EANM 24
WORLD LEADING MEETING

THE HAMBURG COLLECTION

37th
Annual Congress of the
European Association of Nuclear Medicine

HAMBURG

TABLE OF CONTENT

FOREWORD

The **EANM'24 Congress** in Hamburg (Germany) was a milestone, attracting a record 8,680 participants and showcasing the growing global interest in nuclear medicine. As the premier event in the field, it provided a platform for discussing advancements in areas such as theranostics, clinical evidence, radiopharmaceuticals, and imaging technologies aimed at improving patient care.

To capture the key topics from last year's congress, the EANM has collaborated with Cornelia Wels-Maug, Healthcare IT analyst and writer. After attending selected sessions, Cornelia has curated 8 articles summarising the latest breakthroughs in nuclear medicine. These articles, which were enhanced by the presenting experts, offer valuable insights into current trends, advanced diagnostics, and new therapies.

Enjoy the read!

1 | EANM ENDORSES THE USE OF AI IN NUCLEAR MEDICINE – "TO ENSURE THE BEST POSSIBLE CARE FOR EACH PATIENT"

The adoption of AI tools in nuclear medicine has been growing and has shown tremendous promise in improving diagnostic imaging and radiopharmaceutical therapies. However, the need for large amounts of training data, data harmonisation and multi-institutional data sharing are a challenge. Incorporating AI into routine medical care requires not just technology adoption, but also education on its use and comes with navigating ethical, legal, and privacy issues inherent in AI applications.

Artificial intelligence and the human brain

Artificial intelligence (AI) enables computers and machines to imitate human comprehension, learning, problem solving and decision making, among others. Using AI empowers applications to comprehend and reply to human language, notice and identify objects and learn from new information and experiences. Based on this, AI applications can solve problems and support human decision-making.

Recently, most efforts around AI have been in the domain of generative AI (gen AI), an approach that supports the creation of original content e.g., images, text and video by deploying machine learning (ML) and deep learning (DL) capabilities. Modelled after the human brain, a neural network consists of interconnected layers of nodes which process and analyse complex data. They are particularly prone to identify complex patterns and relationships in large amounts of data.

DL is a form of ML that uses deep (or multilayered) neural networks that mimic the complex decision-making capabilities of the human brain. Deep neural networks (DNN) are made up of an input layer, a minimum of two but often hundreds of hidden layers and an output layer. Those multiple layers automate the extraction of features from data sets and make their own predictions about what the data represents. DL is particularly suited to tasks that involve fast, accurate identification of complex patterns and relationships in large amounts of data.

The latest advancements of AI build on the foundations of transformers. Transformers are complex neural network architectures that can encode (or embed) a wide-range of digital data – including text, image, speech, DNA sequences or structured reports. They can build up a so-called attention mechanism over the embedded data. This mechanism is generally considered superior compared to conventional DL approaches, as it can model both local and salient information within the data and has powerful association capabilities within the data. Popular large language models (LLM) are built on transformers.

AI making inroads into nuclear medicine

The digitisation of healthcare brought along the use of AI to gain new insights from the data. At the EANM'24 Congress, Dr Vincent Andrearczyk, Postdoctoral Researcher, University of Applied Sciences and Arts Western Switzerland, Sierre, Switzerland, explained that DL started a sea change in nuclear medicine (NM) in 2012. This phenomenon was linked to the growth in computing power, which was the prerequisite to train DL models.

There is a broad range of AI use cases across all medical fields optimising workflows in administration, research, prevention, diagnosis and therapy – including personalised medicine. Especially the application of AI in medical imaging has expanded over the last years. According to a recent article in the European Journal of Nuclear Medicine and Molecular Imaging (EJNMMI), 76% of FDA approved AI-enabled medical devices can be found in the domain of radiology.[i]

EANM endorses importance of AI

By launching a new committee dedicated to AI just ahead of the congress in Hamburg in October 2024, EANM underscored the importance of AI for NM. Dr Margarita Kirienko, Nuclear Medicine Physician, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy, is the leader of the newly established AI Committee. She stressed the benefits of AI: "AI is transforming medicine, its contribution to nuclear medicine will be particularly important as we deal with complex image data sets. AI enables the development of innovative radiopharmaceuticals that improve diagnostics and nuclear medicine treatments, enhance image quality, lower radiation exposure and, by combining biopsy and lab data, advance personalised therapies. For patients, AI promises high quality care and potentially better outcomes. Our work here is to bring scientific innovations to patients and AI-enhanced nuclear medicine will ensure that each patient receives the best possible care."

