

VOL 2 • NO 1

ePATIENT

NUCLEAR MEDICINE & MOLECULAR IMAGING

*THE FREE NUCLEAR MEDICINE & MOLECULAR IMAGING
EDUCATIONAL MAGAZINE AVAILABLE WORLDWIDE*

NUCLEAR MEDICINE
MADE SIMPLE

MEDICINA NUCLEAR
EN PALABRAS
SENCILLAS

LA MÉDECINE
NUCLÉAIRE
SIMPLIFIÉE

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PANGEA PROJECT

PANGEA



TECONEGAS™

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 imaging¹.

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 images²



LOW DOSE BURDEN

V/Q SPECT with Technegas has a low radiation burden as compared with CTPA³.



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 response⁴⁻⁵.

“ 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 perfusion¹”



DIAGNOSTIC ACCURACY

Clinical studies have shown that V/Q SPECT with Technegas has high sensitivity and specificity in diagnosing PE⁶ and CTEPH⁷ with a very high negative predictive value.

“ We consider V/Q SPECT/CT to be superior in most clinical settings with better overall diagnostic performance⁶”

WHAT IS TECHNEGAS

Technegas is a hydrophobic nanoparticle dispersion of carbon-labelled ^{99m}Techneium⁸.

The nanoparticle size and hydrophobic properties of Technegas provide ideal characteristics for gaseous behaviour and alveoli deposition into the lungs⁹⁻⁹. This provides for a representation on imaging of peripheral penetration of Technegas to the lungs⁹.

According to the European Association of Nuclear Medicine (EANM) guidelines, Technegas is the preferred ventilation agent for ventilation-perfusion (V/Q) functional lung imaging studies¹⁰⁻¹¹. In a few breaths and following SPECT or SPECT/CT, the clinician can produced 3D images providing information on lung function and pulmonary physiology^{2,11}.

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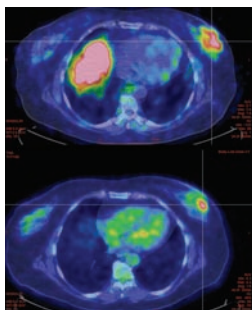
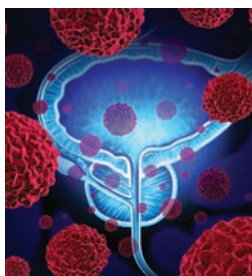
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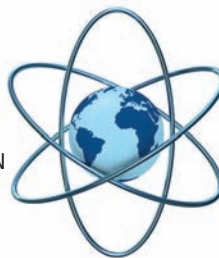
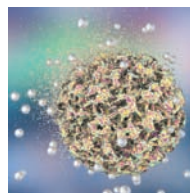
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**Don't miss our next issue on Quantification and the
second part of Theranostics (neuroendocrine tumors).**

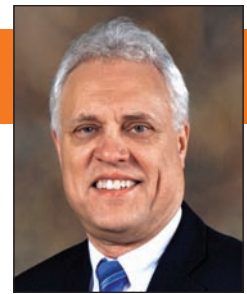
EDITORIAL BOARD

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



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INTRODUCTION TO THE THIRD ISSUE



François Lamoureux
M.D., M.Sc., FRCPC(C)
President Elect, CANM



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



The editorial board, Francois and I are pleased to introduce to our readers the third edition of the magazine Pangea-ePatient. It is about a year since we introduce our first issue and we have received numerous accolade and requests for last year and this past March editions. Our vision and mission for the magazine has remained the same: The idea behind Pangea-ePatient project is to explain and educate in simple terms prescribing physicians, patients, health authorities and hospital administrators from across the world about current and future nuclear medicine diagnostic tests and therapies.

Beside the interview of leaders and chief executive officers in the field of nuclear medicine and a few various articles, we are starting a series on therapies with medical isotopes under the title Theranostics.

Theranostics, the new buzz word in medicine was coined in the early 2000's by the CEO of PharmaNetics to define the vision for his company. It stems from the contraction of two words: therapeutics and diagnostics. Theranostics are one of the significant outcomes of the Human Genome Project. In the medical era of the omics, it is directly related to, if not synonym to precision medicine where diagnostic and therapeutic procedures are individually carved out for patients based on their genotype and phenotype. Most commonly, it refers to the use of a single agent/compound to diagnose and treat a specific disease.

While fitting well with the medical vocabulary of the new millenium, Theranostics are not new. In fact, it has been intimately part of our day to day practice for the practice of nuclear medicine for a long time. Way before the sequencing of the sodium iodine symporter gene in 1996 which characterize the cellular membrane transporter for iodine, nuclear medicine had already used the same physiologic ¹³¹iodine molecule to diagnose and to treat patients with thyroid cancer for a few decades. To this day, the accumulation or lack of uptake of radioiodine by the thyroid gland represents a key non-invasive tool for the diagnosis and treatment of thyroid cancers.

Modern therapy of cancers, neurological and cardiac conditions now relies on the identification and targeting of specific cellular molecules. Using specific probes and labeling them with diagnostic and/or killer medical isotopes, nuclear medicine is now offering the most attractive and quintessential tool in Theranostics and precision medicine to manage patients.

We hope you will enjoy this new issue and use some of the information provided to help managing patients and health care services. ■





Dr. Andrew Scott, M.D.,
*President of the
World Federation
of Nuclear Medicine
and Biology.*

Sze Ting Lee, M.D.,
*Secretary-General,
WFNMB*



Highlights of the WFNMB 2018 Congress, Melbourne

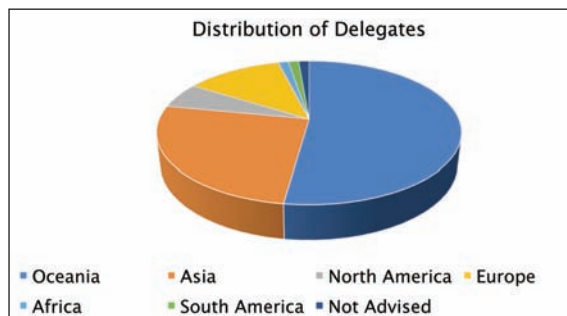
The 12th Congress of the World Federation of Nuclear Medicine and Biology (WFNMB) was held in Melbourne, Australia from the 20th to 24th of April, 2018. This is the quadrennial Congress of the Federation which was last held in Cancun, Mexico in 2014, and only the second time that it has been held in Australia, the first time was in Sydney in 1984, under the presidency of Professor Proven Murray.

The Australia and New Zealand Society of Nuclear Medicine (ANZSNM), who were the co-host of this Congress, also held its 48th Annual Scientific Meeting in conjunction with the World Congress. There were other international societies who also held their meetings at the World Congress, including the World Association of Nuclear Medicine and Therapy (WARMTH), International Society of Radiolabeled Blood Elements (ISORBE), Asian School of Nuclear Medicine (ASNM). The European School of Molecular Imaging and Therapy (ESMIT) also supported the post-congress meeting which was held in Cairns from the 26th-27th of April.

The Congress in Melbourne attracted over 2000 delegates from 78 countries around the world, and was the largest Nuclear Medicine Conference ever held in the Southern Hemisphere.



Attendees of the WFNMB Congress in Melbourne Convention and Exhibition Centre, Melbourne, Australia.



The 12th Congress of the WFNMB was presided by the current President of the WFNMB, Prof Andrew Scott, who was also the co-scientific chair of the Congress together with the President of the ANZSNM at the time, Prof Dale Bailey. The remainder of the Local Organising Committee included the Secretary-General, Treasurer and Scientific Administrator of the WFNMB, Sze Ting Lee, Vijay Kumar and Fiona Scott respectively. For the last 6 years, this local organising committee have been heavily invested in ensuring that the highest quality WFNMB Congress would be hosted in Melbourne, and remain in the memories of all attendees for decades to come.



The LOC of the 12th WFNMB Congress LOC with the Official WFNMB Bell. From LEFT to RIGHT: Vijay Kumar (Treasurer, WFNMB), Andrew Scott (President, WFNMB & Co-Scientific Chair), Fiona Scott (Scientific Administrator, WFNMB), Sze Ting Lee (Secretary-General, WFNMB), Dale Bailey (Co-Scientific Chair).

The LOC of the 12th WFNMB Congress LOC with the Official WFNMB Bell. From LEFT to RIGHT: Vijay Kumar (Treasurer, WFNMB), Andrew Scott (President, WFNMB & Co-Scientific Chair), Fiona Scott (Scientific Administrator, WFNMB), Sze Ting Lee (Secretary-General, WFNMB), Dale Bailey (Co-Scientific Chair).

Being the WFNMB Congress, this was held under the auspices of the international regional associations, including the IAEA, SNMMI, EANM, AOFNMB, and ALASBIMN whereby Presidents of all these associations participated in the Congress and Opening Ceremony.



Ribbon cutting during the Opening Ceremony of the 12th WFNMB Congress.

Together, with a carefully selected Scientific Subcommittee, with internationally renowned track chairs in 14 tracks (listed below), an exceptional scientific program was designed and attracted the large audience to Melbourne for the 5 day scientific program, which was deemed a huge success from a scientific and networking perspective.

TRACK	TRACK CHAIR
Cardiology	A/Prof. Nathan Better, Melbourne Health and Cabrini Medical Centre, Australia. Prof Joao Vitola, Quanta Diagnosis and Therapy, Curitiba, Brazil.
Emerging Leaders	Prof. Henry Bom, Chonnam National University Medical School & Hospital, Korea.
Endocrinology/Renal	A/Prof. Monica Rossleigh, Prince of Wales & Sydney Children's Hospitals, Australia.
Infection/Inflammation	Prof. Mike Sathekge, University of Pretoria & Steve Biko Academic Hospital, South Africa.
Molecular Imaging	Prof. Anna Wu, University of California Los Angeles, USA. Prof. Steven Meikle, University of Sydney, Australia.
Musculoskeletal	Dr. Gopinath Gnanasegaran, Royal Free London NHS Foundation Trust, UK. Dr Stephen Allwright, Mater & Northern Beaches Hospitals, Australia.
Neuroscience	Prof. Christopher Rowe, Austin Health, Australia.
Nuclear Medicine Innovation	Prof. Thomas Beyer, Medical University Vienna, Austria. Prof. Osman Ratib, University Hospital of Geneva, Switzerland.
Oncology	Prof. Homer Macapinlac, MD Anderson Cancer Centre, USA.
Paediatrics	Prof. Robert Howman-Giles, The Children's Hospital at Westmead, Australia.
Physics	Prof. Frederic H. Fahey, Boston Children's Hospital, USA.
Pulmonary	A/Prof. Paul Roach, Royal North Shore Hospital, Australia.
Radiopharmaceutical Sciences	Prof. Alan Packard, Boston Children's Hospital/Harvard Medical School, USA. Prof. Sally Schwartz, Washington University School of Medicine, USA.
Radionuclide Therapy	Prof. Richard Baum, Zentralklinik, Bad Berka Germany.
Technologists	Ms. Kunthi Pathmaraj, Austin Health, Australia. A/Prof. Geoffrey Currie, Charles Sturt University, Australia. Dr Elizabeth Bailey, Royal North Shore Hospital, Australia.

The program involved 257 invited presentations, including 4 plenary sessions, with presentations by two Australian Nobel Laureates, as well as renowned local and international clinical and nuclear medicine experts.

The opening plenary featured an enlightening lecture by Nobel Laureate Prof Brian Schmidt on the "Science and Discovery in the 21st Century", followed by the International Atomic Energy Agency (IAEA) Nuclear Medicine Section Head, Dr Diana Paez, on the Global Perspective of Nuclear Medicine.

The Oncology Plenary session was a multidisciplinary session which featured the second Nobel Laureate of the Congress, Prof Peter Doherty on "The Killer Defence". This was followed by Prof Sherene Loi on "Targeting Immune Checkpoints in Solid Cancers" and Prof Rodney Hicks on "The Role of Molecular Imaging in Monitoring Immunotherapy".



Nobel Laureate Professor Brian Schmidt Australian National University

Nobel Laureate Professor Peter Doherty The University of Melbourne



Opening Plenary: Dr Diana Paez, International Atomic Energy Agency (IAEA), Vienna, Austria.

Oncology Plenary: From LEFT to RIGHT: Nobel Laureate Prof Peter Doherty, The University of Melbourne; Prof Sherene Loi & Prof Rodney Hicks, Peter MacCallum Cancer Centre.



The Neurology Plenary session was a high level plenary session on Dementia imaging, featuring the worldwide experts in the field, which included Dr Stephanie Ward from Monash University, Prof Satoshi Minoshima from University of Utah USA, Profs Chris Rowe and Victor Villemagne from Austin Health.



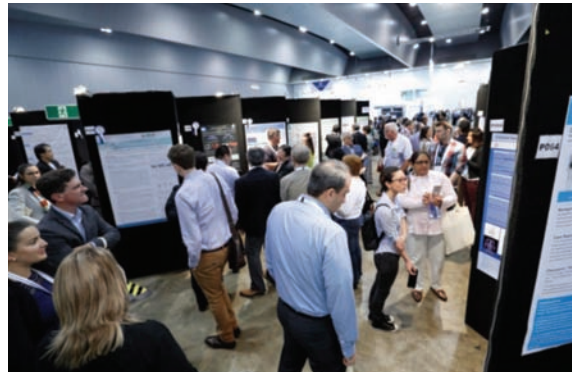
Neurology Plenary Session speakers. From LEFT to RIGHT: Prof Christopher Rowe, Prof Satoshi Minoshima, Dr Samantha Ward, Prof Victor Villemagne

The final plenary session for the Congress was on "The Future of Nuclear Medicine and Molecular Imaging", featuring Prof Sam Gambhir from Stanford University; Prof Ros Francis, President of the ANZSNM; and Prof Ignasi Carrio, Editor-In-Chief of the European Journal of Nuclear Medicine and Molecular Imaging.



The Future of Nuclear Medicine and Molecular Imaging Plenary Session. From LEFT to RIGHT: Prof Ignasi Carrio, Hospital San Pau, Barcelona, Spain; A/Prof Roslyn Francis, University of Western Australia, Prof Sanjiv (Sam) Gambhir, Stanford University, USA.

The remainder of the scientific program consisted of 93 sessions, of which 67 were Continuing Medical Education sessions, accredited by the European Accreditation Council for Continuing Medical Education (EACCME®), with up to 34 ECMEC® credits up for grabs. There were 704 abstracts submitted and were reviewed to be appropriate for presentation at dedicated poster sessions held over 3 days, with vigorous poster debate sessions.



Busy poster session at the 12th WFNMB Congress, Melbourne.

The highest ranking posters in each track were Judged by a panel of expert judges. The WFNMB Best Poster awards in each track were presented at the Gala and Awards Dinner on Monday 23rd April 2018 (right page).

Post-Congress Symposium

The Congress was followed by the post-congress symposium in Cairns, which is located in the Tropical North of Australia, on "Prostate Cancer:PET and Theranostics". This symposium featured speakers from Urology, Oncology and Nuclear Medicine, who all engaged the attendees into staying for all the day sessions before enjoying themselves at the post-congress tours at either a Crocodile Adventure or out to the Great Barrier Reef.



Prof Declan Murphy (Urologist) from Peter MacCallum Cancer Centre



Prof Richard Baum (Nuclear Medicine Physician) from Bad Berka, Germany.



POSTER TRACK	AWARD RECIPIENT	POSTER TITLE
Cardiology	Zhonglin Liu, USA	Assessment of left ventricular remodeling and angiogenesis in ischemic-reperfused rat hearts protected by dodecafluoropentane oxygen-carrier
Endocrinology	Veera Ahtiainen, Finland	13-year outcomes after low vs. high activity of radioiodine to ablate the thyroid after thyroidectomy for cancer: A prospective randomized study
Infection/ Inflammation	Edward Hsiao, Australia	FDG PET/CT assessment of large and craniofacial vessel involvement in patients with clinically suspected giant cell arteritis - interim data of a prospective trial
Molecular Imaging	Yukie Yoshii, Japan	Evaluation of a PET-guided surgery with ⁶⁴ Cu-labeled cetuximab to resect tumors deeply located in the mouse peritoneal cavity
Musculoskeletal	Yun Young Choi, South Korea	Enhanced Diagnostic Performance of Three Phase Bone SPECT/CT for Osteomyelitis by Addition of Blood Pool SPECT/CT
Nuclear Medicine Innovation	Tatiana Kochetova, Russia	The role of bone seeking radiopharmaceuticals in overall survival of breast cancer patients with multiple bone metastases
Neuroscience	Ying Xia, Australia	Cerebrovascular pathology in Alzheimer's disease: findings from the Australian Imaging, Biomarkers and Lifestyle study of aging
Oncology	Jayamane Govindasamy, Australia	FDG PET/CT findings in melanoma patients exhibiting treatment-related inflammatory events during immunotherapy
Paediatrics	Sanowar Hossain, Bangladesh	Comparison of iodine deficiency, selenium level and goiter prevalence among the primary school going children of endemic and non-endemic area of Bangladesh
Physics	Taiga Yamaya, Japan	Imaging performance evaluation of a "helmet-neck" brain PET prototype
Pulmonary	Jann Mortensen, Denmark	Lobar Quantification by V/Q SPECT/CT in Patients With Severe Emphysema Undergoing Endobronchial Lung Volume Reduction
Radionuclide Therapy	Gonçalo Ferreira, Portugal	Results of peptide receptor radionuclide therapy with ¹⁷⁷ Lu-DOTATATE in patients with head and neck paragangliomas
Radiopharmaceutical Sciences	Hiroki Hashimoto, Japan	The simultaneous measurement method for the molar radioactivity, radiochemical purity, and chemical impurity of the [¹¹ C]choline injection
Technologist	Kei Wagatsuma, Japan	Optimization of reconstruction conditions for tau PET imaging using [¹⁸ F]THK5351



CURRENT AND FUTURE ACTIVITIES OF ASIA OCEANIA FEDERATION OF NUCLEAR MEDICINE AND BIOLOGY (AOFNMB)

The AOFNMB is an organization for networking nuclear medicine societies and specialists, human resource development of nuclear medicine professionals, and promotion of nuclear medicine practices in the region (Osaka HQ Office). The AOFNMB consists of forty-four society-members and more than 1000 registered individual members.

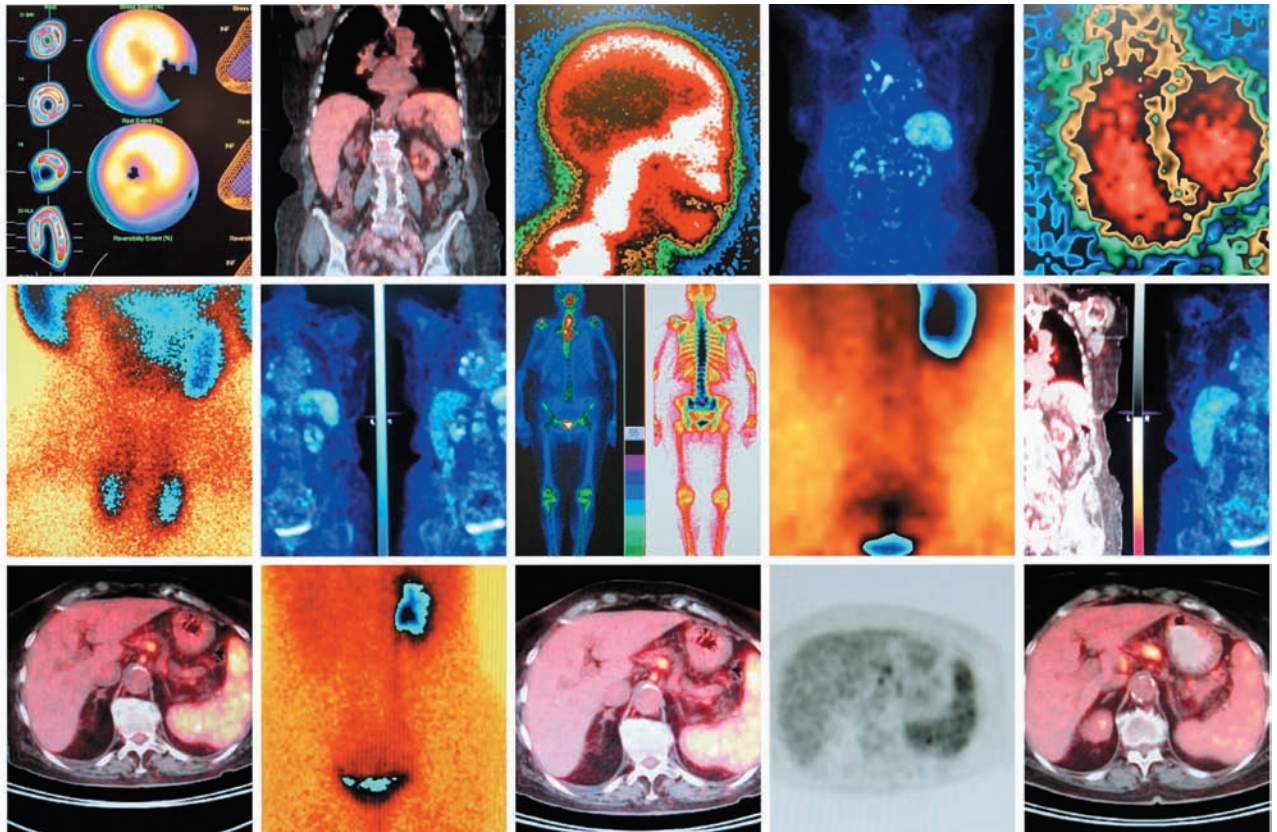
The AOFNMB launched in 1969 in Tokyo, followed by the first Asia Oceania Congress of Nuclear Medicine and Biology (AOCNMB) in 1976 in Sydney. The AOCNMB has been held every 4 year in Manila, Seoul, Taipei, Jakarta, Kyoto, Istanbul, Beijing, New Delhi, Tehran, Jeju, and most recently in Yokohama in 2018. The next AOCNMB will be held in Shanghai at May 9-12, 2019.

In 2013, the AOFNMB started education/training Campus of Nuclear Medicine (Shanghai Office) in Shanghai, Seoul/Chonnam, and Osaka/Fukushima.

More than 50 young nuclear medicine specialists completed the program. In 2014, the examination for nuclear medicine physicians started for the accreditation. In 2018 in Melbourne, the 5th examination was done, and now total of 150 NM physicians is honored as the fellow of Asia Nuclear Medicine Board (Multan Office).

