme El Born, El Gótico et Barceloneta. Choisissez au hasard un monument de Gaudi ou un musée avant de prendre le temps de manger des tapas ou de savourer la cuisine catalane.

Que faire à Barcelone en deux jours?

La deuxième journée d'une visite à Barcelone est consacrée à la découverte du modernisme. C'est une belle journée qui combinera balades en bus et exploration des principaux monuments modernistes de la ville : Casa Milà – La Pedrera, la Casa Amatller, la Casa Batlló, la Casa Calvet, la Casa de les Punxes, le parc Guell, la Sagrada Familia et les monuments historiques, dont beaucoup sont l'œuvre de Gaudi. Il n'est pas dérisoire de prendre le bus touristique, c'est même le meilleur moyen de se rendre d'un point à l'autre en toute liberté.

Que faire à Barcelone en trois jours?

Pour le troisième jour de votre visite, nous vous proposons un itinéraire vous permettant de découvrir plus précisément les richesses de la partie occidentale de la ville : sur la Plaza d'España, le pavillon Mies Van de Rohe, le Poble Espanyol, le Museu Nacional d'Art de Catalunya (MNAC), la Fondation Joan Miró, Montjuïc, le port ainsi que le port olympique, le musée d'histoire de la Catalogne, le quartier gothique et, pourquoi pas, si vous avez encore du temps, le musée Picasso. La culture et le divertissement sont au programme!

Que faire à Barcelone en quatre jours?

Vous êtes satisfait de votre visite à Barcelone mais vous voulez faire une journée de farniente? Cela est compréhensible, les visites sont enrichissantes, mais parfois épuisantes.

Dans ce cas, il n'y a qu'une solution : un court trajet à vélo ou une promenade au bord de la mer. Allez à la plage, profitez des petits chiringuitos et de leurs DJ. C'est donc en découvrant le quartier des pêcheurs – Barceloneta – que votre promenade commencera.

LA CUISINE BARCELONAISE

Du vocabulaire

Les brasseries (cervecerías), comme leur nom l'indique, servent de la bière, mais on peut généralement trouver des bières artisanales ou spéciales, ainsi que toutes sortes de boissons, boissons non alcoolisées, cafés, vins, etc., ainsi que des bars. Pour un repas complet, nous irons au restaurant et pour un repas de fruits de mer, à une marisquería. L'auberge propose une cuisine familiale. La bodega est un bar à vin, un chiringuito est un bar-restaurant en bord de mer. Les grangas sont une sorte de petits cafés où les Catalans viennent prendre leur petit-déjeuner, prendre un thé ou un goûter. Enfin, les Paradores, considérés comme des hôtels de luxe, sont étonnamment abordables en ce qui concerne leur restauration.

À Barcelone, le lunch est généralement servi de 14h00 à 16h00 et le dîner de 21h00 à minuit. Les restaurants à Barcelone ferment souvent le dimanche soir et le lundi.

Lorsque nous parlons cuisine à Barcelone, nous parlons d'une richesse extraordinaire de tous les types de cuisine, en plus de la cuisine locale. Une ville connue pour sa nouvelle cuisine qui, depuis vingt ans, a beaucoup influencé les chefs culinaires d'aujourd'hui, la créativité qui a conduit à la renaissance d'une

cuisine méditerranéenne moins conventionnelle. Une ville qui est enfin ouverte à de nombreuses autres tendances importantes telles que la cuisine végétarienne, très bien représentée aujourd'hui. Nous pouvons également parler de la grande diversité de la cuisine internationale et de la cuisine fusion. Burgers, street food, gastro trucks, asiatique, sushi, bo bun, ramen, tacos, pizzas, cocktails, hors-d'œuvre... Toutes ces tendances n'échappent pas à la population locale.

Pendant votre séjour à Barcelone, prenez également le temps de visiter la Catalogne. La plage de Costa Brava doit son nom de « côte sauvage » à l'unicité de la rencontre soudaine entre mer et montagne. La nature, le climat et l'histoire, le pittoresque de ses ports et de certains villages ont suffi pour lui donner une réputation mondiale. La plage de Costa Dorada, au sud de Barcelone, est dorée et lumineuse, étant sur le littoral maritime, d'où son nom « côte dorée ». ■

BARCELONA CITY PASS

Évitez les files d'attente et économisez 20 % sur les meilleures attractions de Barcelone.

Le Barcelona City Pass est un forfait fantastique qui combine des billets préférentiels avec sauts de queues d'attente et des billets de transport à Barcelone.

DaTscan™
Ioflupane I 123 Injection

Indication for Use

DaTscan (Ioflupane (123I) Injection) is a radiopharmaceutical indicated for visualization of functional striatal dopamine transporter using single-photon emission computed tomography (SPECT) brain imaging. In adult patients with suspected parkinsonian syndromes (PSs), DaTscan SPECT imaging may be used as an adjunct to other established evaluations to help differentiate essential tremor from tremor due to PS related to idiopathic Parkinson's disease (PD), multiple system atrophy (MSA) and progressive supranuclear palsy (PSP). DaTscan is unable to discriminate between PD, MSA and PSP.