Kirienko also added that AI tools support NM physicians in interpreting images and evaluating findings in oncology, cardiology and neurology. The mission of the AI Committee is to advance research, education and adoption of reliable AI tools as well as establish and spread industry best practice and guidelines. The AI committee will also collaborate with the other 13 EANM committees, the seven EANM councils and its board. A collaboration with external societies focused on data sciences is planned as well as the voluntary involvement of community members. Should a medical need for NM arises to work with other clinical departments, relevant collaborations would follow, Kirienko assured and said: "In order to make AI skills accessible for everyone, education is our first focus. For this, we need to understand which challenges nuclear medicine clinicians face so that we can tailor our educational offers accordingly."

Real-world applications of AI in nuclear medicine around imaging

AI tools improve image acquisition and support the decision-making process for interventions on patients. It is also known to enhance image reconstruction from raw data and data corrections for attenuation, scatter and motion as well as post reconstruction and image improvements. As far as the analysis of images is concerned, AI shows promise in the realm of image registration, segmentation of organ and lesions, measurement of biomarkers and multi-omics integration to name but a few examples.[ii]

"AI can be included in all clinical workflows like planning nuclear medicine procedures, image reconstruction, image interpretation or optimising therapies. Preliminary results from studies at our hospital show that using AI in nuclear medicine can lead to faster image acquisition and image segmentation which might enable better activity quantification as well as staging and prognosis of diseases. However, validation in a large clinical study is needed." shared Renata Madru, PhD, Medical Radiation Physics, Skåne University Hospital, Lund University, Sweden, with the audience at EANM'24. She also pointed out that her NM department removed noise in whole body bone scintigraphic images by using convolutional neural networks (CNN) with no resolution loss and was able to reduce scanning time for lesion detection. In view of the more than 100 FDA-approved AI applications, she urged the audience to share their experiences with those AI-tools amongst each other.

Andrearczyk presented at EANM'24 insights from his research in the field of segmentation, which involves identifying and delineating regions of interest (ROI) in various medical images using supervised, unsupervised, semi-supervised and self-supervised segmentation approaches as well as foundation models. Segmentation is clinically relevant as it facilitates the detection of lesions in screening of suspicious cases or follow-ups; planning radiotherapy and surgery; monitoring treatment responses; taking measurements (e.g., hippocampus atrophy for Alzheimer's disease) or predicting prognosis. He reported the findings of a study with circa 900 cases of head and neck cancer that was conducted across 9 centers in different countries.

Automatic segmentation results for most cases were equivalent to expert performance, whereas those for the prediction of recurrence free survival (RFS) achieved a maximum C index ~ 0,7, which was insufficient for clinical use, but left clinicians "very interested" said Andrearczyk. He concluded: "Using a common evaluation method for all teams around the world, we see that the larger the datasets, the better the models perform; smaller datasets need more prior information

to be injected into the model." Overall, the quality of medical image segmentation hinges on data quality, patient movement, low resolution, noise, artifacts and registration. Insufficiently large datasets, lack of fine-grained annotation in addition to heterogenous imaging techniques plus ambiguity in object boundaries and interpretability have a negative impact on the quality of segmentation.