The official journal of AOFNMB is Asia Oceania Journal of Nuclear Medicine and Biology, which started in 2013 (Mashhad Office) and published around 100 papers from 20 countries in the region and beyond during these 5 years.

The AOFNMB is working together with International Atomic Energy Agency, WFNMB, EANM, SNMMI, and other international Nuclear Medicine societies for promotion of nuclear medicine and for our patients. ■





*Dr. Paige Bennett, M.D.,
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Are you connected? Social media and nuclear medicine

Social media provides a vibrant platform for physician consultation, communication, education, and marketing. Nuclear medicine physicians, societies, and practices participate in social media in a variety of ways. If you are not a social media user, please read on. Whether or not you actively use or post items on social media, valuable content exists in the news, education, and marketing arenas in nuclear medicine. It may be valuable for you and your practice to become familiar with social media and even to have a presence there. Connection is the upshot of social media.

Depending on your goals, there are several avenues of social media valuable for physicians. Note that these social media platforms can easily link to a society website, a personal physician website or a practice website.

Doximity and LinkedIn are two sites that allow for professional profiles to be housed. Think of these as a professional Facebook, where professional photos, accomplishments, resumes and updates such as promotions can be showcased. This can be a valuable tool and requires occasional updating, depending on your level of professional activity. These can be an adjunct to your institution or practice website that showcases your personal practice patterns and achievements. This is an important reference for your colleagues, referring physicians, and recruiters.

The ubiquity and ease of Facebook make it a natural choice for societies and physician practices to keep their user communities updated on vital news, events, and even educational posts. For example, the Society of Nuclear Medicine and Molecular Imaging as well as the American Board of Nuclear Medicine both have active community Facebook pages. This is useful because people who are interested in keeping in touch with the societies can simply follow them and learn about new initiatives and professional topics.

The social media platform Instagram hosts several nuclear medicine content providers, including the Society of Nuclear Medicine and Molecular Imaging (@SNMMI), NucleoMed (@Nucleomed), and an educational feed (@nuclear_radiology and @dr_nuclear). This platform allows for a single photo, several photos within a slideshow, or short video content (one minute) along with space for captions. Hyperlinks to websites are not allowed within the captions in Instagram. Therefore, content providers often direct users to the provider's biographical information, where a website hyperlink can be provided.

Twitter is a valuable social media platform in that users follow it for short snippets of information. This can



increase user interest and direct users to other more comprehensive content sites such as websites, Instagram, or Facebook. Additionally, it is useful for healthcare policy discussions. For example, Dr. Geraldine McGinty (@DrGMcGinty) is a radiologist who advocates for healthcare policy, resident education, professional women's issues, and imaging quality via Twitter.

There is a lot of information available within these social media communities if you are simply a consumer of this information. If you're considering becoming part of social media with your professional information, ideas, or educational material, carefully consider your audience and what would motivate the social media user to read or search out your information. Potential audiences in the nuclear medicine community include:

1. Society members.
2. Learners of the healthcare professions.
3. Professionals seeking a larger community.
4. Healthcare activists.
5. Referring physicians.
6. Colleagues.
7. Professional recruiters.

You can see there are myriad ways to participate on these vibrant platforms. So, if you're interested in being up-to-date in the nuclear medicine community and having a professional presence in this online world, consider participating or updating, reading, viewing, responding, and posting. See you on social media!

Editor's Note: This is part one of multiple articles exploring social media and healthcare. In the next issue: Global Nuclear Medicine Education Via the Social Media Site Instagram. ■

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 as 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.

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.

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.



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

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



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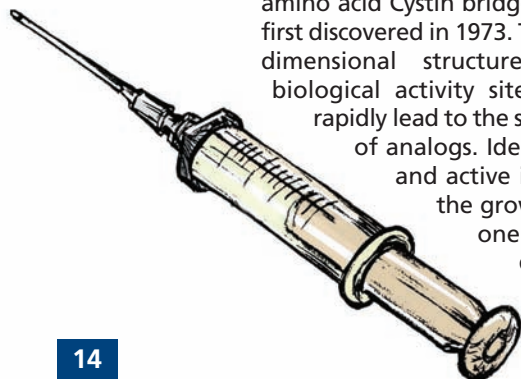
INTRODUCTION:

In the second issue of our magazine we described the therapeutic use of Iodine, the first true Theranostics compound available. In this edition of our magazine we will put the emphasis on the most recent developments in the utilization of medical isotopes for therapy of cancers

The modern landmark for Theranostic nuclear medicine originated in the seventies with the discovery of Somatostatin. Somatostatin, a 14-amino acid Cystin bridge-containing peptide, was first discovered in 1973. The elucidation of its three dimensional structure, its metabolism and biological activity site in the following years rapidly lead to the synthesis of a large number of analogs. Identified as the most stable and active in inhibiting the effect of the growth hormone, Octreotide, one of the derivatives, demonstrated enough in vivo stability to obtain

regulatory approval in 1988 for the treatment of acromegaly and carcinoid tumors.

The coupling of Octreotide to gamma emitting isotopes in the late 80's and early 90's represented a major breakthrough to what we now call molecular targeted imaging. Furthermore it's labeling with yttrium 90 and lutetium 177 in the early 2000's started the modern era of theranostic nuclear medicine by introducing the fast growing field of peptide receptor radionuclide therapy (PRRT). In PRRT, specific receptors present at the surface of tumors can now be detected, imaged, treated and followed up with the same peptidomimetic labeled with either imaging or killer isotopes. Labeled with gallium 68, a positron emitter and lutetium 177 a gamma and beta emitter, the somatostatin analog dotatate has recently emerged as a prime tool to diagnose, treat and follow up the treatment's efficacy of neuroendocrine tumors overexpressing the somatostatin receptor.



Tagged with bifunctional chelating agents, native peptides, hormones, neurotransmitters and peptidomimetics are now emerging as suitable molecules for site-directed targeted imaging and therapy. Among the most promising of these compounds in nuclear medicine are the inhibitors of the prostate specific membrane antigen (PSMA).

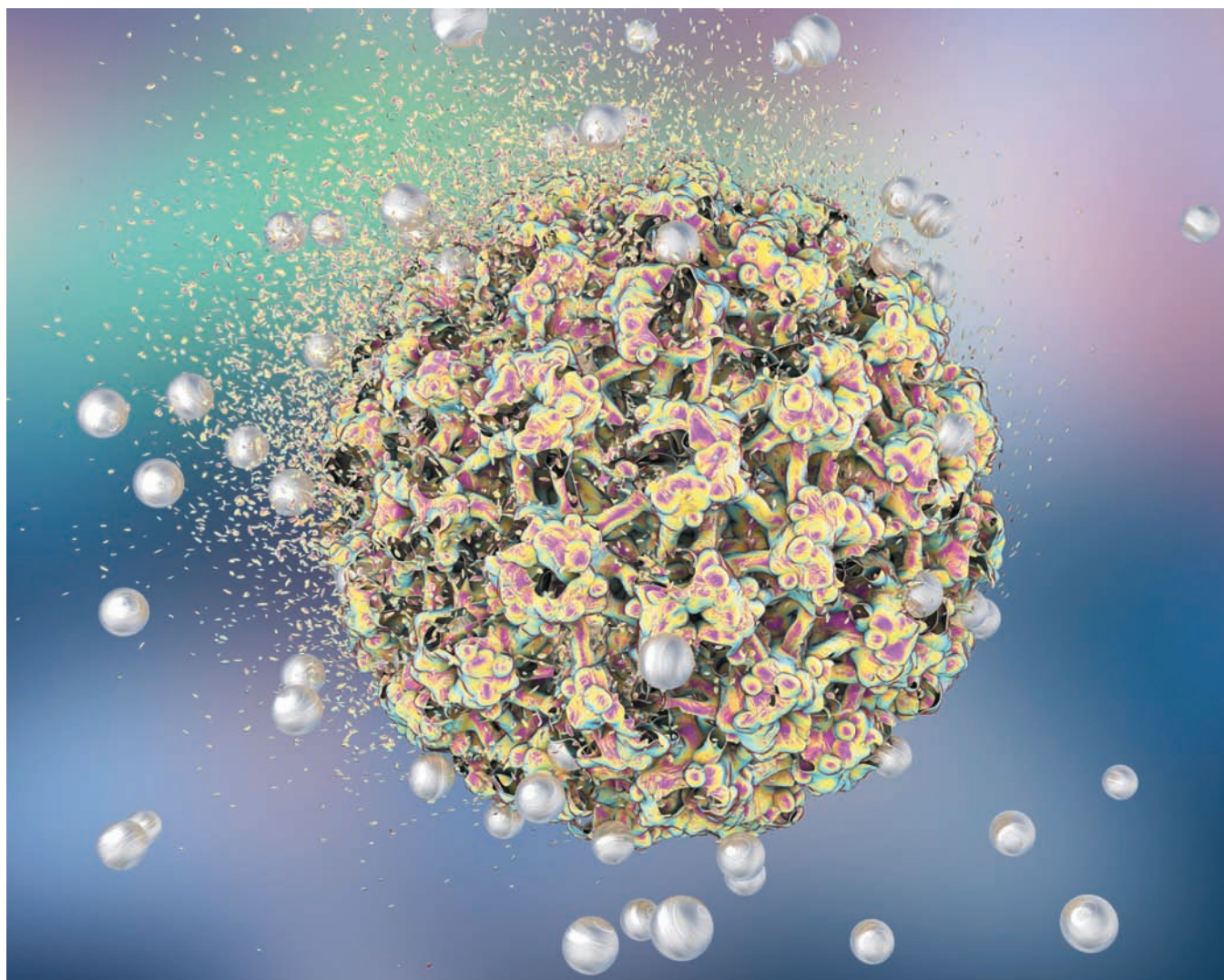
PSMA is a cell membrane receptor which is significantly over-expressed in prostate cancers. Its expression increases with tumor aggressiveness, androgen-independence, metastatic disease, and disease recurrence. Evidence suggests that PSMA may perform multiple physiological functions within the cell: a role in signal transduction, cell migration, receptor function for an unidentified ligand and nutrient uptake such as glutamate and folate have been suggested.

Having a sensitive and specific biomarker to localize primary and metastatic prostate cancer would greatly improve the algorithm for the diagnosis and management of prostate cancer. Other than skin cancer, prostate cancer is the most

common cancer in North America. About one out of seven men in the US will be diagnosed from prostate cancer during his lifetime.

Since 2012, the number of PSMA clinical studies using has exponentially increased. Among these agents, the ^{68}Ga - and ^{18}F -labeled compounds have attracted the most attention, as these compounds can be used for PET/CT imaging. However, the availability of ^{123}I or $^{99\text{m}}\text{Tc}$ also will 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 ^{177}Lu -PSMA ligand therapy. ■





Interview with: Dr. Danfer Huapaya President, ALASBIMN

In november 2017, ALASBIMN has held a very successful scientific meeting in Santiago de Chile. You are now the new President of ALASBIMN. Can you give the international readers of the magazine an overview of the efforts of ALASBIMN to promote Nuclear Medicine in Central and South-America?

The Latin American Association of Societies of Biology and Nuclear Medicine (ALASBIMN) has been supporting the different Nuclear Medicine Associations in our region, trying to make strategic alliances with the different international scientific Societies such as the American Society of Nuclear Cardiology (ASNC) and the IAEA in order to improve the training and learning of nuclear physicians in our region. It also encourages us to research and publish our research papers in the ALASBIMN journal, which helps its dissemination at the regional level. However, we still need to consolidate much more all the associations of Central and South America in order to support each other.

You are very familiar with the strengths and needs of the Peruvian Health Care system. Can you give us an idea of the assets and challenges of the practice of NM in Peru?

Peru is a country of a diverse geography and therefore our resources in the field of health are still scarce giving priority to comprehensive basic health. However, in the last ten years we have significantly improved our technology in the field of imaging. Nuclear medicine has developed a lot in the capital, with 15 nuclear medicine centers and only 3 nuclear medicine centers in some provinces of the north and

south of the country with SPECT, SPECT / CT and three PET-CT scanners that are only located in the capital of the country. Our challenge is to spread even more our nuclear medicine specialty throughout the country and have a greater number of gamma cameras in those places where there is no specialty and generate more jobs for young nuclear physicians who have just graduated from the specialty. Also, one of our limitations is that we do not have many suppliers of radioactive products nationwide and we have limitations with several radiopharmaceuticals, especially in the field of PET-CT.

You have had the opportunity to read the first issue of the NM magazine Pangea-ePatient. What do you think of the magazine and what would your suggestions be to improve it?

I had the opportunity to read the first issue of the journal at the ALASBIMN congress in Santiago de Chile in November 2017 and it seemed like a very educational magazine that promotes different articles and works of the different specialists in nuclear medicine. It would be great to have the Pangea-ePatient magazine in the future through an internet platform and be able to have access in the different countries of Central and South America.

Where will the 2020 ALASBIMN meeting be held?

It will take place in Lima – Peru from November 13 to 16, 2019. ■

XXVII Congreso de la Asociación
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Jackie Herman

President of the Carcinoid Neuroendocrine
Tumor Society (CNETS) of Canada



NETs PATIENTS' PERSPECTIVES

The life of a person diagnosed with cancer changes dramatically in a single moment when they hear the words “you have cancer”. Imagine what it feels like to hear that you have neuroendocrine tumours (NETs), a rare cancer that is “usually” slow growing. Canadians are hearing this news with increasing frequency as the incidence of NETs steadily increases, partially a result of better awareness among the medical profession and better diagnostics. However there are few medical professionals in Canada who truly understand and can effectively treat NET patients. Many suffer for years with misdiagnosis or no diagnosis, even at top Canadian cancer centres. On average it takes 5 to 7 years for NET patients to obtain an accurate diagnosis which results in many having metastatic disease at diagnosis.

NETs are rare neoplasms that involve hormone-secreting tissues and cells everywhere in the body, from the brain (pituitary) to the rectum and virtually every tissue between. They are not only cancers that can grow and metastasize, but they also have a significant impact on patient day-to-day life because NETs make hormones that have debilitating effects on function, both physical and emotional. A complicating factor in the diagnosis and treatment of NETs is that it can present as very slow growing, requiring many years of care and ongoing monitoring or it can also be very aggressive, requiring a more assertive treatment plan.

CHALLENGES IN CANADA FOR NET PATIENTS

A diagnosis of NETs comes with a number of challenges such as late or incorrect diagnosis, once diagnosed lack of access to clinical expertise, difficulty in accessing the most effective and accurate diagnostic tools, coordination of care among several specialists, obtaining accurate and reliable disease specific educational resources and support, burden of a “long-term” battle with the disease and lack of access to clinical trials as research interest and the development of new treatment options are less common in the NET space.

PATIENT IMPACT

NET patients very often find themselves in the position having to quickly become “experts” in

their own diagnosis and self-advocating in an effort to compensate for the inherent shortcomings of our Canadian healthcare system. Lack of healthcare navigators in hospitals and cancer centres often leave patients at a loss as to how to effectively navigate the provincial healthcare systems to obtain the best possible care and effective support.

Accessing NET expertise is one of the biggest challenges for Canadian NET patients as there are few “experts” in this country. Additionally, it is well known that a multi-disciplinary approach to NET management results in much better patient outcomes. However our health care system does not necessarily support this model and patients often bear the weight of an inefficient system and the responsibility of self-education as to who are the most important specialties they need to seek and pursue consultations with. Coordinating multiple appointments among various specialists is incredibly challenging for patients and attempting to get the various members of their team to communicate with each other is another challenge that sadly often falls on the patient. Canadian patients need greater access to specialized NET centres, of which there are currently only a handful in Canada. In these centres, patients typically have access to a large multi-disciplinary team and rarely have to co-ordinate themselves.

Two critical components of NET patient care are (i) the current most advanced diagnostic tool, Ga68 PET/CT, and (ii) the nuclear treatment, PRRT with Lu177. Both of these are currently only available in a clinical trial setting at few select centres in Canada. It is not uncommon for NET patients to travel long distances at significant personal expense for access to this diagnostic and treatment, which is financially and emotionally stressful. Both of these tools are incredibly valuable to NET patients and have the ability to dramatically change treatment plans/disease management and very often offer disease stability. The current clinical trial structure is sometimes not fair and there is not enough capacity to support every patient who needs access. Canadian patients need more access and they expect to be able to get it in their own province.

Patients who have the more common, slow growing form of NETs often face years of requiring access to diagnostics, care and resources, which is not necessarily all that common in cancer care although this does seem to be changing with new developments in treatments that result in longer life span. It does not appear though that our healthcare system is structured to provide this long-term support and NET patients can find themselves struggling to get access to supportive programs and end up seeking answers outside of their care centre, and very frequently turn to other patients for support. On the other hand, patients with the more aggressive forms of NETs are not always sure of where they fit within the NET community. Their journey can be very different from the average NET patient and they struggle to find other patients who have travelled a similar path to turn to for support and sharing of treatment plans etc.

In 2014 the Global NET Patient survey was carried out and included responses from 1,928 patients from 12 countries. The survey, the first of its kind, provided a true picture of the devastating impact of this cancer, how difficult it is to obtain a diagnosis and the benefit of the multidisciplinary approach to care. This survey was a first step in global recognition of the challenges specific to this group of cancers and should be used to develop a path forward to ease some of the burden on this patient population.

FILLING THE GAP

In general more and more patients are relying on advocacy and charitable organizations to fill the gaps left by ineffective healthcare systems. In Canada there is only one charitable organization that supports the NET patient community, CNETS Canada. CNETS Canada offers patients in-person support through a 1-800 number and face-to-face peer support groups. Patients can call CNETS Canada to talk about their diagnosis, find the names of doctors close to them who offer care for NET patients and find out where the closest in person patient support group is located. They are connected with a local support group leader if one exists. CNETS Canada also provides patients with a comprehensive resource guide that was developed in partnership with Canadian NET medical professionals that provides much needed information on the various types of NETs, common diagnostic tools and treatment options.

CNETS Canada provides patients across the country with access to local patient education sessions chaired by their local NET experts and once every two years a national patient conference brings together NET experts of various disciplines from across the country to present to NET patients on general disease information, latest advances in NETs and what is in the pipeline. These are critically important events for patients to not only learn about their

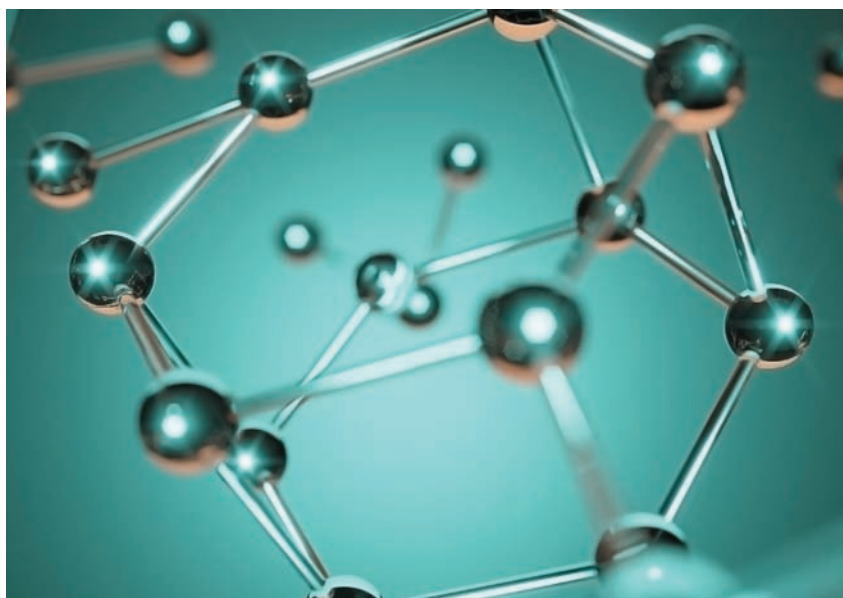
disease but to connect with other patients who have a similar diagnosis. With the wide variety and complexity of NETs even within our own community it can be challenging to find someone with a similar diagnosis.

CNETS Canada also supports Canadian research into NETs through 2-3 grants per year and holds a Canadian NETs Medical and Scientific meeting yearly to bring together the Canadian NET experts to share their knowledge and expertise with the future generation of care providers.

Advocacy is another very important aspect to the work carried out by CNETS Canada and in recent years we have been aggressively advocating for increased patient access to the Ga68 PET/CT and PRRT treatment with Lu177 with some success. We will continue our efforts in this area as access is nowhere near where it needs to be.

While there is no doubt that CNETS Canada provides an invaluable service to the Canadian NET community unfortunately as a volunteer led organization with limited resources CNETS Canada is not equipped to move all of the mountains faced by Canadian NET patients. It is more important than ever that we work together with the medical profession and the healthcare agencies to overcome the many challenges.

In addition to the role played by CNETS Canada, it must be mentioned that there are select centres across Canada that are very dedicated to improving the lives of Canadian NET patients and they are doing incredible work on behalf of this patient population, making a significant difference in the lives of patients. We need more of these centres and more partnerships to make significant advances across the country. We must never forget that patients live in every corner of this great country and all of them deserve equal access to expert care. ■



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INTERVIEW WITH JAMES McBRAYER

You have been actively involved in the field of nuclear medicine for quite a while. Looking back at your career, what are the most significant changes that you have witnessed in the field over the past 10 years?

I have witnessed a great deal of change since starting in nuclear pharmacy as an intern in 1988. Following graduation from pharmacy school, I practiced nuclear pharmacy in the United States, Australia and New Zealand. Since taking on the role of CEO of Cyclopharm in 2008, given the numerous markets we distribute our products to, I have had the ability to view nuclear medicine from a global perspective.

In my opinion the top two changes in the past 10 years in nuclear medicine have been related to advancements in imaging technology and in Positron Emission Tomography (PET).

An example for advancement in imaging technology can be seen in diagnosing Pulmonary Embolism (PE). Nuclear medicine functional imaging with SPECT has reversed a previous trend toward anatomical imaging with CTPA. By replacing 2D Planar for 3D SPECT imaging and shifting from probabilistic outcomes, nuclear medicine physicians are delivering higher levels of sensitivity and accuracy in diagnosing PE at a fraction of the radiation dose compared to that of CTPA.

I believe the other area of major change in the past 10 years in nuclear medicine has been in molecular imaging with PET. In the past decade PET has grown from a few oncology studies primarily using FDG to a growing array of agents used diagnostically in oncology, neurology, cardiology and MSK.