Important Risk and Safety Information About DaTscan™ (Ioflupane I 123 Injection)

CONTRAINDICATIONS: DaTscan is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. **WARNINGS AND PRECAUTIONS** — Radiopharmaceuticals should be used only by those health professionals who are appropriately qualified in the use of radioactive prescribed substances in or on humans. As in the use of any other radioactive material, care should be taken to minimize radiation exposure to patients consistent with proper patient management, and to minimize radiation exposure to occupational workers. **Hypersensitivity Reactions:** Hypersensitivity reactions have been reported following DaTscan administration. Prior to administration appropriate resuscitation equipment should be available. **Thyroid Accumulation of I-123:** The DaTscan injection may contain up to 6% of free iodide (iodine 123). Accumulation of radioiodine in the thyroid gland may result in long term risk for thyroid neoplasia. To decrease thyroid accumulation of iodine 123, administer a thyroid blocking agent at least 1 hour before administration of DaTscan. **ADVERSE REACTIONS:** In clinical trials, headache, nausea, and dizziness were commonly reported as adverse events. Less commonly reported adverse events included vertigo, increased appetite, dry mouth, formication, dysgeusia and injection site pain. In postmarketing experience, serious and nonserious hypersensitivity reactions as well as reports of injection-site pain, headache, dizziness, formication (paresthesia), dysgeusia, nausea and dry mouth have been reported. **DRUG INTERACTIONS:** Drugs that bind to the dopamine transporter with high affinity can interfere with DaTscan binding, therefore may affect the images obtained. The impact of dopamine agonists and antagonists has not been established. **SPECIFIC POPULATIONS — Pregnancy:** Since adequate reproduction studies have not been performed in animals to determine whether DaTscan affects fertility in males or females, has teratogenic potential, or has other adverse reactions on the fetus, this radiopharmaceutical preparation should not be administered to pregnant women unless it is considered that the benefits to be gained outweigh the potential hazards to the fetus. **Nursing Mothers:** It is not known whether ioflupane (123I) is secreted in human milk, therefore, if administration is considered necessary, breast-feeding should be interrupted for 3 days and substituted by formula feeding. During this time, breast milk should be expressed at regular intervals and the expressed feeds should be discarded. **Pediatric Use:** The safety and efficacy of DaTscan in children aged 0 to 18 years has not been established, therefore DaTscan is not recommended in children. **Renal and Hepatic Impairment:** Formal studies have not been carried out in patients with significant renal or hepatic impairment. DaTscan is not recommended in cases of moderate to severe renal or hepatic impairment. **OVERDOSAGE:** In cases of overdose of radioactivity, frequent micturition and defecation should be encouraged to minimise radiation dosage to the patient. Care should be taken to avoid contamination from the radioactivity eliminated by the patient using such methods. **Reporting Side Effects:** You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada.

Report:

- Online at MedEffect;
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program Health Canada, Postal Locator 0701E Ottawa, ON K1A 0K9

Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect.

For more information please consult the product monograph at http://www3.gehealthcare.com/~/media/Documents/MarketoPDFsnogating/ProductMonographCanadaControlNo201481December72017.

The DaTscan product monograph is also available by calling 1-800-654-0118 (option 2, then option 3).

GE Healthcare

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PARKINSON'S DISEASE

100,000/CANADA

6M/WORLDWIDE

It causes a progressive loss of dopamine in the brain, which can cause symptoms that include resting tremor, slowness of movement, stiffness or rigidity of muscles, difficulty with balance and walking, difficulty with fine motor movements.

*Statistics from Parkinson Canada.

First imaging agent of its kind now approved in Canada to help physicians in the diagnosis of patients with a suspected parkinsonian syndrome

DaTscan™ (Ioflupane (123I) Injection) is a radiopharmaceutical indicated for visualization of functional striatal dopamine transporter using single-photon emission computed tomography (SPECT) brain imaging. In adult patients with suspected parkinsonian syndromes (PSs), DaTscan SPECT imaging may be used as an adjunct to other established evaluations to help differentiate essential tremor from tremor due to PS related to idiopathic Parkinson's disease (PD), multiple system atrophy (MSA) and progressive supranuclear palsy (PSP). DaTscan is unable to discriminate between PD, MSA and PSP.

"The timely and accurate diagnosis of movement disorders is the first step toward optimal patient management and treatment. We are glad to bring to physicians in Canada an additional tool that can help them address the challenges associated with movement disorders, and help patients get an earlier diagnosis."

– Marco Campione, Core Imaging General Manager of Americas at GE Healthcare

For more information, please contact 800 387 7146.

Please see additional Important Risk and Safety Information on page 50.

The Product Monograph is available by calling 1-800-654-0118 (option 2, then option 3) or visiting http://www3.gehealthcare.com/~/media/Documents/MarketoPDFsnogating/ProductMonographCanadaControlNo201481December72017.

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