Real-world applications of AI in nuclear medicine around radiopharmaceutical therapies

In the domain of drug discovery for radiopharmaceutical therapies (RPT) AI helps to select the most promising leads to design appropriate theranostics for respective targets. For this ML models are trained with parameters from past theranostic successes and failures (e.g., partition coefficient) to determine which of them best forecasts a given outcome (e.g., blood-brain barrier penetration).[iii]

AI has also been beneficial in radiopharmaceutical dosimetry, which deals with quantifying the deposited energy from the injected agent and its biologic effect on diseased and normal tissues. Dr Johannes Tran-Gia, Senior Post Doctoral Fellow, Department of Nuclear Medicine, University Hospital Würzburg, Germany, explained at the congress how his department uses PET/CT and blood test results to predict absorbed dose in organs at risks (liver, kidney, spleen salivary glands). Using clinical biomarkers and dosimetry parameters he and his colleagues set out to predict overall survival (OS) and progression-free survival (PFS) with the result that ML successfully identified key predictive factors for OS and PFS. When using a DL model to predict absorbed dose distributions based on SPECT/CT data to replace conventional Monte Carlo (MC) methods, the results were encouraging as the DL model achieved high accuracy in predicting dose distribution that closely matched those of MC-based estimates of absorbed dose. In the case of acceleration of SPECT/CT the research showed that DL-based dosimetry was comparable to full MC. "We have to perform an organ-wise segmentation first to see the radiation emitted in the source organ plus the dose factor for all source/target organ pairs. There is a lot of potential for AI to accelerate this workflow, e.g., by enhancing biokinetic modelling and time-activity curve."

Challenges on the way

The adoption of AI generally faces several challenges and pitfalls. These include the need for staff education, software maintenance, equipment upgrades and changes to existing care pathways, which can be disruptive. AI also needs robust AI governance measures and an audit framework to ensure the trustworthiness of the generated results as AI tools can introduce new errors in interpretation. Training staff to understand the limitations of AI tool is also crucial for building trust.

During EANM'24, most concerns voiced in relation to AI focused on the lack of large sets of training data and challenges around sharing and harmonising existing datasets from different institutions.

Madru urged the audience to collect data: "In nuclear medicine we have different organs, radioactive tracers and different biokinetics of tracers, all this makes it difficult, we don't have as much data as we would like to have and collecting it is a challenge!" To this end, Laszlo Papp, PhD, Post Doctoral Researcher, Center for Medical Physics and Biomedical Engineering, Medical University of Vienna, Austria, suggested at EANM'24 to work with federated data: "Depending on the task, deep learning models have a very high number of parameters to train. However, we cannot match this high number with the required amount of training samples. Decreasing the number of parameters would lead to a loss of performance and collecting more data would be difficult, therefore, we should rely on federated data. This, however, requires data and infrastructure which are not in place. Considering that this endeavour is to date underrepresented, there is a parallel need to reinvent AI that can learn from small data with much less parameters to train compared to the state-of-the-art. This process shall result in novel AI models that can model complex non-linear relationships within small data. Eventually, both novel methodological proceedings in AI and initiatives to share data shall have an accumulative effect to advance AI-driven personalised nuclear medicine."

Andrearczyk saw the main hurdle to AI adoption in insufficient data (public, curated and annotated) to train DL models. To overcome this obstacle, he suggested to share data and create large public annotated datasets, enhance federated learning plus

a stronger collaboration between clinicians and AI experts in addition to developing foundation models.

Prof Catherine Cheze Le Rest, Department of Nuclear Medicine, Poitiers University Hospital, France, acknowledged the role of AI as a contributor to the translation of radiomics to the bedside for personalised medicine. "But on the way to this", remarked Cheze Le Rest, "several challenges need to be resolved including data standardisation, reproducibility, transparency usability and trustworthiness."

Looking ahead

Despite challenges associated with AI, there was a clear notion at EANM'24 of the immense potential AI brings to the future of NM. Madru concluded: "AI and radiomics provide more opportunities than threats and the future for implementation of radiomics in nuclear medicine is promising."

In Papp's presentation, "Future perspectives of AI and potential impact in nuclear medicine applications", he inferred that the future of AI would be within the triangle of Transformer, Biomorphic and Quantum technologies with transformer AI allowing contextual multimodal learning, Biomorphic AI permitting more powerful learning representation and Quantum AI simplifying data dimensionality and AI complexity." However, he warned: "None of this will reach full potential if we do not build an EANM-wide federated respectively transfer learning infrastructure." Papp also called to broaden the field of AI in the future with more emphasis on biomorphic AI. "Quantum AI is already with us, although we still not have scalable noiseless quantum machines, the quantum advantage can already be achieved in simulator environments if certain conditions apply. We don't even need quantum computers to engage with the field," said Papp.