PET continues to evolve rapidly by providing the platform for the development of Theragnostics. These diagnostic – therapeutic combinations

acting on targeted biological pathways, predominantly used in oncology, are set to provide nuclear medicine its next major leap forward.

What is Cyclomedica?

Cyclomedica is a wholly owned subsidiary of the Australian listed company Cyclopharm (ASX:CYC). Cyclomedica is best known for our proprietary functional lung ventilation imaging product Technegas. First used clinically in 1986, Technegas is now available in 57 countries around the world. Given Technegas' unique properties, there are no contraindications for its use, it is ideally suited for 3D SPECT imaging and dramatically reduces the potential for hotspots often seen with competitive nuclear medicine products such as DTPA aerosols.

Our largest regional market is Europe where we are referenced in the EANM Guidelines 2009 as the preferred ventilation imaging agent in diagnosing PE. Our largest single country market is Canada. We are approved for use in China and will be looking forward in the coming years to expand the use of Technegas throughout Asia.

We are currently involved in a Phase 3 clinical trial with the USFDA and hope to bring Technegas to the United States very soon.

Lung Ventilation studies for the diagnosis of pulmonary embolism have been successfully performed across the world for many decades with Technegas. Can Technegas play a role for the quantitative evaluation of the lungs function in other diseases?

4 million patients have been imaged with Technegas. Whilst best known for diagnosing PE, with the advancement of more sensitive imaging technologies to include SPECT-CT



combined with newly developed analytical software, Technegas is more relevant today than it was when it was first introduced in 1986.

Given that Technegas can show true functional ventilation to the point of gas exchange at the alveoli, we are seeing strong global interest from respiratory physicians to apply Technegas to both quantify the extent of disease and measure response to therapy. We are working with both nuclear medicine and respiratory physicians around the world in clinical trials targeting severe asthma, chronic obstructive disease, lung volume reduction and lung transplant to name a few. An example of one of these initiatives can be found via the following link: <https://hmri.org.au/news-article/nuclear-imaging-clear-airway-diagnosis>.

What do you anticipate the role of artificial intelligence (AI) be in the field of lung imaging? Nuclear Medicine has always embraced advancements in technology. In lung imaging I have seen, where Technegas is available, that SPECT is replacing Planar imaging. Recent techniques using SPECT co-registered with low dose CT augmented with analytical software is providing another layer of information to clinicians not previously available.

In the September 2017 Lancet commissioned publication entitled "After Asthma: redefining airways disease" global leaders in the field of respiratory medicine call for tests that can incorporate "traits that can be measured" as

well as measures "in the context of social and environmental factors and extrapulmonary comorbidities". Rather than focusing on a singular image interpretation, I see that AI's greatest contribution in patient outcomes will be in delivering personalized respiratory medicine by analyzing the numerous and complex inputs required to deliver on diagnostic, prognostic and therapeutic outcomes.

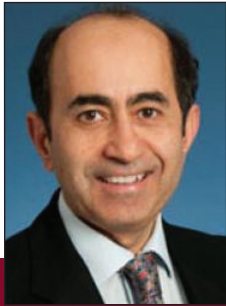
You have had the opportunity to read the first two issues of the NM magazine Pangea-ePatient. What do you think of the magazine and what would your suggestions be to improve it?

This publication is an important educational tool. Similar to AI, Pangea-ePatient is in its own way disruptive. I am entering my third decade in nuclear medicine and have never known of a publication with such global support within the discipline of nuclear medicine combined with such broad reader potential.

I am enthusiastic to learn about the endorsement from so many of the global Societies of Nuclear Medicine and trust that this level of support will only expedite the messages being shared throughout the world to our referring physicians.

Thank you for the honour of contributing to Pangea-ePatient and congratulations on the important work that you are doing. ■





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THE EXPANDING SPECTRUM OF NEUROENDOCRINE TUMORS (NETS)

Glossary of abbreviations.

CgA, chromogranin A, NEN, neuroendocrine neoplasm; NET, neuroendocrine tumor; 5-HIAA, 5-hydroxyindoleacetic acid,

OVERVIEW

Endocrine cells have the capacity to convert substrates into specific hormones that they store for secretion on specific demand. Endocrine cells are divided into three types based on their structure and function (1). Thyroid follicular cells produce thyroid hormone; these epithelial cells are derived from the oral endoderm and their products are iodinated tyrosine-based hormones. Steroid hormones, which are manufactured based on cholesterol uptake followed by specific modifications, include glucocorticoids, mineralocorticoids and the sex steroids estrogen, progesterone and testosterone as well as DHEAS and others; these are produced by a family of cells that are of mesodermal origin including adrenal cortex and gonadal stromal cells. The most numerous hormones are polypeptide hormones, which are synthesized from amino acids, in a highly regulated manner in dedicated endocrine glands, which classically include the pituitary, thyroid, parathyroid, and pancreatic islets, but also include endocrine cells scattered throughout the respiratory and gastrointestinal tracts, as well as the numerous paraganglia of the sympathetic and parasympathetic nervous system including the adrenal medulla. Tumors arising from peptide hormone-producing endocrine cells, regardless of their anatomical location, have been collectively referred to as neuroendocrine tumors (NETs).

The classification of NETs has been complex, with terms such as carcinoid tumor, islet cell tumor, and adenoma in pituitary and parathyroid to indicate low grade lesions, neuroendocrine carcinoma to signify aggressive cancers, and small cell carcinoma to characterize the most lethal of these tumors. The features applied for grading of these lesions vary from organ to organ. Recently, the WHO has proposed to bring this large family of neuroendocrine neoplasms (NENs) under a single

umbrella in an attempt to streamline and apply appropriate terminologies (2). The proposal is to classify all well differentiated epithelial tumors as NETs, with three grades based on their proliferation rates, and to separate the high grade, less well differentiated epithelial neoplasms as neuroendocrine carcinomas (NECs). This proposal is supported by molecular data that have shown distinct genetic alterations in these two different types of tumors that can arise from the same cells. Paragangliomas that are not epithelial are a third category of NEN. The term « carcinoid » is restricted to a syndrome that is caused by serotonin excess.

In this article, we will review the expanding spectrum of differentiated NETs, their presentations, and advances in their diagnosis and management.

HOW COMMON ARE NEUROENDOCRINE TUMORS (NETS)?

NETs are being recognized with increasing frequency. The incidence of gastro-entero-pancreatic NETs has increased dramatically over the last decade, with

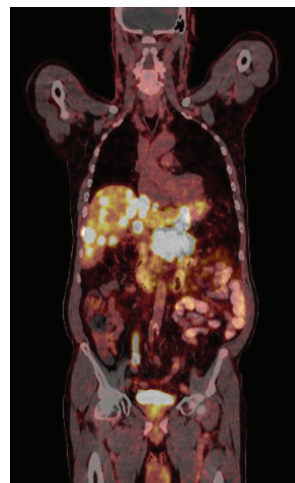


Figure 1. A NET of small bowel is seen infiltrating from its origin in the mucosa of the ileum (top right) through the bowel wall to the serosal surface; the tumor is highlighted by this immunostain for serotonin.

recent annual incidence estimates at 4-5/100,000 both in United States (3) and Ontario Canada (source: Ontario Cancer Registry). One of the National Cancer Institute largest databases on the subject included 13,715 cases of neuroendocrine tumors covering five decades from 1950 to 1999 (4). The most frequently involved anatomical sites were the gastrointestinal tract (67.5%) and the bronchopulmonary system (25.3%). Within the gastrointestinal tract, neuroendocrine tumors were diagnosed most frequently in the small bowel (42%) but also the rectum (27%) and stomach (9%). Five-year survival rates of 88%, 74% and 71%, respectively, were recorded for patients with the most frequent forms of NETs. Of these tumours, 4%, 28%, and 40%, respectively, demonstrated invasive growth or metastatic spread. However, it is critical to note that in nearly 13% of patients with gastrointestinal NETs, distant metastases can be detected at the time of diagnosis, highlighting the importance of increased awareness and early detection.

Other NETs are also being diagnosed more often. Pituitary NETs (PitNETs), which were one thought to be rare, are now known to be common tumors (5).

HOW SERIOUS CAN THEY BE?

NETs span the spectrum from indolent tumors to aggressive malignancies. Their proliferative activity is one of the most accepted biological markers of clinically relevant aggressive behaviour; this is determined by the Ki-67 labeling index, a feature identified by quantification of an immunohistochemical stain that detects a nuclear antigen expressed in dividing cells. Tumors with low proliferation are classified as grade 1 on the World Health Organization (WHO) grading system. Intermediate or grade 2 tumors have higher proliferative activity. The most aggressive or grade 3 tumors are the least common but also carry the worst prognosis with survival measured in months compared to years for the lower grade tumors. Neuroendocrine carcinomas, in contrast, are usually highly aggressive malignancies (Figures 1-3).

Paragangliomas have traditionally been considered benign with rare malignancy (Fig. 2b). The function and location of these tumors can have significant consequences and recently, the WHO has revised their classification; they are no longer classified as benign or malignant but all are considered to have malignant potential and they are only distinguished as metastatic when spread is documented (6).

An important issue for all NETs is the high degree of familial predisposition. Patients with epithelial NETs may have multiple endocrine neoplasia (MEN) syndromes such as MEN1, MEN2 or MEN4. Paragangliomas have the highest incidence of causative germline genetic events at approximately 40%; these include succinate dehydrogenase (SDH)-related disease, von Hippel Lindau disease, MEN2 and mutations in more than 15 other genes (7).

HOW CONSISTENT ARE THE SYMPTOMS OF NETS?

The symptoms arising from NETs can be divided into two major categories. The first category is hormonal, which depends largely on the cell of origin. For example, lung and small bowel NETs frequently manufacture serotonin, resulting in flushing, wheezing, and diarrhea, the constellation of symptoms and signs known as the carcinoid syndrome. However, most other NETs do not manufacture serotonin. Instead, they produce dedicated hormones that are the normal products of their cell and organ of origin. In the endocrine pancreas this can include inappropriate insulin secretion with resultant hypoglycemia, gastrin overproduction leading to recurrent peptic ulcerations, glucagon hypersecretion contributing to diabetes and skin rashes, and vasoactive intestinal peptide (VIP) presenting with severe watery diarrhea. There are also other hormones such as somatostatin, pancreatic polypeptide, and cholecystikinin (CCK) with poorly defined common symptoms that often go without specific diagnosis. Thyroid NETs, known as medullary thyroid carcinomas, produce calcitonin. Parathyroid NETs cause hypercalcemia, PitNETs produce a number of hormones, some of which cause acromegaly or Cushing disease, others affect thyroid and gonadal function and fertility. Some NETs produce hormonal products usually secreted by other NETs, a phenomenon known as ectopic hormone production; the most common of these is ectopic ACTH, giving rise to Cushing syndrome that can be associated with NETs at various sites.

It is important to consider paragangliomas in the NET family since they can produce symptoms that mimic carcinoid syndrome but they do not produce serotonin; the production of catecholamines is relevant in this context.



Figure 2. Histology of NETs. NETs usually are composed of solid nests, sheets, cords and small acini within a highly vascular stroma. (a) Epithelial NETs are characterized by round cells with relatively bland nuclei. (b) Paragangliomas often have larger and more polygonal cells with abundant amphophilic cytoplasm.

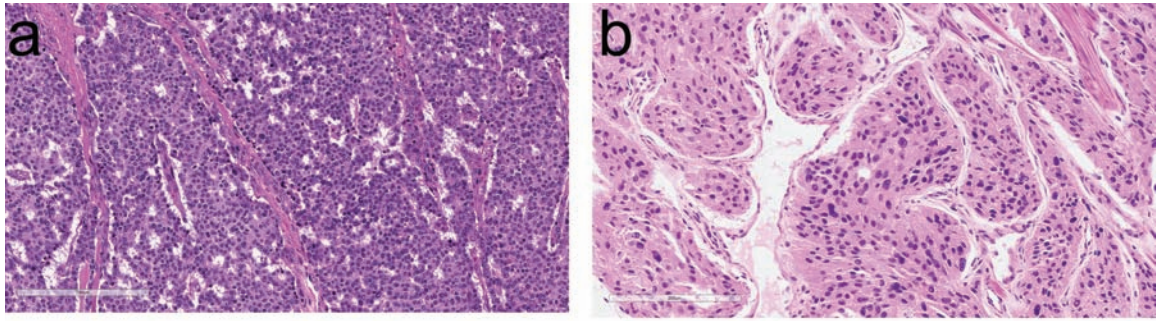


Figure 3. A metastatic NET in liver (a) stains for chromogranin A (b) and gastrin (c).

The second category of symptoms is structural or compressive in nature. These depend on the anatomical site of the disease and its metastases. For example, in the lungs, compressive lesions can result in recurrent pneumonias and/or hemoptysis. Around the biliary duct, growing NETs and their associated lymphadenopathy can result in significant cholestasis with or without pancreatitis. In the pituitary, the sequelae of NETs includes headaches and visual field defects.

HOW ARE NETS DIAGNOSED?

Incidental findings

NETs are increasingly diagnosed as an incidental finding during routine CT, ultrasound, or MR imaging. Incidental detection of gastric and rectal NETs at the time of endoscopy is also becoming increasingly common. While the appearance of NETs is sometimes characteristic, a tissue diagnosis is required for confirmation. In most locations, this can be in the form of a needle biopsy; ideally, a core biopsy is preferred over the more common fine needle aspirate. It is important to keep in mind that while a biopsy can establish the NET identity based on the detection of classic markers including synaptophysin and chromogranin, site-specific transcription factors and hormones (8), prediction of tumor behaviour is difficult to determine on a biopsy sample, since it requires complete staging and accurate proliferation assessment for grading, a feature that can be misleading on a biopsy due to tumor heterogeneity that is well documented in these lesions. The diagnosis of paragangliomas by a pathologist requires a high index of suspicion and special immunostains (8).

Biochemical testing

In instances where the clinical presentation provides a clue to the diagnosis of NET, specific blood and/or urine tests represent the cornerstone of laboratory diagnosis. Such biomarkers fall into two major categories. The generic biomarker for NETs is the peptide chromogranin A which has emerged as the single most useful general marker of neuroendocrine neoplasia. However, many precautions are required for specific application of this test. Of these, fasting conditions in the absence of medications which can falsely elevate serum chromogranin A are essential for reliable interpretation. The more specific markers include serum insulin, gastrin, somatostatin, vasoactive intestinal peptide (VIP), and/or pancreatic polypeptide, and 24 hr urinary 5-hydroxyindoleacetic acid (5-HIAA) that is a metabolite of serotonin. Again, such markers should be requested on the basis of specific symptoms and clinical suspicion as well as the results of pathology testing to enhance the yield and avoid misuse of laboratory resources. The diagnosis of paraganglioma must also be considered and in this setting, biochemical testing involves measuring the N-metabolites of catecholamines: methoxytyramine, normetane-phrine and metanephrine.

Functional imaging

Functional imaging using a variety of radioisotopes has long been recognized as a useful modality in detecting endocrine tumors. Earlier studies relied on metaiodobenzyl guanidine (MIBG) for the detection of catecholamine producing pheochromocytomas and paragangliomas. Subsequently, various groups around the world noted the ability of MIBG to also detect other NETs. However, this technique has now

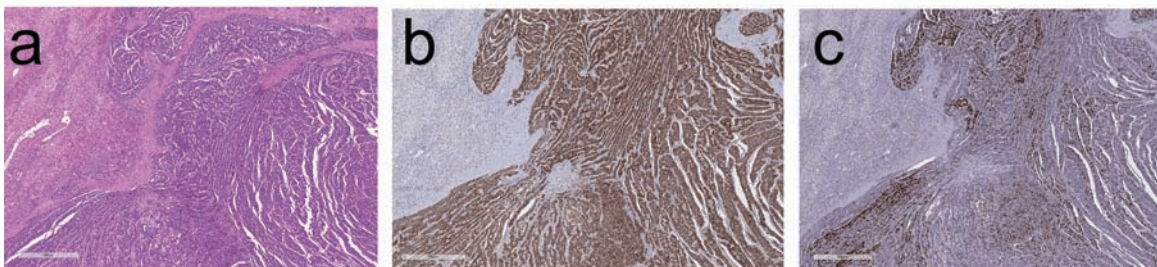


Figure 4. Innumerable lesions of metastatic NET within the abdomen show Gallium 68 avidity on PET imaging.

been largely superseded by somatostatin receptor scintigraphy (SRS). These technologies are based on the inherent abundance of somatostatin receptors expressed by NETs. The earliest generation of SRS relied on Indium¹¹¹ as the tracer resulting in the traditional octreoscan. Subsequent studies, however, have demonstrated the overwhelming advantage of positron emission tomography/computed tomography (PET/CT) with ⁶⁸Ga-labelled peptides such as ⁶⁸Ga-[DOTA,Tyr3]-octreotate (Figure 4), also known as DOTATATE.

TREATMENT OF NETS

Surgery

Whenever possible, complete surgical resection of the suspected NET is the most desirable and successful therapeutic option. Unfortunately, this is not always possible given that a considerable fraction of patients present with metastatic disease at the time of diagnosis. Nevertheless, cytoreductive surgery coupled with detection and excision of the primary tumor is of proven benefit in impacting disease outcome.

Medical options

From a medical perspective, somatostatin analogues represent the cornerstone of most regimens for their ability to control hormone hypersecretion and arrest tumor progression (8). When insufficient, mTOR inhibition and tyrosine kinase inhibitors such as sunitinib represent the next options for intermediate grade tumors (8). For even more rapidly growing, high grade NETs, oral combination chemotherapy with capecitabine and temozolomide has gained wide popularity for its efficacy and relative tolerability (8).

Radiopharmaceuticals

The principle of somatostatin receptor overexpression in NETs has also been exploited and extended for radiotherapeutic applications. Currently, peptide receptor radionuclide therapy (PRRT) using particle-emitting radionuclides is emerging as one of the most promising radiopharmaceuticals with proven objective response rates, survival benefit compared to historical controls, and possibly enhanced quality of life (QOL) (9). It is anticipated that newer methods of PRRT application based on various internal dosimetry paradigms will represent the cornerstone of management of a sizable portion of the NET patient population.

Minimally invasive approaches

Complemented by surgery and radiopharmaceuticals are a host of new interventional approaches (10) including radiofrequency ablation, chemo- and bland-embolization, and nanoknife electroporation.

SUMMARY

Neuroendocrine neoplasms represent a large spectrum of tumors that occur from the base of the brain to the rectum. They are among the few tumors that are increasing in incidence. Their diagnosis requires clinical acumen based on recognition of their subtle features, and is confirmed by appropriate structural and functional imaging, biochemistry and pathology. Their diagnosis implies consideration of potential familial predisposition. A number of treatment modalities are available including surgery, medical and radiotherapeutic targeting.

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NEW FRONTIERS ACCESSIBLE, SOMATOSTATIN RECEPTOR IMAGING



HISTORY

Somatostatin is a hormone discovered in 1972 by Professors Brazeau and Guillemin (Salk Institute), also known as growth hormone-inhibiting hormone. It is a peptide regulating the endocrine system (exocrine and glandular secretion), which acts on the absorption of nutrients, plays a role in neurotransmission, smooth muscle tissue contractility and cell proliferation. This hormone is composed of a set of peptides that can be found in two forms. The first is composed of a sequence of 28 amino acids and is found mostly in the nervous system. The second, called efficient somatostatin, is a derivative of the first, possessing only 14 amino acids. The latter is mainly found in the digestive system.

Somatostatin has a very short biological half-life, ranging from two to three minutes. It binds to one of the five somatostatin receptor subtypes (SSTR1-5) found on the cell surface to activate a cascade of interactions via the G-protein and inhibit the release of multiple secondary hormones. The concentration of these different receptors varies according to the

tissues as well as the histological type of the tumors. The SSTR-2 receptor is the most physiologically expressed.

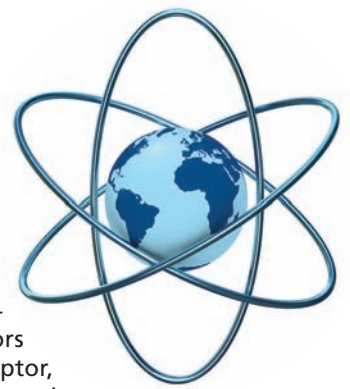
Research has promptly suggested that somatostatin could have tremendous therapeutic potential, thus creating a substantial hope for the treatment of growth hormone hypersecretion in diabetes as well as for the control of gastroenteropancreatic secreting tumors. Due to its very short biological half-life, several somatostatin analogues have been developed to circumvent this limitation. This work led to the discovery of octreotide in 1979, a somatostatin analogue with a half-life of approximately 90 minutes. Octreotide is a synthetic eight amino acid sequence that has more potent inhibitory effects than somatostatin on the secretion of growth hormone, glucagon, or insulin. Nowadays, it is frequently used in the treatment of certain pituitary hormone disorders such as acromegaly and very frequently in patients with neuroendocrine gastroenteropancreatic tumors to reduce symptoms and slow tumor progression.

NEUROENDOCRINE TUMORS

Although neuroendocrine tumors (NETs) are thought to be rare, national and global statistics show that their incidence is increasing (five cases per 100,000). This growth is mainly due to the fact that doctors are more familiar with the clinical manifestations caused by the hormonal activity of NETs and not by an increase in the number of cases. The major advances in biochemical and imaging diagnostic tools also explain the improved diagnosis of these types of tumors. The prognosis depends on the location, grade and on the rapidity of detection from the time of onset. A specific hormonal secretion will be sought in case of evocative symptoms. Chromogranin A (a glycoprotein produced in the secretory granules of neuroendocrine cells) is one of these commonly used markers, and the value will be high in 85% of patients with digestive NET. On the other hand, its specificity is only 68% because several conditions can cause its elevation. Of these, chronic use of proton pump inhibitors is the most common indication. Other causes include chronic lung disease, inflammatory joint and digestive diseases, renal failure, several non-digestive cancers, heart failure and even acute coronary syndrome.

The diagnosis of NETs is made using endoscopic, radiological and nuclear medicine techniques. Many of these tumors will be visible by CT and MRI with a sensitivity ranging between 30 and 40%. The ability to accurately determine the location and extent of the tumor is of paramount importance because the only curative action available is surgical resection. In the wave of specialist medicine, nuclear medicine has distinguished itself by offering an imaging test aimed at a biological characteristic of NETs, that is, the expression of the

somatostatin receptor. The concept of somatostatin receptor imaging was introduced in 1994 by the introduction of a nuclear medicine agent called Octreoscan (Mallinckrodt Pharmaceuticals). This agent marked the beginning of a revolution in receptor imaging to identify, by non-invasive testing, the extent of tumors overexpressing the somatostatin receptor, almost undetectable by other imaging modalities.