Closing with Kirienko's assessment sets a good foundation for further research: "The possibilities of impactful research and real-world applications of AI are tremendous. As we look ahead, the integration of AI will redefine the boundaries of what we can achieve in nuclear medicine. It is an exciting time to be at the intersection of technology and healthcare."

Cornelia Wels-Maug,
December 5, 2024

REFERENCES

[i]Department of Nuclear Medicine & Molecular Imaging (EB50), Medical Imaging Center, University of Groningen, University Medical Center Groningen, Hanzeplein 1, PO 9700 RB, Groningen, The Netherlands

[ii]See Artificial Intelligence in Nuclear Medicine: Opportunities, Challenges, and Responsibilities Toward a Trustworthy Ecosystem, The Journal of Nuclear Medicine, Vol. 64, No. 2, February 2023

[iii]See Artificial Intelligence in Nuclear Medicine: Opportunities, Challenges, and Responsibilities Toward a Trustworthy Ecosystem, The Journal of Nuclear Medicine, Vol. 64, No. 2, February 2023

2 | DIAGNOSING ALZHEIMER'S DISEASE – THE SOONER THE BETTER

The role of nuclear medicine in early Alzheimer's diagnosis

Nuclear Medicine (NM) is particularly associated with the diagnoses of cancer, but also infection and inflammation. More recently NM has come to play an important role in diagnosing and managing Alzheimer's disease (AD) in vivo, which, until then, could solely be reliably diagnosed by post-mortem examination of the brain. NM imaging techniques have ushered in a new epoch of diagnosing AD as they are able to detect abnormalities in the brain at a very early stage and before the onset of symptoms. This allows clinicians early interventions and disease management measures and thus delaying disease progression. The latest approval of drugs that remove amyloid, especially Lecanemab, signifies a breakthrough in treating AD and will also increase the demand for NM imaging as those drugs require multiple scans to monitor disease progression.

The growing burden of Alzheimer's, respectively dementia

AD is a "fatal neurodegenerative condition characterised by deterioration in cognition and memory, progressive impairment in the ability to carry out activities of daily living, and a number of neuropsychiatric symptoms."[i] It usually manifests in individuals of advanced age who are more than 65 years old.

According to the World Health Organization (WHO), AD is the most common cause of dementia, contributing to approximately 60-70% of cases, whereby dementia is presently the seventh leading cause of death in the world.[ii] The WHO estimated that as of 15 March, 2023, globally 55 million people had dementia (an estimated 33 million to 38.5 million respectively caused by AD) with an annual growth of almost 10 million additional cases worldwide.[iii] The rising cases of AD represent a major challenge for society and healthcare systems – especially since there is no cure for AD yet.

The pathogenesis of Alzheimer's disease

Typical symptoms of Alzheimer's disease include memory loss, disorientation, agitation, and speech disorders as well as aggression and a loss of inhibition. These signs vary in severity among those affected and intensify in the course of the disease.

In 1906, the German psychiatrist Dr Alois Alzheimer was the first to describe this pathology in length, which was then named after him. His findings were based on interactions with one of his patients, Auguste Deter, who spent the last five years of her life in a psychiatric hospital. During this time her cognitive ability seriously declined and when Alzheimer examined her brain after her untimely death, he noted it had shrunk in certain areas and showed several abnormal deposits – plaques and tangles.

One of the initial detectable brain changes in AD pathogenesis is an accumulation of cerebral amyloid-β (Aβ or Abeta) plaques that appear before the onset of clinical symptoms. At a later stage, just before the occurrence of cognitive problems surface, tau neurofibrillary tangles spread in the brain and an increasing loss of neurons happens along with a decrease in the glucose metabolism. The underlying reason for the accumulation of neuritic plaques and neurofibrillary tangles is not fully known as well as the reason for the non-uniform distribution in the cortex.

Diagnosing Alzheimer's: The sooner, the better

From a pathobiological perspective, AD begins decades before the first memory deficits emerge, which means that the disease develops in the brain long before the first symptoms occur. Nevertheless, diagnosing AD is not straightforward as only until recently the only way to diagnose AD reliably was via a post-mortem examination of the brain. However, NM can diagnose

AD and other neurodegenerative diseases at a very early stage.

Visualising the invisible – nuclear medicine contributes to diagnosing AD

The non-invasive imaging techniques of NM have ushered in a new epoch of diagnosing AD in vivo as they are able to detect abnormalities in the brain before the onset of symptoms. This approach is also reflected in the UK's National Institute of Aging-Alzheimer's Association's (NIA-AA) 2018 research framework for AD, which suggested to shift the definition of AD from a syndromal to a biological construct based on the presence of three groups of biomarkers – amyloid deposition, pathologic tau and neurodegeneration whilst using cognitive symptoms to stage severity.[iv]

Positron Emission Tomography (PET) scans are one of the most common NM techniques for assessing AD. They visualise brain activity and the presence of amyloid plaques and tau tangles. Radiotracers like florbetapir, flutemetamol and aducanumab bind to amyloid plaques and facilitate the computation of the amyloid burden in the brain. Furthermore, using ^{18}F-Fluorodeoxyglucose (FDG-PET) allows to obtain tomographic images of the neuronal dysfunction or neurodegeneration, which manifest before structural abnormalities like atrophy can be observed. Single Photon Emission Computed Tomography (SPECT) scans reveal distinct patterns of brain activity and are used for assessing cerebral blood flow and metabolic activity in the brain. Changes in blood flow patterns can indicate areas affected by AD.

Amyloid Positron Emission Tomography (PET) have proven to be particularly useful in confirming respectively excluding AD as a positive amyloid PET scan makes an AD diagnosis likely.[v]

Managing Alzheimer's disease with drugs

The commonly voiced sentiment at the Annual Congress of the European Association for Nuclear Medicine, EANM'24, was a validation of the importance of an early diagnosis to delay the progression of AD and allow patients to receive an appropriate medical treatment. Prof Dr Henryk Barthel, Medical Director, Department of Nuclear Medicine, Städtisches Klinikum Dessau, Germany, confirmed this based on his own experience: "Once you have tau and atrophy, it's already too late as neurodegeneration is irreversible. I would like to see more prevention trials and give drugs to those who are still asymptomatic to obstruct the onset of symptoms. In oncology, nobody waits until symptoms occur, we should take the same approach in Alzheimer's too. More data is necessary to get the concept of an early scan into the clinic."

However, this is already happening in other countries. After a decade, amyloid PET scans nowadays receive broad insurance coverage, shared Barthel. For example, the Centers for Medicare and Medicaid Services (CMS) in the U.S. have reimbursed the routine clinical use of amyloid PET-CT scanning for the visualisation and quantification of Aβ protein fibrillary deposits since 2023. This is closely linked to the U.S. Food and Drug Administration (FDA) approving anti-amyloid therapies, which require monitoring of the disease progress and necessitate multiple NM scans per patient. This, in turn, has resulted in the decision of CMS to refund these scans.

Approval of Donanemab and Lecanemab bestow hope

Although there is no cure for AD, effective drugs targeting the protein fragments that build up in the brain – Aducanumab, Donanemab and Lecanemab – are available now. These drugs target the enzymes that split amyloid precursors and hinder different steps of the amyloid build-up. Of those three drugs, Donanemab and Lecanemab are the most promising plaque-busting immunotherapy drugs on the market.

Donanemab (Kisunla) for the treatment of mild cognitive impairment or mild dementia due to AD was approved by the FDA in July 2024 and was submitted to the European Medicine Agency (EMA) for approval in August 2023. Donanemab is currently under review at EMA, with a decision anticipated during the first quarter of 2025. It also awaits approval in other countries. The drug has demonstrated to slow the clinical decline by 35% over an 18-month period. Like other anti-amyloid drugs, Donanemab treatment is associated with the development of amyloid-related imaging abnormalities (ARIA), a potentially severe side effect linked to brain microbleeds and swelling.