OCTREOSCAN

Octreoscan (Indium-111 pentetretotide) has been available for several years in all nuclear medicine centers in Quebec and elsewhere in the world. It offers a sensitivity ranging from 52-92% and a specificity of 92% for the detection of NETs. It is a sequence of eight amino acids similar to octreotide to which a chelating group has been added in order to insert a radioactive isotope, indium-111. This isotope is essential for monitoring the distribution of the radiopeptide which, once injected intravenously, will specifically target the expression of the somatostatin receptor on the cell surface. Of the five known subtypes of somatostatin receptors, the Octreoscan preferentially targets SSTR-2, 3 and 5 receptors. At the level of gastroenteropancreatic NETs, the STR-2 receptor is the most frequently expressed compared to the SSTR-4, which is only very rarely expressed. All the NETs express differently the five receptor subtypes and the expression of the receptor is not specific to the NETs since benign lesions (e.g. pituitary adenoma, meningioma, hemangiomas) and neoplasia (e.g. breast, lung, lymphoma) can also express the receptor. Also, during the progression of a tumor from a

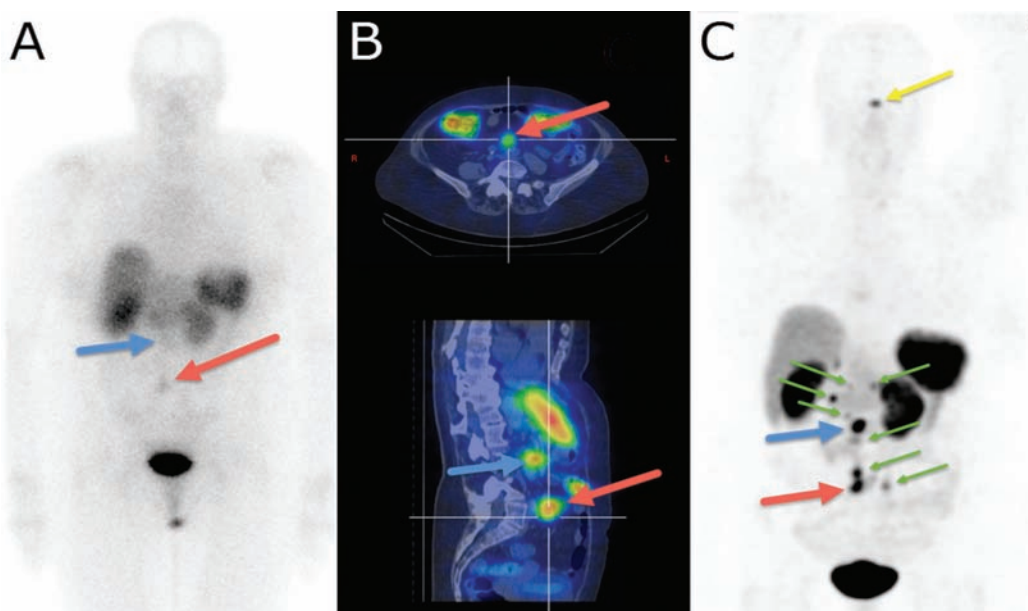


Figure 1. Images obtained at Octreoscan (A and B) and Octreotate (C) in the same patient at an interval of one month. Octreoscan scintigraphy (A): the red arrow points to a somatostatin receptor overexpressing lesion and the blue arrow indicates an abdominal equivocal lesion. SPECT-TDM with Octreoscan (B): two lesions clearly visible (arrows red and blue). PET-Octreotate (C): confirms that both lesions visible to Octreoscan over-express somatostatin receptors in addition to seven other lesions (green arrows). Physiological pituitary uptake (yellow arrow).

Table 1.

Advantages and disadvantages of PET-Octreotate imaging compared to Octreoscan

Advantages

- It takes 25 minutes in one day instead of two to three days.
- Lower dosimetry, advantageous for the pediatric population (2.1mSv / 100MBq vs 8mSv / 100MBq).
- 5 mm resolution compared to 1-1.5 cm, more sensitive.
 - Locates more unsuspected lesions.
 - Change in management in > 50% of patients.
- Cost-effective, lower than the cost of Octreoscan for high-speed imaging installations.
- Available every day. Octreoscan must be ordered one week before use.

Disadvantages

- The half-life of the radiotracer (68 minutes) makes exporting impossible.
 - Patients must move to the imaging center.
- Must be synthesized on site, a few minutes before use.
 - Requires an experienced and available team.
 - Only one possible synthesis per six-hour period.
- False positives also more visible: hepatic hemangioma and bone.

than 1 cm (Figure 1, A and B). To increase the ability to image smaller lesions, the examination should take two to three days, requiring great flexibility from the patients.

EVOLUTION TOWARDS POSITRON EMISSION TOMOGRAPHY

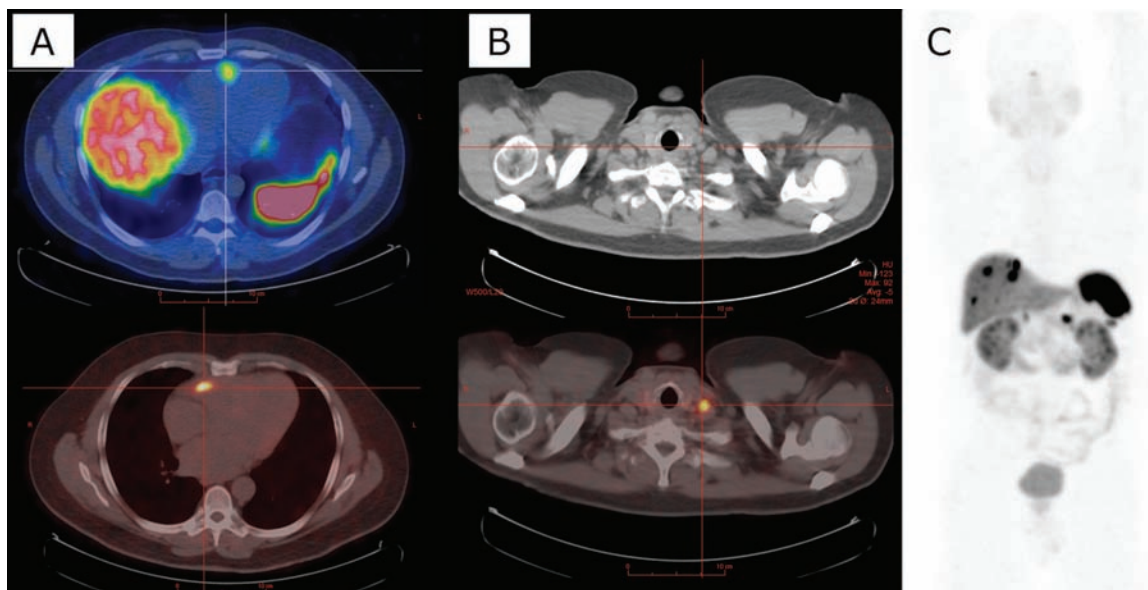
Today, several departments of nuclear medicine in Quebec have been upgraded to integrate a positron emission tomograph (PET) into their equipment fleet. These ultra-high-tech devices, which are more sensitive and quicker than conventional nuclear medicine devices, offer great advantages by opening the door to customized molecular imaging. The advantages of fluorodeoxyglucose imaging (FDG) are now well known in oncology for a very high proportion of neoplasias. However, for NETs, FDG-PET is not indicated for the majority of low-cell-proliferation NETs (less than 20%). FDG-PET sensitivity becomes higher for NETs with a more aggressive biology and an unfavorable prognosis. Due to the inability to properly image well-differentiated NETs with FDG, an imaging similar to Octreoscan has been developed, commonly called DOTATOC, DOTANOC or DOTATATE PET/CT.

differentiated to undifferentiated state, the expression of the receptor decreases until it disappears. These factors must therefore be considered to ensure the effectiveness of somatostatin receptor imaging.

Moreover, this type of imaging requires a gamma-camera type device which is nowadays present in the form of hybrid apparatuses combining both a gamma detector and an axial computed tomography (CT) scan. This combination considerably increases the sensitivity and specificity of the examination, but remains ineffective in imaging tumors less

Similarly to Octreoscan, Octreotate (DOTATATE) is an eight amino acid sequence associated with a chelator that will allow a PET isotope, Gallium-68, to be inserted into the peptide. However, the amino acid sequence is different from octreotide. Minimally, PET-Octreotate imaging has the same advantages and indications as Octreoscan, making it a replacement. But compared to Octreoscan, PET-Octreotate (Figure 1 C) has a higher sensitivity, ranging 81-94% and a specificity of 82-90%. This increase in accuracy compared to Octreoscan is explained by a 12-fold higher affinity of the Octreotate for SSTR-

Figure 2. PET-Octreoscan imaging showing unsuspected lesions. Image A (top and bottom): NET cardiac metastasis in two patients. Image B (High CT, Low Fusion PET-CT): 3 mm cervical metastasis of a small bowel tail. Image C (PET): NET of the pancreas with multiple liver metastases.



2 somatostatin receptors and a sensitivity gain of PET devices capable of imaging lesions as small as 5 mm. This increase in sensitivity results in a modification of the therapeutic approach in more than 50% of patients who previously had a conventional negative imaging with the Octreoscan. Octreotate PET imaging has considerable benefits for the patient as imaging takes place in a single day and takes only 25 minutes. The examination is also less irradiating, making it the exam of choice for the pediatric population.

The main disadvantage of Octreotate is its availability due to its physical half-life of 68 minutes compared to the Octreoscan of 2.8 days. This limitation is a consequence only because of the use of Gallium-68 as an isotope, which cannot be replaced. Consequently, the Octreotate must be synthesized on site by an experienced team, can be transported only a short distance and must be used within minutes of its synthesis. No place for error is allowed, as only one synthesis can be obtained per six-hour period and each synthesis makes it possible to image a patient, for a maximum of two patients per synthesis if two PET devices are available. Table 1 summarizes the advantages and disadvantages for the patient and the clinician of PET-Octreotate versus conventional Octreoscan imaging.

Since the summer of 2016, a Canadian center (CIUSSS de l'Estrie CHUS, Sherbrooke Molecular Imaging Center - CIMS) offers PET-Octreotate as a replacement for conventional Octreoscan for both adult and pediatric population. Since this is an imaging test not approved by Health Canada, patients must first consent to the injection of the Octreotate. In case of refusal, conventional Octreoscan imaging will be offered. Less than six months after its implementation, more than 100 studies have been conducted with Octreotate for patients from British Columbia, Ontario and Quebec. The most common findings are the extension of the NET (Figure 2, ABC), determine the degree of somatostatin receptor expression in anticipation of radiopeptide therapy (Lutetium-Octreotate), measure the response to treatment and characterization of brain lesions (meningioma).

Given the growing popularity of PET-Octreotate, the imaging center expects to reach a pace of 150-200 exams for 2017. Due to the presence of two PET devices, it is estimated that a maximum of 280 examinations could be performed annually. Table 2 summarizes the indications for PET-Octreotate. ■

If you feel that any of your patients may benefit from this examination, please contact us at:

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Table 2:

Indications for which the Octreotate replaces the Octreoscan

- Locate a NET or tumor expressing the receptor to somatostatin and its metastases:
 - Gastroenteropancreatic tumors: carcinoid, gastrinoma, insulinoma (50%), glucagonoma, VIPoma, bronchial, small cell carcinoma.
 - Tumors of the sympathetic and parasympathetic system (pheochromocytom, paraganglioma, neuroblastoma, ganglioneuroma, glomus).
 - Medulloblastoma.
 - Oncogenic osteomalacia.
 - Merkel-cell carcinoma.
 - Medullary carcinoma of the thyroid
 - Other tumors: breast (Figure 3), lymphoma, hypernephroma, hepatoma, pituitary adenoma, meningioma
- Select patients for whom the tumor is progressing and may benefit from radiopeptide therapy (Lutetium or Yttrium)
- Measure response to treatments.
- Locate recurrence sites in symptomatic patients or in the progression of tumor markers.
- Determine the degree of expression of somatostatin receptors in order to characterize a lesion that is difficult to biopsy.
- Characterization of a suspicious meningioma brain lesion, impossible to biopsy, in anticipation of radiotherapy.

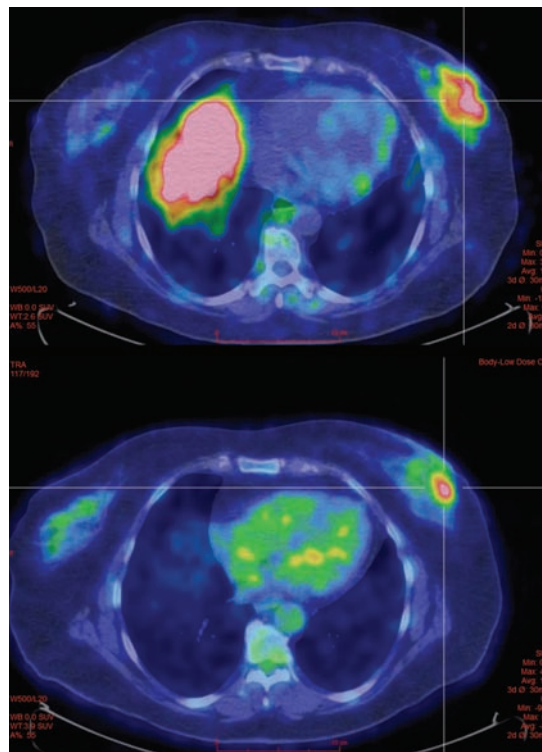
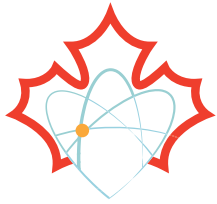


Figure 3. Octreotate imaging (top) and FDG (low) within one week in a patient with a left breast infiltrating canal neoplasia. The octreotate allows to better visualize and delimit the local extension.



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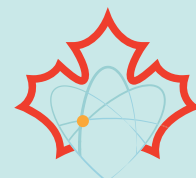


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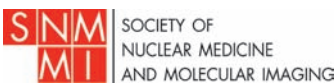
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Picture taken at the
Society of Nuclear Medicine
and Molecular Imaging meeting
in Denver, 2017

From left to right:
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DR. Bennett Grennspar, president SNMMI
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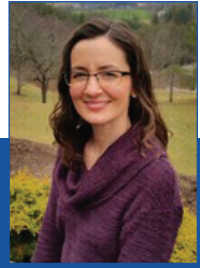


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Workflow and Treatment of NETs with Lutetium 177- Dotatate

As detailed in the article of Ezzat and Asa, NETs are difficult to diagnose and to treat. Symptoms of the disease are usually vague and it could take up to 10-15 years before a formal diagnosis can be established.

Treatment wise, while surgical resection is the most desirable therapeutic option, it is often elusive because a considerable number of patients present with metastatic disease at the time of diagnosis. Medically, somatostatin analogues have been the pillar of most therapeutic regimens for their ability to control hormone hypersecretion and slow/arrest tumor progression.

The vast majority of neuroendocrine tumors have receptors that bind somatostatin. NETs can be made visible by means of a scan by coupling a lightly radioactive compound to the protein or hormone somatostatin and then injecting the radiopeptide in patients.

The early effort to treat NET patients with medical isotopes and somatostatin analogs involved high doses of Indium 111 Octreotide. This form of radiation had a very short radius of action, caused little or no collateral damage to nearby cells and was most effective on very small tumors. In the late 1990s and early 2000s, two others isotopes with better "cancer killer" characteristics started to be used clinically in Europe to treat NETs.

This past January, the Federal Drug Administration in the USA approved Lutetium 177-Dotatate (Lutathera® - Advanced Accelerator Application [AAA]) for the treatment of somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs)

The Netter 1 randomized pivotal phase 3 study leading to the approval of Lutathera® not only showed good tumor response; it also demonstrated to prolong the survival of patients with this type of tumors. It is indicated in adults for the treatment of well-differentiated neuroendocrine tumors in the metastatic or inoperable stage, overexpressing somatostatin receptors, and progressive somatostatin analogues. There are currently no off-label indications. However, clinical trials in neuroendocrine tumors of the lungs are currently underway.

Since its approval by the FDA, more than 1000 doses of Lutathera® have been used in various medical centers across the US to treat NET patients.

At Wake Forest Baptist Medical Center, patients with NETs are seen by a multidisciplinary team of health care professionals. Radionuclide therapies are administered by radiologists and nuclear medicine specialists and Lutathera® is administered in nuclear medicine as part of its Theranostics program and clinic.

The Wake Forest Lutathera® planning and treatment protocol can be described and summarized as follows.

LUTATHERA® PRE-TREATMENT PROCESS

In order to proceed with the administration of Lutathera®, we required:

1. A positive gallium 68-dotatate PET scan.
2. A nuclear medicine therapy consult order is placed by a NET specialist.
3. A patient consult by a nuclear medicine physician is conducted that includes a physical examination, the discussion of radiation safety precautions and treatment plan details.
4. Satisfactory clinical and mental status, blood cells count, liver and renal function and metabolic panel.
5. A therapy plan ordered by a nuclear medicine physician through the EPIC EMR system after all patient evaluation is complete.
6. The absence of patient long-acting somatostatin analogs (e.g., long-acting octreotide) administration for at least 4 weeks and any short acting somatostatin analog for 24 hours.
7. Patient's last meal 4 hours before treatment.
8. A negative pregnancy test if appropriate.
9. A signed informed consent.

We used a dedicated radionuclide therapy suite with private bathroom and monitoring nurse office within the nuclear medicine department. Radiation safety and infusion equipment and supplies are stored in the suite cabinets. The bathroom floor and toilet seat are wrapped up with protective paper.

After a thorough physical exam, the patient is invited to sit in a comfortable reclining chemotherapy administration chair.

Two separate infusion lines are placed and secured for the separate administration of the renal protective amino acid solution and the Lutathera® therapy dose.

LUTATHERA® ADMINISTRATION

Oral prednisone and intravenous anti-emetics are given to the patient thirty minutes before the start of the amino acid solution. Thirty minutes after the start of the 4hrs intravenous administration of the lysine-arginine amino acid solution at a rate of 250 ml/hr, Lutathera® is given. Lutathera® is administered using either the gravity method or using a shielded automated syringe pump over a period of thirty minutes.

Cardiac condition, renal function and overall clinical assessment permitting, an additional 0.5-1 L of saline is administered to the patient for the next 3 hours starting at the end of the Lutathera® infusion using the same intravenous line.

Blood pressure, heart rate and oxygen saturation are monitored every thirty minutes for the first two hours then every hour for the rest of the procedure. We administer additional anti-emetics in case of severe nausea or vomiting during the amino acid solution infusion.

Five to six hours after the start of the protocol, the patient is fully assessed by our nuclear medicine physician and nurse. If indicated a 30 mg of Sandostatin LAR is administered in the muscle of the arm or buttock. Radiation safety instructions are reemphasized and

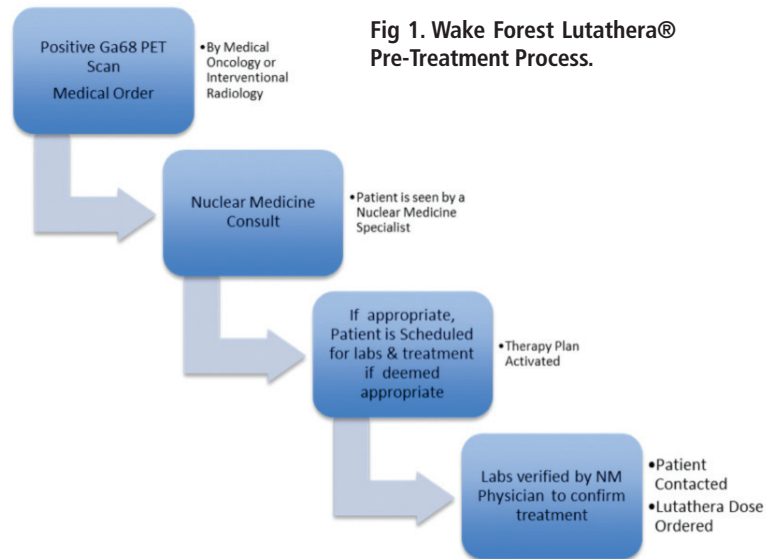


Fig 1. Wake Forest Lutathera® Pre-Treatment Process.

home medications (if needed) are prescribed. The patient is given an appointment for a follow up consult and lab tests 4 weeks later for reassessment.

TREATMENT REGIMEN:

The treatment regimen in adults consists of 4 administrations of Lutathera® (7.4 GBq / 200 mCi +/- 10% at the date and time of infusion). The interval between each infusion is 8 weeks (\pm 1 week), that can be extended in case of toxicity. ■

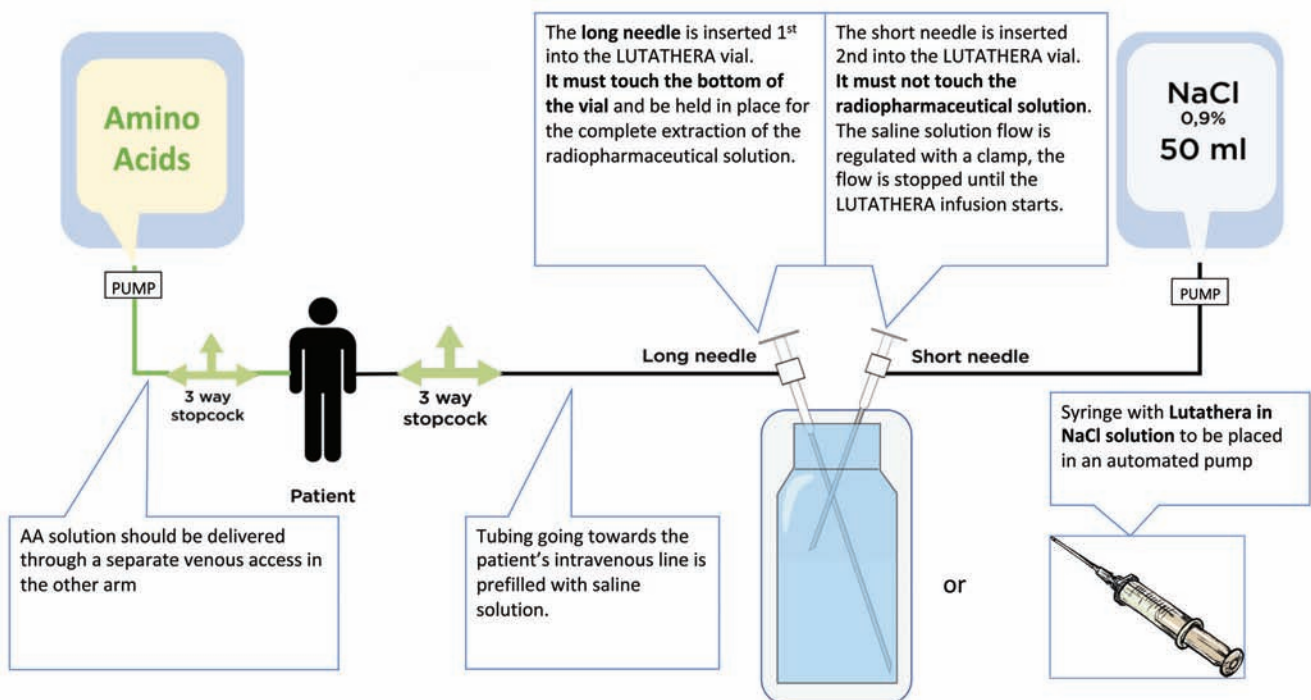


Fig. 2 Lutathera® administration using the gravity method (modified from the AAA, Inc - Lutathera® brochure)

Stephan Probst, MD

*Chief of Nuclear Medicine
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PSMA DIAGNOSTICS AND THERAPEUTICS 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. For reasons only partly understood, positron emission tomography (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. Prostate specific membrane antigen (PSMA) PET is finally unlocking the potential of PET for prostate cancer patients.