In July 2023, after unanimous endorsement of its clinical efficacy by an advisory committee, the FDA granted traditional approval to Lecanemab (Leqembi), a long-awaited new medication for treating mild cognitive impairment (memory and thinking problems) or mild dementia due to AD. Lecanemab slows the rate of disease progression by approximately 20-30% after 18 months, which translates to an approximately 6-months delay in symptom progression after 18 months, explained Barthel. It is licensed in the U.S., Japan, China, South Korea, Hong Kong, Israel, the United Arab Emirates and the UK. In November 2024, after re-examining its initial opinion, EMA's human medicines committee (CHMP) recommended to grant a marketing authorisation to Leqembi. EMA rejected a marketing request in July 2024 on the grounds that the side effects, including potential brain bleeding, outweighed the benefits. This is the reason why EMA's latest endorsement of Leqembi is limited to patients with a lower risk of potential brain bleeding.[vi]

Lecanemab has been hailed by Alzheimer's researchers and charities for being the first approved treatment that tackles the early stages of the disease, rather than managing the symptoms. Barthel also voiced his hopes at EANM'24 for the "therapeutic opportunity" and "great value" Lecanemab and Donanemab offer for patients with AD, whereby the latter is still not being available in Europe.

The latest approval of Lecanemab in Europe is a pivotel moment for tackling AD as it will further stimulate research into Alzheimer's and will expand the role of NM in the treatment of neurogenerative diseases to a greater extent.

Cornelia Wels-Maug,
November 29, 2024

REFERENCES

[i] https://academic.oup.com/epirev/article-abstract/30/1/15/623289?redirectedFrom=fulltext as seen on 3.11.2024

[ii] https://www.who.int/news-room/fact-sheets/detail/dementia as seen on 3.11.2024

[iii] https://www.who.int/news-room/fact-sheets/detail/dementia as seen on 3.11.2024

[iv] See NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease, in: Alzheimers Dement. 2018 Apr;14(4):535-562. doi: 10.1016/j.jalz.2018.02.018. https://pubmed.ncbi.nlm.nih.gov/29653606/s

[v] The Role of Amyloid Pet in Imaging Neurodegenerative Disorders: A Review, J Nucl Med. 2022 Jun;63(Suppl 1):13S–19S. doi:10.2967/jnumed.121.263195, https://pmc.ncbi.nlm.nih.gov/articles/PMC9165727/

[vi] See https://medicalxpress.com/news/2024-11-european-watchdog-partially-alzheimer-drug.html#:~:text=Britiain's%20medicines%20regulator%20approved%20lecanemab,Drug%20Administration%20early%20last%20year

3 | THE PERFORMANCE OF NUCLEAR MEDICINE IN STAGING BREAST CANCER – ABREAST OR AHEAD OF CONVENTIONAL IMAGING?

The role of FDG PET/CT in no special type breast cancer

Breast cancer (BC) is the most diagnosed cancer in women globally. Its heterogenous nature makes an accurate diagnosis and determination of the extent of the disease so crucial when deciding on the most effective treatment. While Nuclear Medicine (NM) does not replace conventional imaging (CI) in the staging, F^{18}-fluoarodeoxyglucose positron emission tomography/computed tomography (FDG PET/CT) has established itself as an important imaging technique that can provide functional insights into the disease's extent, especially in detecting regional lymph node involvement and evaluating distant metastases. Its use is guided by specific clinical scenarios and ongoing research into its effectiveness and optimisation in BC staging. To this end, further research into new tracers is progressing, with [^{68}Ga]/[^{18}F]-Fibroblast activation protein inhibitor (FAPI) showing promising results in the field of BC.