PSMA is an enzyme and cell surface protein of the prostate which is highly upregulated in prostate cancer. Early antibody-based attempts to target PSMA such as ProstaScint® suffered from many drawbacks such as low count rates due to ^{111}In labelling, pairing with less precise SPECT imaging, slow blood clearance and very poor target-to-background ratios – needless to say this radiopharmaceutical was a clinical failure.

Novel urea-based small molecule PSMA PET ligands such as ^{68}Ga -PSMA and ^{18}F -DCFPyL do

not suffer from these drawbacks and the clinical significance of these discoveries soon became apparent. For the major prostate cancer body imaging indications, namely staging of high risk disease and restaging of post-treatment biochemical failure, 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.

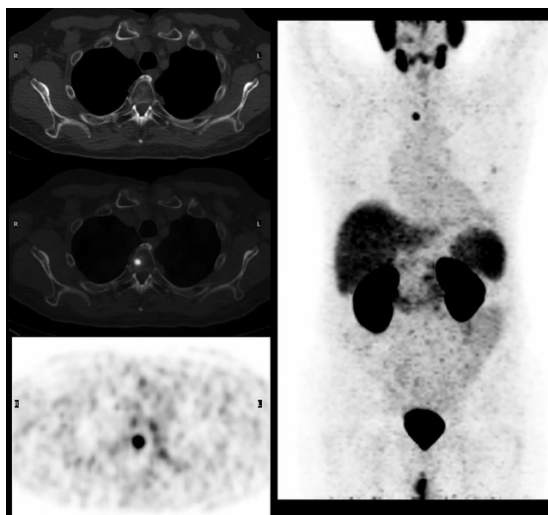
PSMA PET FOR STAGING OF HIGH RISK PROSTATE CANCER

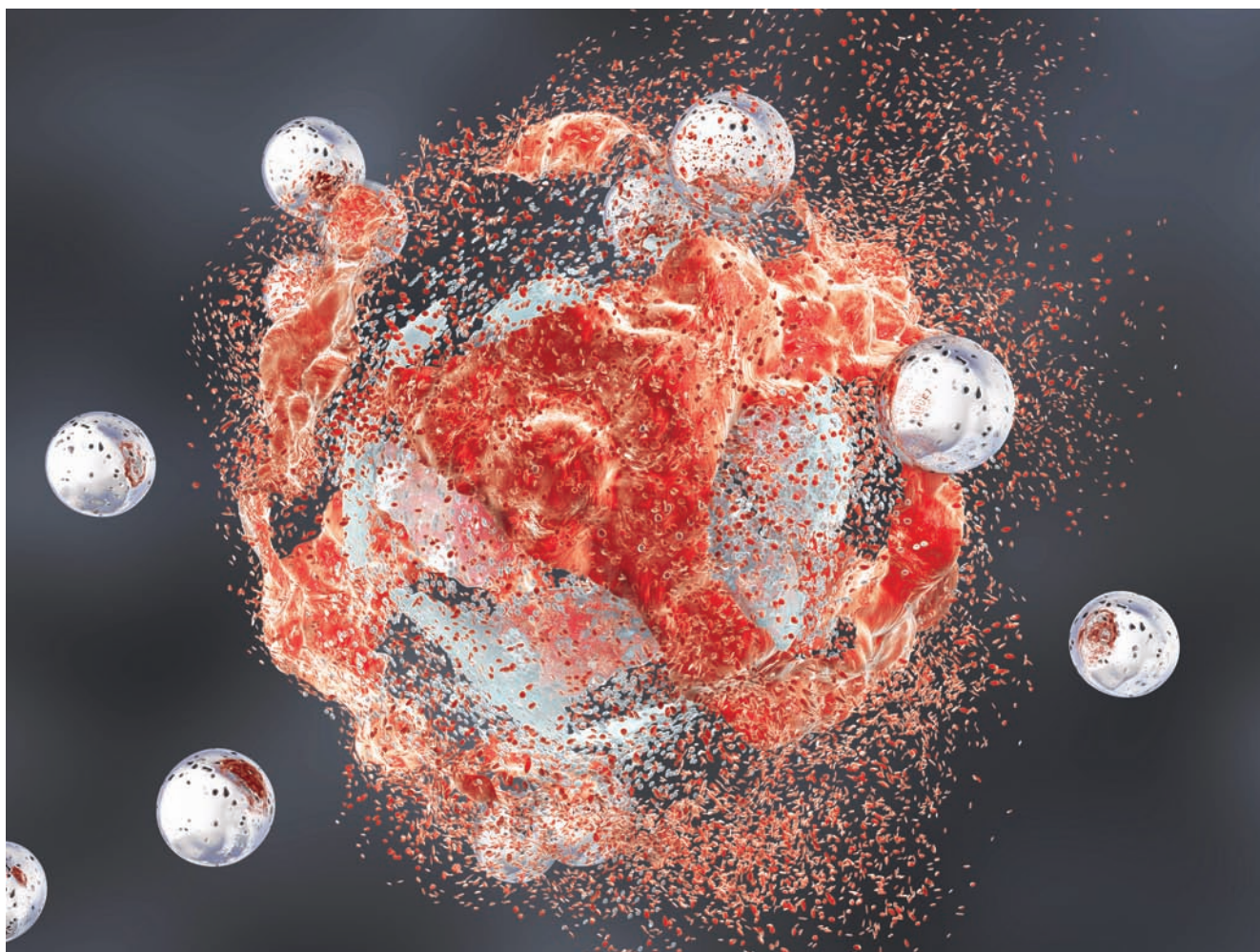
In the setting of high risk prostate cancer (such as those with high Gleason scores, high PSA or advanced clinical T stages), up to 10–20% have extra-prostatic disease not detected by conventional imaging. In patients with nodal disease amenable to surgical excision or pelvic radiation, this allows physicians to adapt and personalize therapy. Patients with distant metastases at diagnosis are offered systemic therapy and spared invasive surgery or the side effects of radiation which would not be beneficial to their disease.

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 within 10 years; there is currently no consensus regarding optimal management of this disease state. 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 THERANOSTICS FOR METASTATIC PROSTATE CANCER

Theranostics (a portmanteau of therapeutics and diagnostics) is a new field of medicine which combines targeted therapy based on similarly-targeted diagnostic tests. In addition to the progress made with the PSMA PET agents described above, targeted radionuclide therapy for men with metastatic prostate cancer is another highly promising development in the prostate cancer landscape. This targeted therapy for prostate cancer uses injectable Lutetium-177 (^{177}Lu) labelled PSMA peptides which seek and destroy prostate cancer cells with radiation, wherever they are in the body. Early human studies evaluating the safety and efficacy of ^{177}Lu -PSMA therapy have demonstrated promising results with a significant proportion of men with metastatic prostate cancer, who have already failed other therapies, responding clinically to ^{177}Lu -PSMA.

PSMA CANADIAN LANDSCAPE

Despite very promising results, none of the above molecules are currently Health Canada approved, however the PET agents are available under research protocol at a few select Canadian centers. A large Canadian phase-III trial of ^{68}Ga -PSMA PET was approved to begin by Health Canada in May 2017 and could lead to approval of the molecule, much to the benefit of patients. The phase-III ^{18}F -DCFPyL trial is also well underway at two Canadian sites, namely the Jewish General Hospital in Montreal and the Centre Hospitalier Universitaire de Quebec (CHUQ) in Quebec City. No ^{177}Lu -PSMA therapy trials are currently in active enrollment in Canada as of this writing, but this may change in 2018.

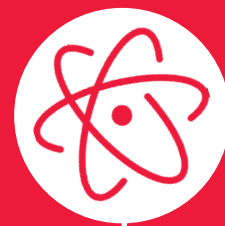
CONCLUSION

The discovery of PSMA PET and PSMA therapy 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. Although much work remains to be done to bring these discoveries to Canadian prostate cancer patients, the future is promising. ■



Interview with: Dr. Lizette Louw

*Specialist Nuclear Physician
WITS University & CH Baragwanath Academic Hospital
Donald Gordon Medical Center
SASNM: Immediate Past President
ANP: President*



You have been practicing Nuclear Medicine for a few years and you are now in your second year of your Presidency of the South African Society of Nuclear Medicine. How do you see the field of Nuclear Medicine evolving over the next 5 years across the world?

Nuclear Medicine continues to grow and is slowly but surely becoming “standard of care”. Theranostics is an exciting and very important area of growth for us. I foresee further expansion in this field over the next few years. PET/CT is already well established, but new tracers will be added to the armamentarium we have available for this unique modality, which in turn will lead to further expansion in the range of conditions PET/CT is useful for.

Although Nuclear Medicine is an established service in many parts of the world, there are still many countries with no, or only limited Nuclear Medicine services. I would love to see Nuclear Medicine services become not only established in every country, but also easily accessible and affordable to all patients. Further developments should take place for Technetium based tracers in order to provide a quality service in areas where PET/CT is not available or not affordable.

We should however never forget our roots. Even when we grow, we should continue to nurture the simple and valuable Nuclear Medicine investigations such as bone scan for non-oncologic indications.

You are very familiar with the strengths and needs of the South African Health Care Health Care system. Can you give us an idea of the assets and challenges of the practice of NM in South Africa.

In the private sector Nuclear Medicine is readily available in the urban areas, where it has become almost saturated. In the rural areas there are fewer patients who can afford private health care. These patients have to then travel long distances for investigations. The rural practices are also hit harder whenever there is an isotope shortage such as we recently experienced when NTP was on shutdown for several months. In the urban areas the practices can order daily bulk eluate from the commercial radiopharmacies to be delivered to them, but the rural practices rely solely on the use of their own Technetium generator.

Despite the widespread acceptance of PET/CT by medical funders, there are still entire provinces in South Africa without even a single PET/CT camera! At present

PET/CT is available in only 5 of our 9 provinces, for both the private and public health sector.

We have a big discrepancy between high and low income groups, with a very large portion of our population either in the low income group or unemployed and therefore cannot afford private healthcare. These patients make use of the public healthcare system, which is underfunded and poorly administrated. Within the academic centres all the newest Nuclear Medicine services are available, such as PET/CT with F-18 FDG, Ga-68 DOTATATE or Ga-68 PSMA, as well as the general Nuclear Medicine investigations and therapy with radioactive iodine or MIBG. However, in the non-academic public health centres Nuclear Medicine services are more scanty, or not available at all.

Despite these challenges, the Nuclear Medicine community in South Africa is very close knit! Our conferences have a family-get-together feel and our visitors often comment on the warmth between us. The academic centres continue to deliver high quality research with international publications and conference presentations being a common occurrence. We actively participate and are well represented on the International platforms such as IAEA, WARMTH, NMGI, WFNMB etc. In true South African style, we have a resilient and innovative spirit; no matter what challenges we encounter, we will succeed.

You have had the opportunity to read the first two issues of the NM magazine Pangea-ePatient. What do you think of the magazine and what would your suggestions be to improve it?

I loved the magazine from day 1! I’m confident that it will continue to grow and gain popularity across the globe.

Where will the 2019 SASNM meeting be held?

SASNM (South African Society of Nuclear Medicine) have a meeting every alternate year. We just had a meeting in early August 2018 in Pretoria, the administrative capital of South Africa. The next meeting will be in 2021 in the beautiful city of Cape Town, the legislative capital of South Africa. Personally I hope it will be held on a wine farm! ■





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MOLECULAR IMAGING AND THERAPY FOR PROSTATE CANCER

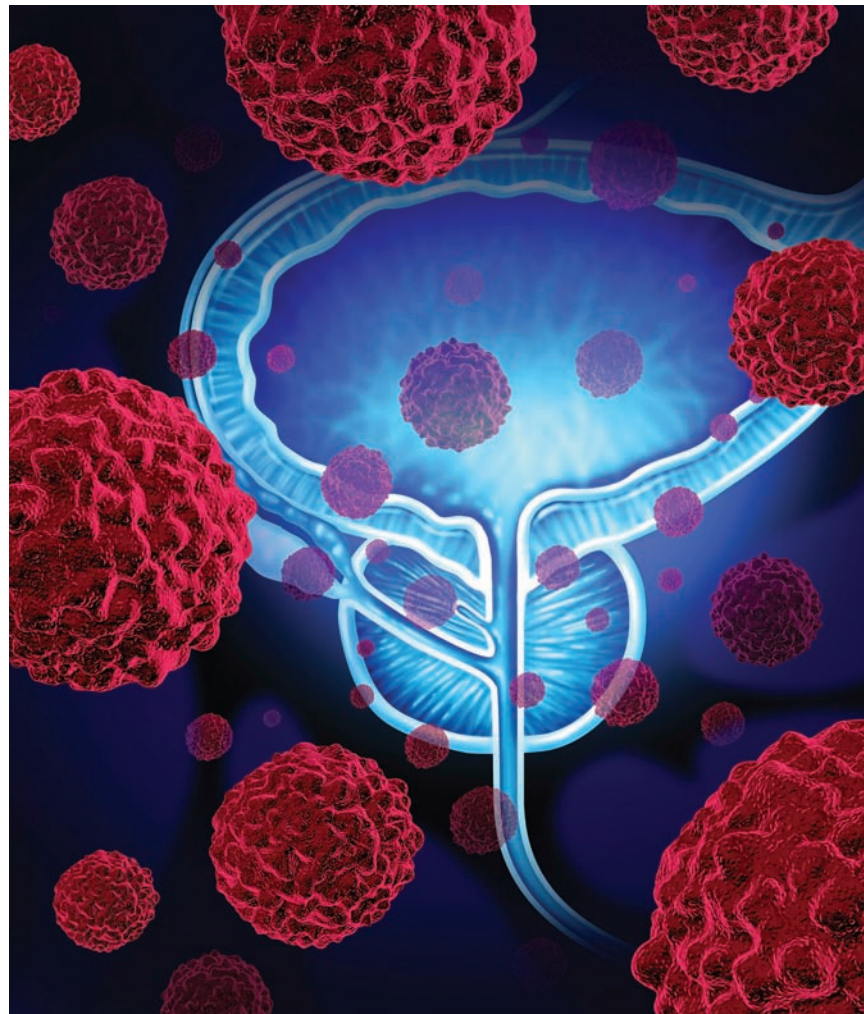
INTRODUCTION

The promise of molecular medicine is rapidly bearing fruit and nowhere is this more apparent than in the prostate cancer diagnostic and therapeutic landscape. Several molecular imaging and therapeutic innovations have made their way from the lab to the clinic in the past few years. Two molecular medicine standouts are PSMA PET/CT imaging and radium-223 therapy, although the former is not yet Health Canada approved. Given that prostate cancer is the most prevalent form of cancer in men and second most common cause of cancer death in North America, these technologies will likely play an outsized role in health care delivery in the decades to come.

PMSA PET/CT

In general, diagnostic imaging can address two matters, structure and function. Anatomy can be studied using structural imaging modalities such as plain film radiography (X-ray) or computed tomography (CT), or molecular processes, physiology and function can be imaged with radiopharmaceuticals in single-photon nuclear medicine imaging and positron emission tomography (PET). The strength of the molecular imaging methods is that they are more sensitive and these changes precede anatomic changes in the course of the disease. Positron emission tomography / computed tomography (PET/CT) is a nuclear medicine procedure based on the measurement of positron emission from radiolabeled tracer molecules with correlative CT imaging. This technology allows in vivo molecular processes to be mapped and measured on whole body images.

Prostate specific membrane antigen (PSMA) is an enzyme and cell surface protein. Human PSMA expression is highest in the prostate, roughly a hundred times greater than in most other tissues and is highly upregulated in prostate cancer. PSMA has long been identified as an imaging target, but the first antibody-based attempt, capromab pendetide (ProstaScint®) suffered from many drawbacks namely targeting the



intracellular domain of PSMA, low count rates due to ^{111}In labelling, very slow blood clearance and overall very poor target-to-background ratios – needless to say, it was never widely adopted. The next generation urea-based small molecule PSMA ligands such as ^{68}Ga -PSMA did not suffer from these drawbacks and the clinical value soon became apparent. For the major prostate cancer body imaging indications, namely high risk staging and post-treatment biochemical failure, ^{68}Ga -PSMA PET easily exceeds the sensitivity, specificity and accuracy of conventional imaging modalities such as CT +

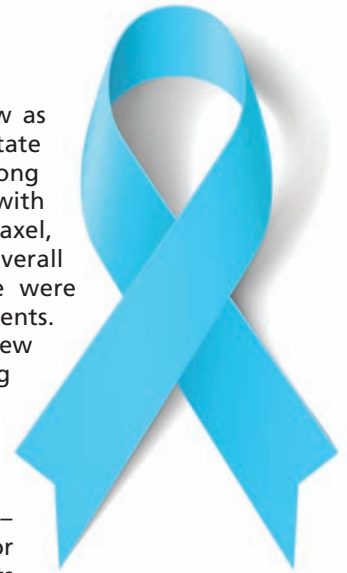
bone scan and even outperforms the prior gold-standard ^{18}F -fluorocholine PET/CT. The advantage of PSMA PET is especially evident in patients with ultra-low PSA levels; detection rates of almost 60% have been reported in biochemical recurrence after radical prostatectomy in a PSA-range 0.2–0.5 ng/ml. In such early stages of recurrence, curative-intent salvage procedures (e.g. secondary lymphadenectomy, targeted radiation therapy) become possible.

On the horizon, third generation small molecule PSMA PET ligands labelled with ^{18}F , such as ^{18}F -DCFPyL, are in phase 3 trials now. These seem to maintain all of the advantages of ^{68}Ga -PSMA PET and additionally benefit from a longer 110 minute half-life and better scalability stemming from cyclotron production. FDG never gained widespread adoption in prostate cancer imaging due to poor sensitivity for low-grade and well differentiated cancers, but PSMA PET has been opening up the world of advanced PET imaging to prostate cancer patients. These imaging tools and upcoming PSMA-based therapeutics, which utilize the same urea-based molecules complexed to the beta-emitter ^{177}Lu , offer great promise to prostate cancer patients.

RADIUM-223

First line therapies for metastatic prostate cancer often involve androgen ablation, also known as castration. While castration is initially highly effective at controlling the disease, almost all cancers eventually become resistant to treatment

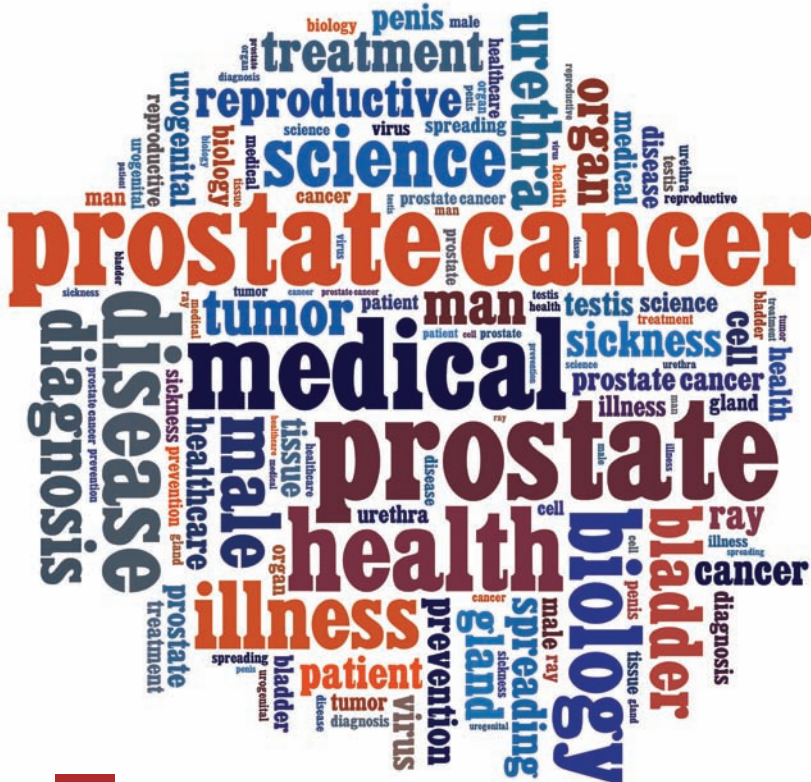
and enter a phase known as castration-resistant prostate cancer (CRPC). For a long period ending in 2004 with the approval of docetaxel, treatments with overall survival (OS) advantage were elusive for CRPC patients. Recently, two new androgen-signaling pathway inhibitors, abiraterone and enzalutamide, were approved based on similar OS advantage – however the prognosis for metastatic CRPC patients remains guarded at best.



CRPC metastases have a very strong predilection for bone with up to 90% of patients developing osseous lesions. These osseous metastases – and ensuing so-called skeletal related events – confer an increased risk of death, a lower quality of life, high healthcare utilization and increased morbidity. Skeletal related events (SRE) fall into four categories, namely: Use of external beam radiation to relieve bone pain in a palliative setting, tumor-related pathological fracture, tumor-related spinal cord compression and tumor-related orthopedic surgical intervention.

While many other solid tumors kill via soft-tissue metastases, deaths from prostate cancer are often due to bone disease and its complications. Given that bone disease and SREs are strong drivers of morbidity, mortality and healthcare costs in CRPC, there is considerable interest in new therapeutic options for this group of patients. Prior bone-targeted therapies such as bisphosphonates, denosumab, and beta-emitting radioisotope treatments all failed to show OS advantage, although some did offer moderate pain palliation.

In 2014 radium-223 (Xofigo®), was approved by Health Canada based on the large phase 3 ALSYMCA trial which showed OS benefit, clinically significant reduction in bone pain and a delay in time to first SRE. Radium-223, administered IV as the dichloride salt RaCl_2 , is a bone-seeking, alpha-emitting radiopharmaceutical which selectively targets bone metastases. As a calcium mimetic, it is incorporated into the bone matrix by osteoblastic activity and delivers high doses of alpha radiation. Given the very short path-length of alpha particles in vivo, the adjacent bone marrow is largely spared, yielding a superior toxicity profile as compared with the previous generation of therapeutic bone-seeking radiopharmaceuticals labelled with the beta emitters strontium-89 and samarium-153.

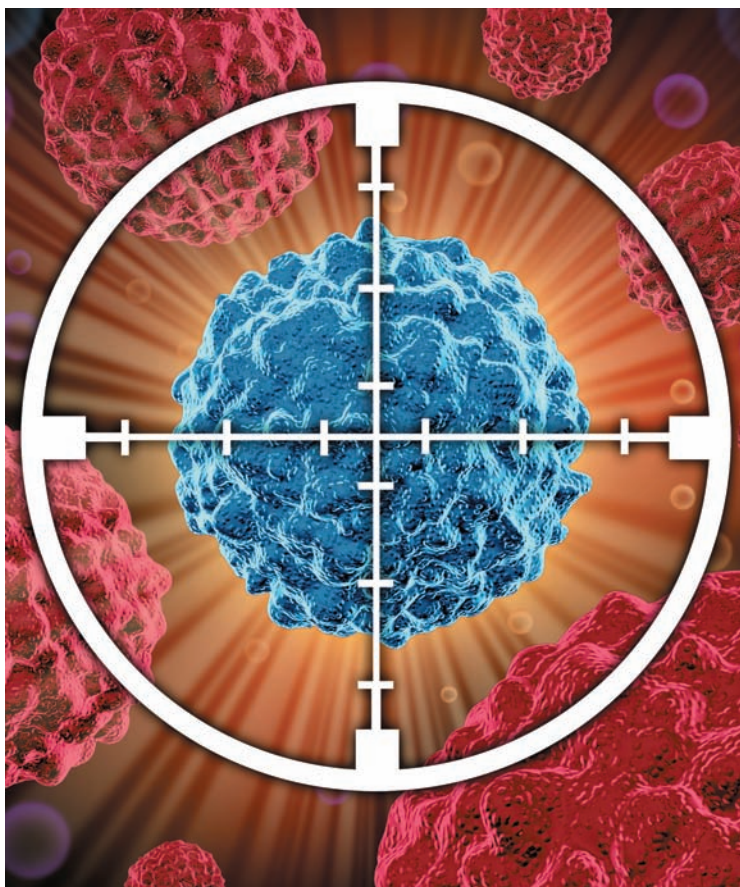


Radium-223 is thought to exert a direct anti-tumor effect, although in many cases this is not reflected by any significant serum PSA decline, unlike many other anti-neoplastic prostate cancer treatments.

Administered in Nuclear Medicine departments on a monthly basis over 6 months, the treatment is simple, extremely well tolerated and it is safe for the patients to go home to their families immediately following the short IV infusion. A majority of patients have no treatment-related side effects whatsoever. Unlike systemic cytotoxic chemotherapy regimens, where patients often need to decide between quality of life and quantity of life, with radium-223 no such trade-off exists. Quality of life scores are improved with significant reductions in bone pain and a delay in time to first SRE. Radium-223 will remain an important therapeutic tool in the management of CRPC patients with bone metastases.

CONCLUSION

The age of molecular medicine is upon us, and nuclear medicine physicians, urologists, medical oncologists have a lot of new tools at their disposal. From cutting edge diagnostic modalities like PSMA PET and life-extending therapies like radium-223, prostate cancer patients have never had better care than today. ■



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Kalevi Kairemo

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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. ¹⁷⁷Lu-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 metastatic disease during the first visit, and one patient where it was used as first-line treatment. All these patients demonstrated a major response with ¹⁷⁷Lu-PSMA radioligand therapy, i.e. complete response by imaging and substantial reduction of PSA. ¹⁷⁷Lu-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 lumbosacral 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



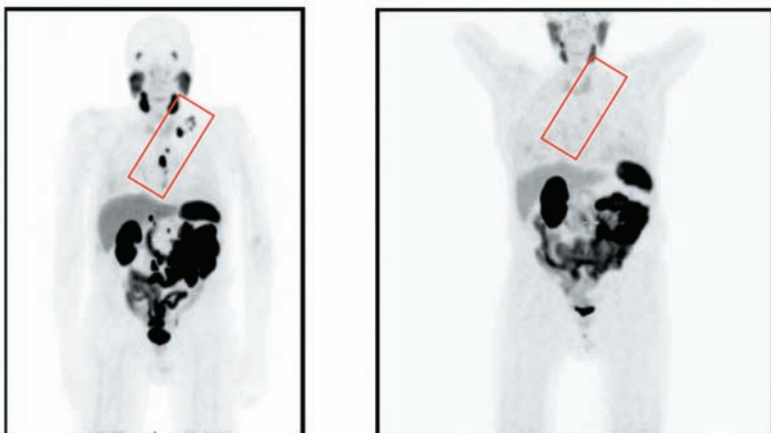
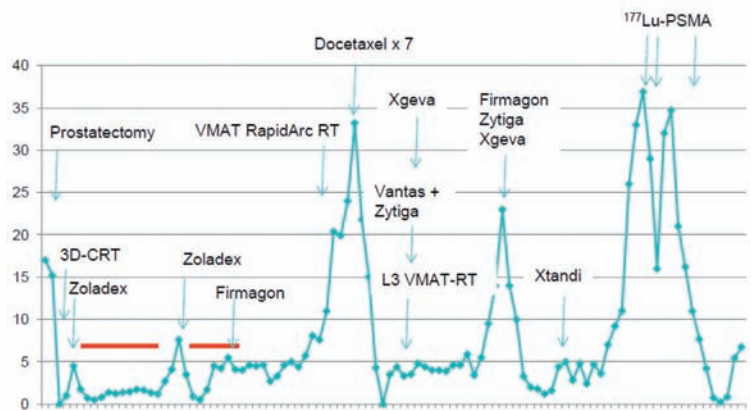
to be stopped in one month due to epileptic seizure. Six months later, dexamethasone combined with cyclophosphamide started to improve immunogenic response, but it had to be stopped due to the diarrhea, swelling and infection. Abiraterone started again, but four months later PSA was 33 ng/ml. On the 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 cm³.

¹⁷⁷Lu-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 ⁶⁸Ga-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, pollakisuria 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 demonstrated 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 ¹⁷⁷Lutetium-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.

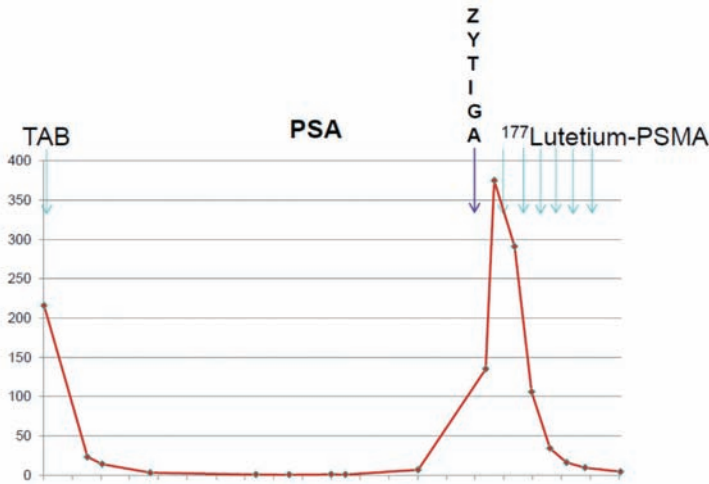
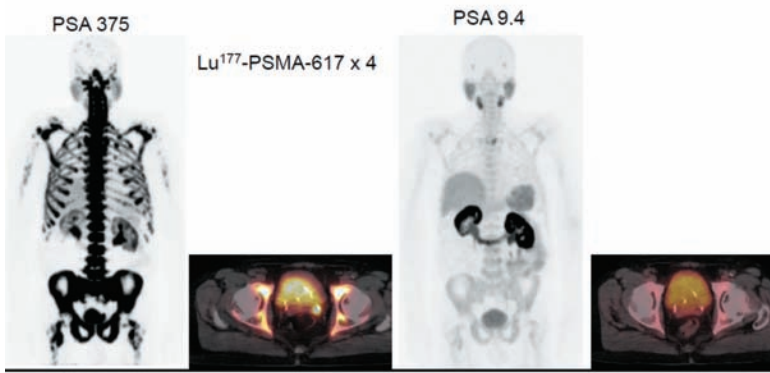
¹⁷⁷Lu-PSMA therapy started in May 2017. It caused tiredness and he had also swelling in feet and ankles, but surgical stockings helped that. The patient had also severe depression and anguish.



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

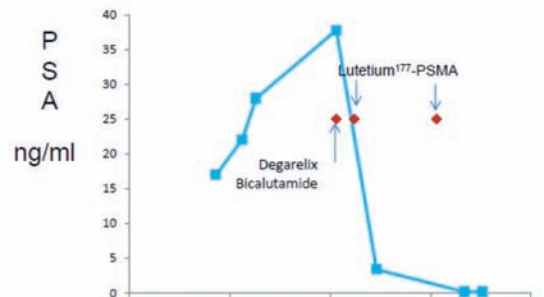
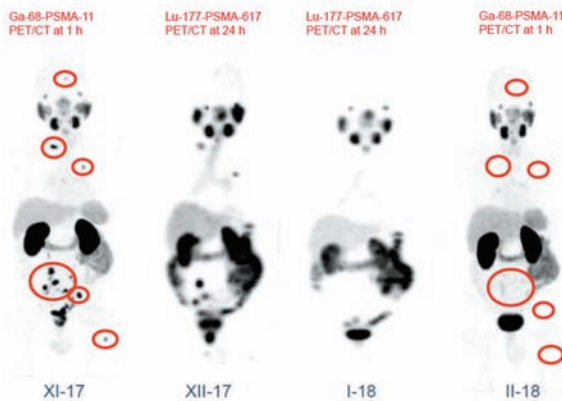


only one subtle uptake on the left in Th3 which could be seen as in Fig.2, but the activity could already be considered normal, because the SUVmax value was only 3.8. This was considered as a dramatic response. PSA decreased from 375 ng/ml down to 4.2 ng/ml during the follow-up ¹⁷⁷Lu-PSMA therapy. This 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 ⁶⁸Ga-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 ⁶⁸Ga-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 cm³ 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 cm³), 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 Lutetium¹⁷⁷-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 ⁶⁸Ga-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 cm³ + lymph nodes 75 cm³) demonstrated a visual metabolic complete response. Quantitative "PERCIST"-response turned out to be -93%. ■





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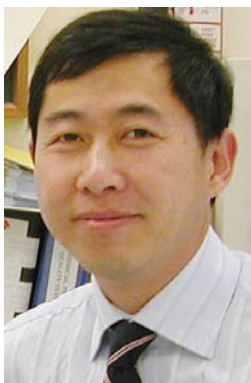
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Interview with: Dr. Sijin Li, President of the Chinese Society of Nuclear Medicine



China is the most populated country on Earth. For most of us, it is difficult to imagine how the Chinese population can access the nuclear medicine services that the Chinese patients need. Can you give our readers a synopsis of the status of nuclear medicine services across China and the role that the Chinese Society of Nuclear Medicine plays to promote nuclear medicine in China?

Nuclear medicine started in China in the 1950s. After 60 years of development, nuclear medicine has become an important part of medicine and an independent department in most hospitals in China. In the last decade, departments of nuclear medicine were established in most municipal hospitals. Even some developed-county level hospitals can provide nuclear medicine services nowadays. The services provided by nuclear medicine include in vivo imaging (PET/CT, PET/MRI, SPECT/CT, and SPECT), radionuclide therapy (out-patient and in-patient services) and in vitro analysis. According to the national survey of nuclear medicine in 2016, there are 891 departments of nuclear medicine, 246 PET/CT scanners, 6 PET/MR scanners, 774 SPECT/CT (or SPECT) scanners, and 101 cyclotrons, 1832 beds for radionuclide therapy. In 2016, about 500,000 PET/CT studies were performed (86.9% on oncology, 0.8% on cardiac and 2.7% neurology, respectively). About 2.1 million SPECT and SPECT/CT studies were performed (top 5 of SPECT/CT or SPECT studies were bone imaging, thyroid imaging, renal function imaging, cardiac imaging and I-131 imaging, respectively). Approximately 0.6 million cases of radionuclide therapy were performed (including 0.17 million cases of hyperthyroidism, 0.15 million cases of applicator therapy, and 60,000 cases of DTC).

Chinese Society of Nuclear Medicine (CSNM) was established in the 1980s. The regular term of service is 3 years. It is now the 11th committee, and there are 11 study groups under the branch of Nuclear Medicine. They are oncology group, PET group, cardiology group, neurology group, radiopharmacology group, science and education group, foreign exchange group, functional imaging group, treatment group, and so on. CSNM devotes itself to many

different fields, including popularization, technology promotion and academic communication of nuclear medicine; constituting guidelines and standardizing clinical use of nuclear medicine; serving as counsellors for the government administrations on policies and regulations related to nuclear medicine; proposing advices to the related government administrations about how to develop nuclear medicine. Due to the great efforts of CSNM, the related Chinese government administrations have paid more and more attentions to nuclear medicine, and formulated a series of policies to guarantee the healthy development of nuclear medicine. CSNM holds annual meetings every year. In the 2017 annual meeting, there were over 1500 participants. Each study group also organizes academic activities on an annual basis. In addition, nuclear medicine branches of provincial medical association have been set up and a variety of academic activities were organized annually. In recent years, in response



to the government's new health care reform to build a new type of medical system with "serious illness should be treated within the county", CSNM proposed the development strategy of "one nuclear medicine department for one county" and established new nuclear medicine department in county-level hospitals in many provinces in China. The establishment of nuclear medicine departments in county-level hospital will usher in a new and rapid development opportunity for nuclear medicine in China.

You are very familiar with the strengths and needs of the Chinese Health Care system. Can you give us an idea of the assets and challenges of the practice of NM in China?

China is a big country with over 1.3 billion population. Dealing with health and medical care problems is really a huge project. Chinese government has worked out policies and provided financial supports to guarantee that every citizen, no matter urban or country inhabitants, be covered by medical insurance. However, due to the huge population, the level of current medical insurance service is basic. SPECT and SPECT/CT studies, which are reimbursed by medical insurance, play a very important role in diagnosis and prognosis of various diseases, especially on tumor and cardiac diseases, evaluation of therapeutic effects, and guiding individual strategy of therapy. In addition, both hyperthyroidism and thyroid cancer treated by ^{131}I therapy are also reimbursed by medical insurance. However, in

most provinces and cities, PET/CT studies haven't been reimbursed by medical insurances. Besides insurance problems, there are several other difficult problems and challenges we have to face. For example, ^{99}Mo - $^{99\text{m}}\text{Tc}$ generators are, at times, in short supply. Furthermore, some important imaging agents, such as ^{123}I -MIBG, cannot be regularly obtained in China. Besides that, the shortage of professionals is one of the big challenges to the development of nuclear medicine in China in the future.

China is the fastest growing nuclear medicine community in the world. How can the world nuclear medicine community contribute to the success of your and the Chinese Society of Nuclear Medicine endeavors?

CSNM always devotes itself to communicating with the world nuclear medicine community since it was established. During the recent years, many staff members attended SNMMI and EANM to present their works and the progresses of nuclear medicine in China. Many young students studied abroad and came back to China. Meanwhile, many experts worldwide also have made great contributions to the development of nuclear medicine in China via multiple ways, for example, by introducing their latest developments in nuclear medicine in China and by collaborating with Chinese nuclear medicine centers. Finally, we hope that the world nuclear medicine community could offer more learning opportunities for Chinese professionals of nuclear medicine and help CSNM to develop and promote the development of nuclear medicine technology for medical services, especially in oncology, cardiology and neurology in China.

You have had the opportunity to read the first issue of the NM magazine Pangea-ePatient. What do you think of the magazine and what would your suggestions be to improve it?

The Pangea-ePatient magazine is not confined to the traditional approach of nuclear medicine journals. It explores a new educational and practical tool adapted to the current educational needs. It is a rewarding magazine which provides people from different disciplines rich information. After reading the first issue of the Nuclear Medicine magazine Pangea-ePatient, I like this journal very much. In the first issue, many different perspectives are presented, including code of operation, education and training, scientific research progress and the development of nuclear medicine. Additionally, this magazine uses a variety of languages, which is really unique! However, considering the journal's international purpose, we believe English may be the best choice as it is the official language. Thank you very much. ■





Mikael Strindlund
President and CEO of
Hermes Medical Solutions



Interview with Mikael Strindlund

You have been actively involved in medical imaging quite a while. Looking back at your career what are the most significant changes that you have witnessed in the field of medical imaging?

I have now been working in the medical device and medical IT space for some 25 years. Interesting enough, I would say that over the past 5 years there has been a significant change in the healthcare world. Much more focus is now on the patient, a drive towards personal well-care instead of healthcare.

We see a clear shift towards patient centric solutions. At the same time, there is considerable pressure to optimize the allocation of resources in order to provide the most benefit for the patient. There is a lot of pressure coming from reimbursement entities (both public and private) forcing healthcare providers benchmarking and quantifying patient outcome.

We are today looking at the entire diagnosis and the treatment pathway for the patient AND it's all about "First Time Right" – both how we diagnose and treat the patient but also a First Time Right for the healthcare providers. No-one of us wants to be a trial – we dare to question the opinion of the physician, we want references, 2nd and 3rd opinions, we want the best care ever. In addition, we request individualized and personalized healthcare - nothing more and nothing less.

For the healthcare provider, another challenge is to provide the best and personalized care at reasonable cost structure. The healthcare providers - on the other side – try to drive healthcare towards standardization and industrialized care.

Hermes used to be a family owned company. 2 years ago, it became a corporate entity and you are now its CEO. What are the vision and mission of the new corporation for Hermes Medical and how will it affect its relationship with present and future customers?

Hermes is pursuing innovation initially started for more than 40 years ago. We are privileged working with the best institutions across the world, supporting research and partners developing cutting edge technologies.

We continue to strengthen and deepen the very close relationships we have with our customers. The strength of Hermes is to have the close and quick turnaround time of workflow and process improvements our customers suggest in cooperation with us.



We strive to continue to be the leading provider of end to end enterprise solutions within the field of nuclear medicine. We are vendor agnostic and offer best in suite regarding integrated informatics solutions to enable clinical excellence and business intelligence – improving diagnostic and treatment pathways, resulting in significant enhanced clinical, operational and financial outcomes. In the last two years, we have made significant investments to consolidate and strengthen our position in the market. This includes our R&D activities as well as our sales and service support organizations.

The vendor neutral solutions Hermes offers, are truly in line with the ongoing consolidation of healthcare providers to larger enterprises. We see this trend all over the world. Integration and connectivity are becoming more and more important every day. By simplifying and standardizing workflow, the clinical outcome is significantly improved at much less costs. It also allows for a higher grade of flexibility among the staff, across different sites in remote reading as well reduces the need for education and human errors. Intuitive and adaptive user interfaces and the access to relevant patient data are key items for a patient centric and cost effective health care.

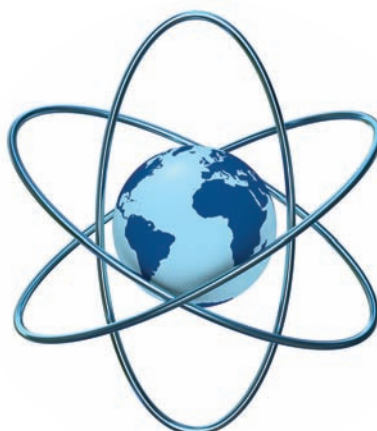
What do you anticipate the role of artificial intelligence (AI) be in the field of nuclear medicine?

Artificial Intelligence is a big topic momentarily. It's extremely important to understand that AI is an umbrella of different categories and approaches like machine learning, deep learning, supervised learning, neural networks, etc. Thinking that Artificial Intelligence will replace the clinician's diagnostic is a mistake. However, aggregating different source of information and helping the clinician in his decision-making process is where AI will definitely play a role. AI-based measurements and quantifications are tools we will see in near future. We at Hermes are working in different fields of active decision support tools. All with the aim to significantly improve efficiency as the healthcare providers are under pressure to deliver high-quality services and care. A new challenge the industry today is facing is availability of patient data for software development and the complex ongoing challenges surrounding data protection as a hurdle for the access to health and patient data.

You have had the opportunity to read the first two issues of the NM magazine Pangea-ePatient. What do you think of the magazine and what would your suggestions be to improve it?



I like the magazine a lot. I think it's essential to communicate the benefits and latest updates in Molecular Imaging to referring doctors and patients. Maintaining communication channels open worldwide is the only way forward if we want to expand clinical applications of Molecular Imaging. A nice add-on would be to present clinical cases that are both challenging for the referring doctor and nuclear medicine physicians. All with the focus on patient's WellCare and the best clinical outcome. ■





Dr. Florent Cachin
Professeur de biophysique
Médecine Nucléaire à l'Université Clermont
Auvergne



Entrevue avec : Dr. Florent Cachin

La Société Française de Médecine Nucléaire (SFMN) conduit tous les ans une enquête recensant matériels et ressources humaines. Coordonnée par le Pr Olivier Couturier et avec une exhaustivité supérieure à 95% elle permet d'avoir une vision relativement fine des forces en présence sur les territoires français. Ses résultats sont publiés sur le site de la SFMN (www.sfmn.org).

En résumé, 1 516 978 actes de médecines nucléaires ont été réalisés en 2017 dont 1 077 114 TEPs. Environ 95% des examens TEP sont réalisés après injection de 18F-FDG. Scintigraphies osseuses et cardiaques se partagent 70% de l'activité TEMP.