Breast cancer is the most commonly diagnosed cancer worldwide

According to the World Health Organization (WHO), there were 2.3 million women diagnosed with BC worldwide in 2022 and 670,000 died in that year from it.[i] BC is the most commonly diagnosed cancer globally today and is the most commonly diagnosed cancer in women.[ii] In 2022, BC effected individuals in every country of the world and in 157 out of 185 states it was the most common cancer type.[iii] The international Agency for Research on Cancer estimates that in in 2030, there will be 2.6 million incidences of BC in females worldwide and a mortality rate of 0.80 and it forecasts 3.16 million incidences of BC and a mortality of 0.98 in 2040[iv]. With approximately 99% of BC occuring in women and the remainder in men, being female is the strongest risk factor for developing BC.[v]

Breast cancer comes in many subtypes

BC is a heterogeneous disease that has a spectrum of subtypes with distinct biological and histological features that respond differently to treatment modalities and result in different clinical outcomes. In her presentation at the EANM'24 congress, Dr Elizabeth H. Dibble, MD, Associate Professor of Diagnostic Imaging, The Warren Alpert Medical School of Brown University, Rhode Island, USA, described the histologic subtypes of BC: invasive ductal, also referred to as no special type (NST) BC being the most prominent subtype (75-80%), followed by invasive lobular carcinoma (ICL; 10-15%) and special types (5%) like neuroendocrine, mucinous, tubular.

The four main biological subtypes of BC are based on the expression of hormone receptors (HR), including oestrogen receptors (ER) and/or progesterone receptors (PR) and levels of the human epidermal growth factor receptor 2 (HER2). Out of those four biological subtypes of BC, Dibble pointed out that luminal A (HR+/HER2- and low-grade/low proliferation) together with Luminal B (HR+/HER2- and high-grade/high proliferation) represent the highest case load (65%), with luminal B significantly less common than luminal A. Furthermore, HER2+ (HR+ or -/HER2+; 15-20%) and triple-negative (TN) subtypes (HR-, HER2-;10-15%) are less often encountered, but each of those subtypes tends to be faster growing and more aggressive than luminal A and luminal B[vi], whereby TN BC is the most difficult subtype to treat and the most lethal. BC can potentially spread to any organ, however, metastases occur most commonly in the skeleton, liver, lung and brain.

The importance of staging BC Nuclear imaging ahead of conventional imaging techniques

Due to the heterogenous nature of BC, an accurate diagnosis and determination of the extent of the disease as well as identifying prognostic factors are crucial for optimally managing the treatment of BC. NM plays a central role in this and so does exploring new tracers in combination with different imaging technologies to optimise the diagnoses: "It is critically important to stage and restage patients accurately to optimise treatment decisions, provide prognostic information and improve outcomes at all stages," Dibble reminded the audience. For this, the choice of the most appropriate imaging technology for each subtype of BC ¬as well as tracers in the case of nuclear (also referred to as molecular) imaging – are of outmost relevance and were the topic of many presentations during EANM'24.

Molecular imaging has become vital in BC as it allows non-invasive visualisation of the biological markers and potential therapeutic targets in both the primary carcinoma and metastases; however, it is not routinely used, although the importance of nuclear imaging in the primary diagnosis, locoregional and systemic staging, monitoring and predicting response to therapy as well as confirming progression or recurrence has been on the rise.[vii] This shift is closely linked to the growing interest in personalised medicine, including molecular targeted therapy, immunotherapy and theranostics.[viii]

A recently published article in the British Journal of Imaging clearly states the benefits of nuclear imaging over CI techniques: "As to BC diagnosis, radionuclide molecular imaging has demonstrated indisputable advantages over traditional anatomical imaging strategies that rely on finding the altered anatomical structure of breast tumors, such as mammography, ultrasound, magnetic resonance imaging (MRI), and computed tomography (CT)."[ix]

The role of FDG PET/CT in no special type breast cancer

Compared to CI techniques, "diagnostic radionuclide-based molecular imaging systems exhibit much greater sensitivity and ability to precisely illustrate the biodistribution and metabolic processes from a functional perspective in breast cancer,"[x] which can possibly secure an earlier diagnosis and prompt treatment.