Côté équipement, 136 TEP dont 3 TEP/IRM sont présents sur le territoire correspondant à une machine pour 500 000 habitants. 434 caméras TEMP sont disponibles soit 6,5 caméras par millions d'habitants.

Coté acteurs et structures de soins, 749 praticiens de médecines nucléaires (internes inclus) officient dans 217 centres. Un peu plus de trente internes par an choisissent la spécialité de médecine nucléaire. Leur durée de formation est de quatre ans. 54% des structures disposant d'un service de médecine nucléaire sont des structures publiques. Elles sont alors toujours associée à une radiopharmacie ce qui très rarement le cas pour les services privés. Rapportés au nombre de millions d'habitants, structures, équipements et ressources humaines sont dans la moyenne haute des pays européens.

Quels sont les principaux défis de la médecine nucléaire dans l'immédiat et dans le futur en France?

Au cours de mes 25 années d'expérience en médecine nucléaire, j'ai cru pouvoir noter, sans angélisme ou idéalisme inconsidéré, une augmentation notable de l'aura de notre spécialité. Cela s'explique par le fait que nos examens sont devenus décisionnels lors de la prise en charge de nos patients. Cela est particulièrement vrai en oncologie et cardiologie où les traitements sont très souvent modifiés ou réadaptés suite à la réalisation des examens de médecine nucléaire. Ce dynamisme doit se poursuivre. Parmi les nombreux défis à relever, certains me paraissent important à rappeler :

Qui suis-je ?

Nommé Professeur des Universités, praticien hospitalier en Biophysique – Médecine Nucléaire en 2013, j'assume actuellement la direction universitaire du département d'imagerie et du service de médecine nucléaire du Centre de lutte contre le Cancer Jean Perrin, dirigé par Le Pr le Pr Penault-Llorca à Clermont Ferrand. J'assume aussi la direction scientifique de notre établissement depuis 2013.

En recherche, je coordonne l'équipe 2 de l'UMR INSERM 1204 « Imagerie moléculaire et stratégie théranostique » dirigée par le Dr E Miot-Noirault. Cette unité développe conjointement les biomarqueurs tissulaires et des radiopharmaceutiques, entre autres dans le cancer du sein et le mélanome préfigurant à mon sens le devenir de l'oncologie nucléaire. Mes sujets d'intérêt sont principalement le développement de radiopharmaceutiques en thérapie et diagnostic

J'assume avec grand plaisir la présidence de notre société depuis mai 2017 ; entouré d'un bureau et d'un conseil d'administration que je remercie ici très chaleureusement

Pourriez-vous nous décrire la situation actuelle de la médecine nucléaire en France

- Spécialité clinique
- Nombre de centres
- Nombre de spécialistes
- Nombre de résidents en formation
- Nombre d'unités TEP.
- Ect.

- rester innovant avec mutualisation de toutes les forces académiques et industrielles pour favoriser le développement des nouveaux traceurs. La réglementation devra cependant être adaptée, sans doute plus assouplie, avec aussi bien sûr pour objectifs la qualité et la sécurité. La médecine nucléaire reste avant tout une discipline médicale étudiant la biologie de processus physiopathologique à l'aide de radiopharmaceutiques innovants.

- savoir prendre le virage de la radiothérapie interne vectorisée. Cela nécessitera de faire évoluer probablement nos structures pour répondre à une forte demande, mais aussi à adapter la formation initiale des praticiens pour assumer la gestion complète de tels traitements. Je suis d'avis que le médecin nucléaire doit bien sûr réaliser la thérapie mais également en assumer les effets secondaires et probablement savoir à terme conduire des associations avec des chimiothérapies simples. À terme, il faut s'attendre à un changement important du périmètre de notre spécialité.

- attirer les étudiants en médecine: Je souhaite souligner ici l'importance des enseignements de biophysique et médecine nucléaire dispensés par les confrères aux étudiants en médecine. C'est en effet pendant ces années de formation, que l'enseignant par la qualité de ses cours pourra "éveiller" l'étudiant à la médecine nucléaire et ainsi à terme dynamiser la spécialité. Le dynamisme d'une spécialité se juge par aussi son attractivité auprès des jeunes

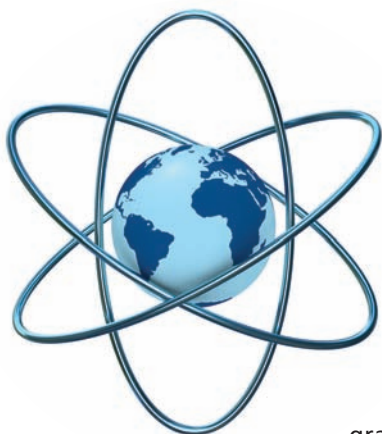
Qu'elle est et sera la contribution de la médecine nucléaire dans le développement de la théranostique et de la médecine personnalisée?

Médecine personnalisée et/ou de précision, stratégies théranostiques sont les nouveaux concepts originaux proposés et discutés dans tous les congrès scientifiques depuis maintenant une quinzaine d'années. L'objectif de telles stratégies est une stratification optimale des patients grâce à l'identification de cibles biologiques pertinentes.

Ces méthodes assurent une prise en charge thérapeutique personnalisée avec un gain d'efficacité évident en oncologie mais également une utilisation plus optimale des dépenses publiques. Par nature, la médecine nucléaire est un outil de médecine personnalisée. Mieux elle est probablement la seule stratégie théranostique réellement intégrée permettant à la fois le diagnostic d'une cible biologique et le traitement de cette même cible après pharmacomodulation du vecteur et réadaptation du radioélément. La contribution de la médecine nucléaire dans le développement de la théranostique et de la médecine personnalisée est donc évidente ! la révolution est déjà en marche par exemple avec le PSMA.

Il convient cependant d'être vigilant et surtout de rester très actif dans le développement des radiopharmaceutiques théranostiques. La médecine nucléaire devra trouver à sa place au milieu des autres méthodes dites "omiques" qui présentent





l'avantage de mesures multiparamétriques et multicibles. La clé est très certainement de savoir convaincre les thérapeutes, oncologues par exemple, de l'utilité de la médecine nucléaire.

Cela sous-entend la conduite d'essai clinique de grande envergure, de qualité méthodologique irréprochable, démontrant un bénéfice sur la survie. Cela sous-entend aussi que chaque médecin nucléaire prenne son bâton de pèlerin et vienne porter la bonne parole dans les réunions de concertation multidisciplinaire..

Comment voyez-vous l'impact de l'arrivée de l'intelligence artificielle (IA) en médecine nucléaire?

Ah ! l'IA est dans toutes les conversations, réunions et congrès. Elle est vécue par certains comme une menace! Le besoin en médecins nucléaires va considérablement diminué. L'interprétation des examens sera complètement automatisée. Cela n'est probablement pas si simple !

Il ne me semble pas évident que, contrairement à d'autres spécialités, notre discipline soit si facilement automatisable. Comme précisé ci-dessus,

nous explorons par imagerie des processus biologiques qui sont fort nombreux. Les critères de lecture diffèrent ainsi d'un type examen à l'autre intégrant des notions d'interprétation objectives mais parfois plus subjectives. De plus, notre métier ne s'arrête pas à une simple lecture automatique ou non d'un examen. Il est aussi un exercice médical, une consultation médicale avec interrogatoire, compte rendu écrit oral de l'examen, bref une relation privilégiée patient-médecin... non automatisable. Enfin la radiothérapie interne est difficilement automatisable...

Il conviendra de toute façon de nous adapter et la médecine nucléaire à l'habitude.. Apprécier les changements importants de notre spécialité dans les 10-15 dernières années. : TEP, ganglion sentinelle, multimodalité... Notre discipline a toujours été très dynamique et très innovante. La SFMN s'empare de la question et vient de mettre en place un groupe de travail dont les objectifs seront de faire un état des lieux des connaissances, des menaces et mais aussi des opportunités. Des actions seront bientôt proposées par le groupe.

En tant que président de la Société Française de Médecine Nucléaire qu'est votre plus grand souhait?

Une médecine nucléaire dynamique innovante et attractive pour les jeunes. ■



WORLD FEDERATION OF NUCLEAR MEDICINE & BIOLOGY

PRESIDENCY CANDIDATE : Dr. Jean-Luc Urbain



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

- MD: University of Louvain, Belgium
 - Board Certified in Internal Medicine
 - Board Certified in Nuclear Medicine
- Ph.D.: Temple University, Philadelphia
 - Molecular Biology and Genetics
- CPE: Certified Physician Executive
- University of Louvain, Temple University, Cleveland Clinic, University of Western Ontario, VHA, Wake Forest University
- Membership: EANM, SNMMI, CANM
- > 1000 lectures in Europe, NA, Asia, SA, Middle East, AF
- Radiant Educational Award, Canada; Homi Bhabha Scientific Award, India
- Main interests: Personalized Medicine, Theranostics, NM Education



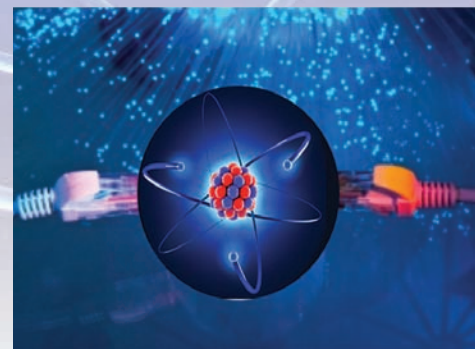
As your President,

I will work relentlessly with all of you from across the world:

1. To Firmly Establish the Value of NM Diagnostic & Therapeutic Procedures in Patient Management in all regions of the World
2. To Continue Promoting NM across the Globe through the Pangea-ePatient Magazine
3. To further Develop our global NM Community Social Media Platform



THERANOSTICS



*Juan Luis Londoño Blair
Médico Nuclear
Jefe servicio Medicina Nuclear
San Vicente Fundación
Hospital Universitario
Columbia
South América*



RADIOSINOVIOERTESIS EN HEMOFILIA



Introducción

La hemofilia es una enfermedad hereditaria que altera la capacidad del cuerpo de controlar el sangrado. Una de las características de la hemofilia es la hemorragia intra articular (hemartrosis). La hemartrosis a menudo comienza en la niñez, cuando el niño empieza a caminar⁽¹⁾. Una hemartrosis puede dar lugar a una sinovitis de bajo grado, que predispone generalmente a una articulación, llamada la articulación blanco a una hemartrosis recurrente, con lo cual comienza un ciclo vicioso de sinovitis crónica, artritis inflamatoria y artropatía progresiva.

El objetivo del tratamiento en los pacientes hemofílicos es el de romper este círculo vicioso lo más pronto posible, eliminando la hemartrosis y suspendiendo de esta forma el proceso de degeneración articular, permitiendo al paciente alcanzar una madurez esquelética con articulaciones funcionales, minimizando de esta forma la incapacidad y mejorando la calidad de vida y reduciendo el costo total del tratamiento⁽²⁾.

El buen entendimiento de la fisiopatología de los procesos de la enfermedad es vital y el médico nuclear debe estar familiarizado con ésta y otras formas de tratamiento. La colaboración interdisciplinaria con otras especialidades, como reumatólogos o cirujanos ortopédicos, es clave en este tipo de tratamiento.

Incidencia y tipos

La hemofilia es una enfermedad hereditaria, ligada al sexo, autosómica recesiva. El 85% ocurre por deficiencia del factor VIII (Hemofilia A o clásica), que tiene una incidencia de 1 en 5.000 niños. La hemofilia B (enfermedad de Christmas) es el 15% restante, con una incidencia de 1 en 30.000 niños. La hemofilia ocurre en todos los grupos étnicos y raciales.

El 25% de los nuevos casos de hemofilia A ocurren sin historia familiar, como casos esporádicos, que ocurren por mutación genética, con una tasa de ocurrencia alta entre todas las alteraciones genéticas.

Se estima que existen unos 350.000 pacientes con hemofilia en el mundo y unos 28.000 en los Estados Unidos.

Fisiopatología

La artropatía producida por la sinovitis crónica y la artritis degenerativa progresiva es la complicación músculo esquelética más común y devastante en los pacientes hemofílicos y es consecuencia de la hemartrosis recurrente.

El proceso comienza con una hemorragia articular simple, en la cual los productos de degradación sanguínea, como la hemosiderina y la ferritina que contienen hierro se absorben en la membrana sinovial. El exceso de hierro causa alteración de los

sinoviocitos con ruptura lisosomal y liberación de encimas condrolíticas ⁽²⁾. Aproximadamente 4 días luego de la hemorragia, el sinovio se vuelve reactivo, con áreas de proliferación vellosa, con incremento marcado de la vasculatura, lo cual lo vuelve susceptible de nuevos episodios de sangrado.

Los cambios inflamatorios en la sinovitis hemofílica son similares en algunos aspectos a los de la artritis reumatoidea y la sinovitis vellonodular pigmentosa. Las células fagocíticas sinoviales, tipo A (células fagocíticas superficiales) están cargadas con hemosiderina. Existe infiltración perivascular con linfocitos y plasmocitos en las etapas iniciales, que son reemplazados por histiocitos repletos de hemosiderina en las etapas tardías. La vasculatura que está por debajo de la superficie se vuelve hiperplásica, con dilatación de los sinusoides venosos, que toman apariencia aneurismática. La artropatía hemofílica es a menudo rápidamente progresiva, con erosiones en la superficie articular, que comienzan antes de la adolescencia.

Las erosiones del cartílago tienen márgenes gruesos que rompen la membrana sinovial engrosada con el movimiento de la articulación, lo cual puede causar hemartrosis crónica, en la cual la articulación siempre está con derrame a pesar del uso del factor antihemofílico (factor VIII). La historia natural de la sinovitis hemofílica es la de progresión hacia una artropatía terminal y artrofibrosis. En el estadio final la membrana hiperplásica, densa y pigmentada evoluciona desde metaplasia hasta fibrosis y presenta contracturas, que finalmente llevan a anquilosis fibrosa. De forma típica, los pacientes con artritis inflamatoria desarrollan atrofia muscular progresiva y subluxación de la articulación, con quistes sinoviales gigantes peri articulares.

Las articulaciones más comúnmente comprometidas son las rodillas, codos y tobillos. Las caderas, hombros y articulaciones subtalares tiene un compromiso menos frecuente. La poliartropatía es común en hemofilia severa, poco común en hemofilia moderada y rara en hemofilia leve.

Definiciones

Sinoviólisis isotópica, radiosinoviólisis, sinovectomía por radiación o radiosinoviortesis son los términos empleados para designar al tratamiento intra-articular con radioisótopos que busca destruir la membrana sinovial en diferentes patologías ⁽³⁾.

Radiocoloide es el término empleado para referirse a una sustancia coloidal que va ligada a un isótopo radioactivo.

Diagnóstico

Antes de comenzar con una radiosinoviólisis, se debe confirmar el diagnóstico con rayos X, ecografía (ECO) y/o resonancia magnética nuclear (RMN). El diagnóstico diferencial entre sinovitis y hemartrosis se puede determinar con ECO y RMN. Los rayos X sirven para valorar el grado de artropatía hemofílica en el momento del diagnóstico.

Clasificación radiológica

Existen dos sistemas de clasificación radiológica de la artropatía hemofílica: la clasificación de Pettersson, que se usa en investigaciones y la clasificación modificada de Arnold – Hilgartner. Cada grado de esta clasificación representa una alteración patológica significativa que influencia el pronóstico y el manejo.

Manejo

La clave para la prevención exitosa de la artropatía hemofílica es el manejo de la hemartrosis inicial antes de que desarrolle sinovitis crónica y erosiones en la superficie de la articulación. La hemartrosis en la articulación sana debe ser manejada de forma agresiva con aspiración, administración de factor antihemofílico, terapia física y seguimiento clínico. La colocación de una férula por unos pocos días puede reducir el riesgo de sangrado recurrente y facilitar la resolución de la sinovitis. Las indicaciones para la aspiración de una articulación con artropatía moderada a avanzada se limitan a los casos con dolor y limitación funcional, ya que es demasiado tarde para prevenir la destrucción de la superficie del cartílago.

La administración intra articular de esteroides y la colocación de yeso circular por 2 semanas es efectiva en algunos pacientes con hemartrosis crónica, en etapas iniciales.

Se usan profilaxis primaria y secundaria para limitar y controlar el sangrado articular. La primaria se inicia en la niñez luego del primer episodio de sangrado, para prevenir hemartrosis futuras y limitaciones funcionales posteriores. A los pacientes se les administra una dosis diaria de factor para prevenir hemartrosis espontáneas.

En la profilaxis secundaria se inicia el factor lo más pronto posible luego de un episodio de hemartrosis y se continúa hasta que la articulación regrese a su estado normal, para prevenir el daño de la articulación.





La terapia física, en especial el fortalecimiento, es importante para prevenir la hemartrosis recurrente y se utiliza usualmente hasta 2 – 4 semanas luego de un episodio de hemartrosis, para continuar con terapia física en casa de forma permanente. La sinovitis se clasifica como crónica, cuando persiste por más de 2 – 6 meses⁽¹⁾.

Sinovectomía

Esta técnica debe realizarse antes que ocurra destrucción irreversible de la articulación. Es muy efectiva en la reducción de la frecuencia de sangrado pero no puede mejorar la degeneración existente de la articulación y el dolor artrítico persistirá sin cambios. La sinovectomía artroscópica ha reemplazado la técnica de cirugía abierta, pero ambas técnicas son útiles en la reducción de la frecuencia de hemartrosis, con tasas de éxito de 80% en la abierta y 70% en la artroscópica. Existe la técnica de sinovectomía con láser.

Si bien la sinovectomía abierta o artroscópica son técnicas muy efectivas en la remoción del sinovio hipertrófico, tienen complicaciones potenciales. Requieren de altas dosis del factor antihemofílico y, en ocasiones, hospitalizaciones prolongadas. La complicación más importante es la artrofibrosis, con severa disminución de la motilidad. Otra técnica es la de sinovectomía química, con sustancias como el thiotepa, ácido ósmico, D-penicilamina y Rifampicina, que busca reducir las complicaciones de la sinovectomía quirúrgica.

Radiosinoviolisis

Historia de radiosinoviolisis en hemofilia

La Radiosinoviolisis, una forma local de radioterapia, fue usada por primera vez de forma experimental por Fellingner et al en 1952⁽⁴⁾. La radiosinoviolisis fue introducida en 1963 en Estados Unidos en artritis reumatoidea. El tratamiento de la membrana sinovial con materiales radioactivos en pacientes con hemofilia fue realizado por primera vez en 1971 por Ahlberg y Petterson con Oro – 198 (¹⁹⁸Au). Estos autores postularon que la radiación de los isótopos radioactivos causaba fibrosis del sinovio, con disminución de la extensa vasculatura, disminución de la sinovitis y de la frecuencia del sangrado.

Fernández – Palazzi et al publicaron inicialmente en 1984 y luego en 1986 sus resultados con ¹⁹⁸Au, Renio – 186 (¹⁸⁶Re) y con Ytrio - 90 (⁹⁰Y), con una mejoría reportada en el 88% de los casos⁽⁵⁾. En 1991 Erken publicó sus resultados usando ⁹⁰Y, con excelentes resultados. En 1993 y luego de 14 años de seguimiento, Rodríguez Merchan publicó una serie grande de pacientes tratados con (¹⁹⁸Au). En 1994 Rivard et al reportaron los resultados de 92 radiosinoviolisis con Fósforo – 32 (³²P) coloidal (en forma de fosfato crómico) y luego, en 1994 Siegel, Luck et al reportaron sus resultados con este mismo isótopo.

Principio de acción

Las partículas coloidales marcadas con isótopos son rápidamente fagocitadas por los macrófagos de la membrana sinovial inflamada. Las partículas se localizan luego en las cavidades vacuolares de la sustancia intercelular.

Las partículas beta liberadas por la desintegración de los átomos radioactivos que hacen parte del radiocoloide causan daño a las células de la membrana sinovial, que comienza con excitación e ionización de los átomos y moléculas en este medio, creando un gran número de partículas subatómicas secundarias. También se forman radicales libres que inician efectos bioquímicos, que a su vez ocasionan apoptosis y ablación de la membrana sinovial inflamada. Las dosis que se reciben en la membrana sinovial son del orden de 0.01 – 2 Gy/Mbq (dependiendo del radiofármaco y del estadio de la enfermedad), con dosis totales de hasta 100 Gy⁽⁴⁾.

Isótopos radioactivos

Varios isótopos radioactivos emisores de partículas beta para uso intra articular han sido aprobados para el tratamiento de algunas patologías de la membrana sinovial: silicato o citrato de ⁹⁰Y, ³²P en fosfato crómico, sulfuro de ¹⁸⁶Re y citrato de Erblio – 69 (⁶⁹Er). Existen otros en investigación como el Renio – 188 (¹⁸⁸Re), el Disprobio – 165 (¹⁶⁵Dy) y el Holmio – 166 (¹⁶⁶Ho)⁽⁶⁾.

El radioisótopo ideal es aquel que ⁽²⁾:

- Sea emisor beta puro
- Que tenga una penetración de 3 – 5 mm (para que tenga efecto solo en la membrana sinovial y evite el potencial efecto de irradiar a los tejidos vecinos, incluyendo el cartílago de crecimiento)
- Esté en forma coloidal, con un tamaño aproximado de 1000 Å (para prevenir su absorción y evitar efectos sistémicos)
- Que tenga una vida media intermedia (para permitir una acción gradual de la energía y evitar efectos inflamatorios inmediatos)

De éstos, el ³²P en forma de fosfato crómico es uno de los isótopos más usados en Norteamérica y Latinoamérica. Es un emisor beta puro, con una penetración de 3 – 5 mm, que permite que se concentre en la membrana sinovial y que tenga poco daño sobre los tejidos que le rodean, incluyendo el cartílago de crecimiento. Se usa en forma coloidal, que tiene un tamaño aproximado de sus partículas de 600 – 2000 Å, con lo cual se previene su absorción y se evitan los efectos sistémicos. Su vida media intermedia, de 14 días permite una deposición gradual de energía, lo cual evita las reacciones inflamatorias inmediatas, que se presentan con otros isótopos de vida media corta. Es el radiofármaco preferido en el tratamiento de la sinovitis hemofílica, por su perfil de dosis absorbida, su posibilidad de administrar una alta dosis de radiación con poca penetrabilidad en un período de tiempo suficientemente largo como para permitir una circulación pasiva en el espacio articular ⁽⁷⁾.

Actividad administrada de fosfato crómico de ³²P en adultos: 0.3 – 2 mCi:

- En rodilla: 1 mCi diluido en 1cc de solución salina, que aportará unos 10.000 Rads (100 Gy) en la articulación.
- 0.5 mCi en codos, tobillos y hombros.
- Niños 2 – 6 años = 1/3 adulto
- Niños de 6 – 10 años = 1/2 adulto
- Niños de 10 – 16 años = 75% ⁽⁸⁾.

Otros isótopos

El ¹⁸⁶Re tiene una penetración entre 1.2 y 3.7 mm pero está compuesto de partículas pequeñas (10 Å) y produce radiación gama y beta. El ¹⁹⁸Au también es un emisor beta y gama, con una vida media de 2.7 días y una penetración de cerca de 1.2 a 3.6 mm y que tiene algún grado de absorción sistémica. El ⁹⁰Y, un emisor beta puro, se ha usado de forma exitosa en la sinovitis hemofílica; tiene un tamaño de partícula que fluctúa entre 1000 y 2000 Å y tiene una penetración máxima de 4 mm, pero tiene una vida media corta (2.4 días) y tiene reacciones secundarias por inflamación ⁽²⁾.

Selección del isótopo

Para seleccionar el isótopo deben considerarse factores como:

- Su vida media: la severidad de la reacción inflamatoria se asocia con la tasa de exposición. Un isótopo con una vida media relativamente larga (días) tiene ventajas con respecto a los de vida media corta (horas). La vida media larga causa un depósito gradual de energía, lo cual minimiza el potencial de respuesta inflamatoria aguda ⁽⁸⁾.
- El tamaño de la partícula: existe una relación inversamente proporcional entre el tamaño del radiocoloide y su tendencia a escapar del espacio articular. El tamaño grande disminuye el potencial de filtración y el drenaje linfático.
- Tipo de partículas: Los emisores beta puros tienen menor tasa de dosis en todo el cuerpo, con respecto a los que emiten radiación beta y gama de forma simultánea (¹⁹⁸Au, ¹⁸⁶Re y ¹⁶⁵Dy). Los emisores beta puros tienen un rango menor de penetración en los tejidos.

El radiocoloide ideal para la radiosinoviolisis debe cumplir estos 3 requerimientos:

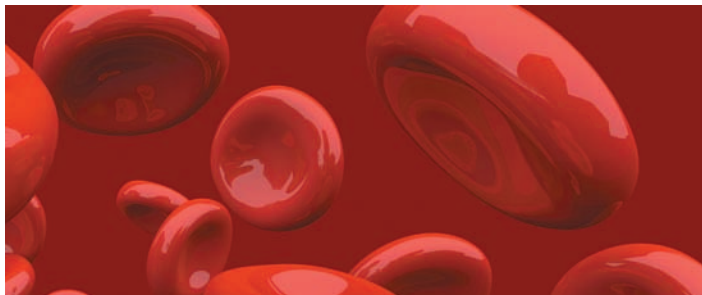
- El coloide debe ser una partícula lo suficientemente pequeña para ser fagocitada pero no muy pequeña, para que permanezca en la articulación antes de su fagocitosis. Los rangos apropiados de tamaño fluctúan entre 2 – 10 µm.
- La unión entre el radioisótopo y la partícula debe ser estable durante el curso de la radiosinoviolisis
- Las partículas radiomarcadas se deben distribuir de forma homogénea en el espacio intra articular sin que inicien una respuesta inflamatoria.

Aunque algunos autores usan el mismo radioisótopo en articulaciones de diferente tamaño, basados en que el tamaño de la articulación determina el espesor del tejido sinovial, se ha recomendado usar radioisótopos de diferente energía en las diferentes articulaciones: El ⁹⁰Y se recomienda solo para las rodillas, por sus partículas beta de alta energía, con una penetración tisular media de 3 – 4 mm; mientras que el ¹⁸⁶Re, con una penetración media de 1 – 2 mm se recomienda en articulaciones de tamaño medio, como el hombro, codo, muñeca y tobillo ⁽⁹⁾ ⁽¹⁰⁾.

Indicaciones y contraindicaciones de la radiosinoviolisis

Indicaciones

La indicación principal para la radiosinoviolisis es la sinovitis hipertrófica crónica asociada con hemartrosis



recurrente que no responde al tratamiento hematológico⁽¹¹⁾:

- Artritis reumatoidea
- Artritis indiferenciada con sinovitis
- Enfermedad inflamatoria articular de otro origen (enfermedad de Lyme, artritis psoriática, espondilitis anquilosante)
- Derrame sinovial persistente (p. ej. luego de endoprótesis)
- Osteoartritis con sinovitis
- Sinovitis vellonodular
- Hemartrosis y sinovitis en hemofilia (hemartrosis recurrente no controlada por el tratamiento hematológico)⁽¹²⁾.

La indicación para radiosinoviolisis en pacientes con hemofilia es la presencia continua de derrame articular o hemartrosis y tres o más episodios de hemorragia en la misma articulación en los últimos 6 meses⁽⁹⁾.

Contraindicaciones

Las contraindicaciones absolutas incluyen⁽⁴⁾:

- Embarazo
- Lactancia
- Ruptura de quiste de Baker
- Infección local de la piel
- Hemartrosis masiva

Contraindicaciones relativas:

- Edad menor de 20 años (debe valorarse el riesgo/beneficio)
- Evidencia de pérdida de cartílago significativa
- Inestabilidad de la articulación con destrucción ósea

Criterios de exclusión⁽⁶⁾:

- Inestabilidad de la articulación
- Destrucción ósea
- Osteoartritis (grado IV)
- Quiste de Baker
- Infección de la articulación o de la piel
- Hemofilia de menos de 2 años de evolución
- Episodios de sangrado agudo

Las ventajas de la radiosinoviolisis frente a la sinovectomía quirúrgica son⁽⁸⁾:

- Requiere una mínima dosis de factor antihemofílico
- Es un procedimiento ambulatorio
- Pueden tratarse de forma simultánea varias articulaciones
- Existe un bajo riesgo de hemorragia en pacientes con inhibidores del factor antihemofílico
- Puede administrarse solo con anestesia local, con beneficio en pacientes en quienes no puede realizarse cirugía (enfermedades sistémicas)
- Bajo costo del procedimiento
- Disminuye hospitalizaciones

Requisitos técnicos

Todos los isótopos emisores de partículas deben ser administrados en sitios dedicados y habilitados por las autoridades nacionales competentes; en ambiente estéril y con procedimientos estériles.

El manejo de los radioisótopos requiere de precauciones especiales por las altas tasas de dosis que pueden ser absorbidas en los dedos de quien las manipula. Deben blindarse de forma adecuada las jeringas con blindajes de plástico o acrílico. Se han calculado dosis en los dedos de 22,1 Sv/Mbq cuando no se usa blindaje, comparativamente con dosis de 0.4 Sv/MBq cuando se usan blindajes de acrílico.

Consentimiento informado

El consentimiento informado por escrito es mandatorio. La información debe administrarse de forma verbal y escrita y debe cubrir el procedimiento, sus riesgos y beneficios.

A los pacientes se les debe informar sobre la naturaleza radioactiva del tratamiento y su mecanismo, indicaciones y contraindicaciones. Debe informárseles que la respuesta puede tardarse hasta 1 mes, con mejoría progresiva hasta los 6 meses. Inicialmente puede ocurrir un incremento en la sinovitis y el dolor. Se les debe informar sobre los posibles efectos secundarios y complicaciones, incluidos los riesgos de una punción articular, como infección, hemorragia local o extravasación; el riesgo de radionecrosis si la administración no es exclusivamente intra articular (muy raro); la posibilidad (teórica, aunque aún no comprobada) de neoplasias; el riesgo post inyección de piroxia o alergia (muy raro) y el riesgo de trombo embolismo después de la inmovilización de la extremidad por 48 horas.

	³² P	⁹⁰ Y	¹⁸⁶ Re	¹⁹⁸ Au
Radiación β	-	2.7 mm	-	3.6 mm
Penetración	3 – 5 mm	1.0 mm	1.2 – 3.7 mm	0.9 mm
Radiación γ	No	No	Si	Si
Energía	1.71 MeV	0.98 MeV	1.1 MeV	0.96 MeV
Tamaño	600 – 2000 Å	1000 – 2000 Å	10 Å	300 Å
Vida media	14.3 días	2.4 días	3.7 días	2.7 días

Tabla 1. Características de los isótopos radioactivos más utilizados en radiosinoviolisis

También se les debe informar que el procedimiento tiene una tasa de éxito del 60 – 80% y que puede repetirse luego de un mínimo de 6 meses⁽⁴⁾.

Procedimiento

La profilaxis con el factor se comienza 1 – 2 horas antes del procedimiento y se continúa por algunos días después⁽⁹⁾. La dosis de factor antihemofílico con factor VIII es de 50 U/kg y 25 U/kg a las 24 y 96 horas después del procedimiento. A los niños con deficiencia de factor IX se les administra concentrado de factor IX en dosis de 100 U/kg antes del procedimiento y 40 U/kg a las 24 y 72 horas⁽⁷⁾. Luego de la administración del factor se deben garantizar niveles plasmáticos de al menos 50% de lo normal.

La punción articular debe realizarse bajo estrictas condiciones de asepsia por personal médico y de enfermería, con supervisión del médico nuclear con entrenamiento y licenciamiento específico en el uso de radiofármacos y en radioprotección.

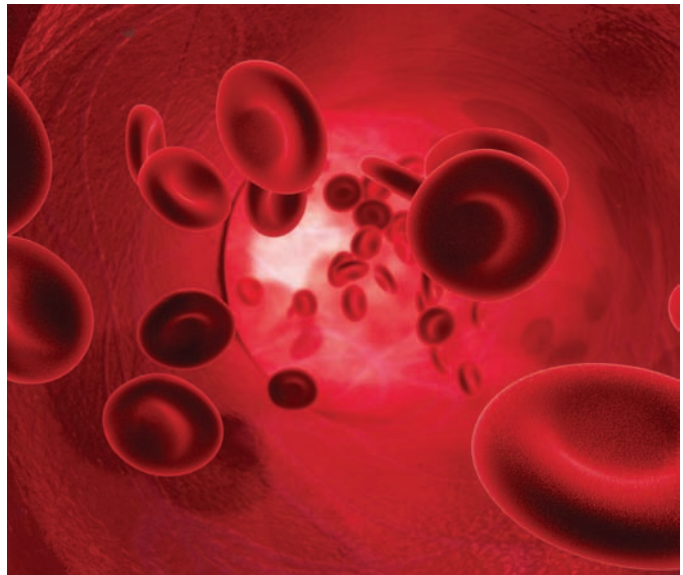
Deben usarse guantes estériles y debe aplicarse anestesia local antes de la punción. Debe garantizarse que la punción está intra articular, lo cual en la rodilla es relativamente fácil. En articulaciones pequeñas puede requerir la ayuda de un intensificador de imágenes.

Se administran hasta 10 ml de Lidocaína para anestesiarse la piel y los tejidos profundos, incluyendo la cápsula articular y la membrana sinovial⁽¹³⁾. Generalmente con una aguja 16 o 18 es suficiente, pero en algunos casos se necesita un catéter 12 o 14 para evacuar una hemartrosis viscosa. Luego de la punción, todo el líquido debe ser evacuado (sangre o líquido sinovial) y una vez se esté seguro de estar en el espacio intra articular, se administra el radiocoloide en un volumen de 1cc utilizando una jeringa separada, con protector de acrílico. En caso de usarse ³²P, se administran cantidades de 1mCi en articulaciones grandes (rodilla y codos) y 0.5 mCi en articulaciones pequeñas. De forma empírica, se usa la mitad de la dosis en niños.

Luego de la administración del radiocoloide, debe garantizarse que éste no quedará alojado en el canal de inyección, por el riesgo de radionecrosis en los tejidos, mediante el lavado durante la extracción de la jeringa y la aguja con solución salina al 0.9% o con glucocorticoides de larga acción, que a su vez ayudan a reducir el potencial de sinovitis aguda.

Luego se aplica presión a medida que se efectúa un rango completo de movimiento para dispersar el radiocoloide en toda la superficie sinovial. La articulación tratada se inmoviliza durante 2 días y se recomienda reducir la actividad física durante 2 semanas⁽²⁾.

En caso de administración a varias articulaciones, se sugiere hospitalizar al paciente. Pueden realizarse imágenes en la gamacámara o tomar mediciones con contadores Geiger – Müller en la articulación comprometida, en la contralateral, en el hígado y en el bazo, inmediatamente después de la inyección.



Considerando el estado actual en el mundo acerca de los materiales radioactivos y de su costo, se requiere de organizar grupos de pacientes (6 – 8 pacientes) a quienes se les practicará radiosinoviolisis. Es posible que los pacientes tengan un tiempo de espera de unos 3 – 6 meses hasta que el grupo se complete, tiempo en el cual se debe aplicar un buen tratamiento profiláctico⁽¹²⁾.

Efectos secundarios

- Un efecto temprano y temporal es el incremento del dolor articular ocasionado por la sinovitis inducida por la radiación
- Pueden ocurrir linfedema o fiebre en raras oportunidades
- Los efectos secundarios severos como radionecrosis son muy raros
- La inducción de neoplasias es un potencial teórico pero nunca se ha demostrado⁽⁴⁾.

Instrucciones para los pacientes

A los pacientes se les debe advertir que tengan inmovilizada la articulación por al menos 48 horas. Si ocurre una exacerbación temprana del dolor, puede tratarse con medidas antiinflamatorias. El paciente debe revisarse a los 4 – 6 días después de la terapia, en busca de posibles efectos secundarios.

El paciente debe evitar la exposición innecesaria de otros miembros de la familia y del público.

La excreción urinaria o fecal del radiocoloide no es un problema en estos pacientes; sin embargo, deben instruirse sobre el incremento de las medidas de higiene.

Seguimiento

Luego de 3 – 4 meses, el especialista tratante debe evaluar para posible actividad inflamatoria de la membrana sinovial y sobre la respuesta a la terapia. La evaluación clínica se centra en la tendencia al sangrado y en la recuperación de la función de la articulación tratada (rango de motilidad).

Costos

El costo promedio del tratamiento con ³²P, incluyendo el factor antihemofílico, los honorarios médicos; los gastos hospitalarios y la terapia de rehabilitación es de US\$ 2.850 en Estados Unidos versus US\$ 61.140 para sinovectomía quirúrgica (abierta o artroscópica)^{(1) (2)}.

La radiosinoviólisis requiere solo 1 o 2 dosis del factor y no requiere en la mayoría de los casos de terapia física o de hospitalización. Cuando se practica en varios pacientes de forma simultánea, los costos pueden ser de US\$ 1.300 a 1.800 por paciente.

Potencial de malignidad

Existe una preocupación teórica en cuanto a que los linfocitos circulantes puedan experimentar incremento de la retención en la membrana sinovial inflamada. No se ha demostrado incremento en la tasa de leucemia en niños. Después de más de 30 años del uso de la radiosinoviólisis no se ha demostrado daño articular o sistémico publicado en la literatura^{(11) (12) (14)}.

La radiosinoviólisis puede realizarse a cualquier edad en pacientes hemofílicos, siempre y cuando esté bien indicada y realizada de forma adecuada. En niños pequeños debe realizarse bajo anestesia general. Aún hasta 30 años luego de su uso, la radiosinoviólisis no ha demostrado daño articular o sistémico ni tampoco complicaciones hematológicas o neoplásicas por los materiales radioactivos. Los estudios cromosómicos realizados en pacientes que han recibido radiosinoviólisis, sin importar cual radiocoloide se ha usado, han demostrado que no se produjeron anomalías cromosómicas premalignas. Tampoco se demostró penetración de los radiocoloides al cartílago articular y tampoco que éstos alcancen la placa de crecimiento⁽¹⁵⁾.

Eficacia de la radiosinoviólisis

En promedio, la radiosinoviólisis tiene una eficacia del 75% a 80% a largo plazo. Desde el punto de vista clínico, la eficacia se mide en la reducción del número de hemartrosis, con desaparición completa de estos episodios por varios años en muchos casos. Debe tenerse en cuenta que en el 20 – 25% de los casos la radiosinoviólisis falla en el control de la hemartrosis. En estos casos puede repetirse. No se recomiendan más de tres procedimientos, en intervalos de 3 – 6 meses^{(11) (12)}.

La radiosinoviólisis con ³²P en forma de fosfato crómico tiene unos resultados clínicos excelentes, con un promedio de reducción de hemartrosis del 75% (75 – 100% en el 80% de los casos primarios y 62% en los casos secundarios, hasta 3 años luego de la administración primaria)^{(1) (2)}.

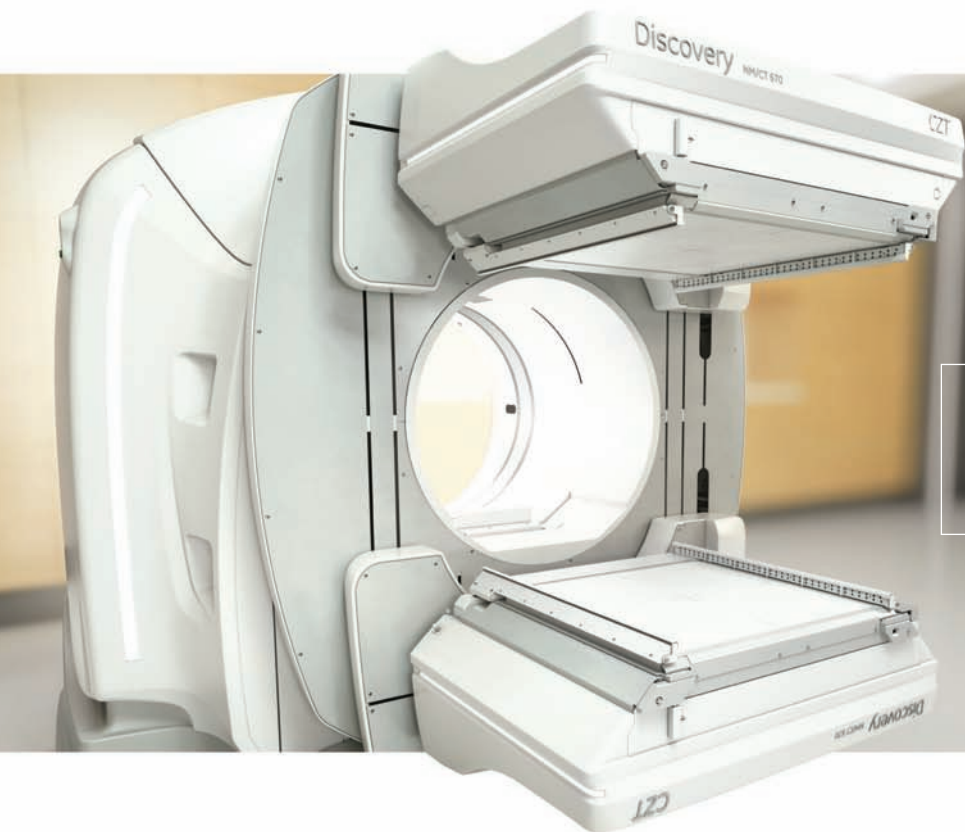
Múltiples articulaciones

Los hemofílicos comúnmente tienen más de una articulación blanco. Se puede realizar más de una radiosinoviólisis en el mismo procedimiento. Se recomienda realizar no más de dos inyecciones al mismo tiempo y no inyectar la misma articulación de

forma bilateral; debe considerarse realizar el procedimiento en lo posible en el mismo lado, por ejemplo codo y rodilla, codo y tobillo, etc, para no incapacitar al paciente de forma extensa en sus funciones normales⁽¹¹⁾. ■

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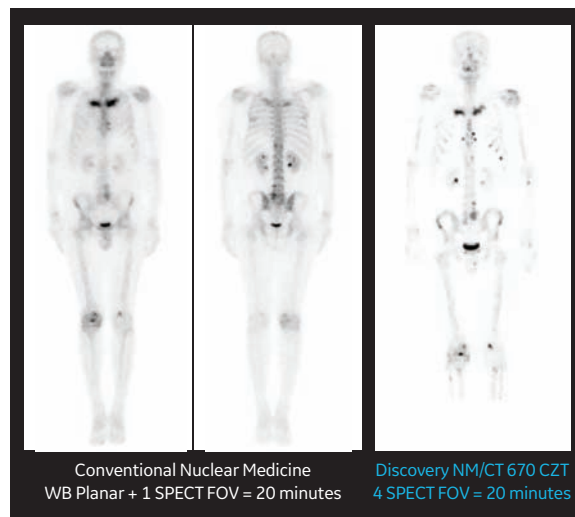


Discovery™ NM/CT 670 CZT

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Discovery NM/CT 670 CZT is the only commercially available, general purpose SPECT/CT system powered by CZT technology. With CZT, each photon captured from the patient is directly converted into an electrical signal that accurately identifies its location and energy. This reduces the signal loss and noise inherent to conventional SPECT/CT technologies. See the results for yourself with a SPECT contrast-to-noise ratio that's been improved by more than 40 percent, a sharper system spatial resolution of 2.8 mm and the choice of reducing acquisition time or dose by up to 75 percent.¹

Combined with Xeleris™ 4.0 quantitative applications, these improvements in detection technology can help you in your efforts to diagnose and stage diseases earlier by allowing you to detect smaller lesions and quantify them more accurately.² We see it as much more than a new imaging product, it's a SPECT/CT system for true discovery.



20 mCi Tc99m HDP. Images courtesy of Hospices Civils de Lyon, France, Prof. Scheiber.



Less than 4 minutes each for Bone SPECT and WB Bone exams³

gehealthcare.com



¹ CNR demonstrated in using NEMA IEC Body Phantom at 50% scan times with Evolution and compared to Discovery 670 Pro/ES/DR. Spatial resolution at detector surface. Acquisition time or dose reduction using Clarity 2D/Evolution compared to Discovery NM/CT 670 Pro/ES/DR without Clarity 2D/Evolution as demonstrated with NEMA IEC Body Phantom.

² Based on clinical practice.

³ Demonstrated with NEMA IEC Body Phantom together with Clarity 2D and Evolution. Compared to a typical 15 minute scan on Discovery NM/CT 670 Pro/ES/DR without Clarity 2D and Evolution.



Defining Enterprise Molecular Imaging

PROVEN, PRECISE, PERSONALIZED