A special focus at EANM'24 was the role of 2-[^{18}F]FDG PET/CT in NST BC, the most dominant of all forms of BC. FDG PET/CT visualises metabolic activity and as F^{18}-FDG uptake – respectively glucose metabolism – is elevated in malignant tumours, the scan can indicate the presence of metastatic disease that might not be apparent using CI. There is extensive evidence that 2-[^{18}F]FDG PET/CT can be useful in "initial staging, assessing neoadjuvant systemic treatment response, assessing treatment response in the metastatic setting, searching for loco-regional or metastatic recurrence, and re-staging after therapy, as well as radiation therapy (RT) planning."[xi]

In his presentation at EANM'24, Dr David Groheux, MD, PhD, Department of Nuclear Medicine, Saint-Louis Hospital, Paris, University Paris-Diderot, French National Institute of Health & Medical Research (INSERM), Paris, France, looked at different scenarios where FDG PET/CT has proven to be of particular value in managing NST BC, but also pointed out some limitations. He emphasised that FDG PET/CT is particularly well suited to detect regional lymph node involvement and distant metastases: "CI techniques like bone scintigraphy, liver ultrasound, chest X-ray, CE-CT are generally less effective than PET/CT," he explained. In literature it is documented that 2-[^{18}F]FDG PET/CT shows a better diagnostic accuracy to detect distant metastases of NST BC compared to a combination of CI techniques. This is due to its higher sensitivity (97–99% vs 56–75%) and specificity (95–99% vs 88–99%).[xii]

Furthermore, 2-[^{18}F]FDG PET/CT has been a useful tool for response assessment, allowing for early identification of non-responding tumours, providing information regarding adverse therapeutic effects, and defining the right moment to implement changes in therapeutic approach or shift to a subsequent line of treatment with benefits of disease control and cost-effectiveness.[xiii] In this way, 2-[^{18}F]FDG PET/CT plays its part in advancing personalised medicine.

Considering the baseline staging of breast cancer, Groheux referred to two American studies which showed that staging based on 2-[^{18}F]FDG PET/CT came at no additional costs. He also pointed out that the

mean cost was lower with 2-[^{18}F]FDG PET/CT compared to staging with a combination of CI. Furthermore, he quoted a study which demonstrated that the radiation dose was lower for 2-[^{18}F]FDG PET/CT than CI (14 mSv versus 21mSv).

However, 2-[^{18}F]FDG PET/CT also has limitations."For Stage I breast cancer, 2-[^{18}F]FDG PET/CT is not suitable as it can have false positive results," explained Groheux. This can be caused by inflammation, infection or benign lesions such as fibroadenoma or intraductal papilloma. There are also causes for false negatives results, such as small lesions, low-grade tumours or specific histological subtypes such as the lobular histology.[xiv]

The world's leading nuclear medicine societies endorse FDG PET/CT for NST breast cancer

Until recently, there were many published articles on the role of F-^{18} FDG-PET/CT in patients with NST BC, but leading international NM societies had not been involved in the development of international guidelines on this subject. Hence, experts from EANM and the Society of Nuclear Medicine and Molecular Imaging (SNMMI) along with representatives in the field of BC (American College of Radiology (ACR), European Society of Surgical Oncology (ESSO), European Society for Radiotherapy and Oncology (ESTRO), European Society of Breast Imaging/European Society of Radiology (EUSOBI/ESR) European Society of Breast Cancer Specialists (EUSOMA)) jointly worked on and published a new, multidisciplinary guideline on the topic. It was released on 14 May 2024.[xv]

Following literature review and expert discussions, the guideline came to the verdict that quantitative PET features were valuable prognostic parameters, whereby 2-[^{18}F]FDG PET/ CT plays a role from stage IIB through stage IV in baseline staging. It also advises: "When assessing response to therapy, 2-[^{18}F]FDG PET/ CT should be performed on certifed scanners, and reported either according to PERCIST, EORTC PET, or EANM immunotherapy response criteria, as appropriate."[xvi] 2-[^{18}F]FDG PET/CT may be useful to assess early metabolic response, particularly in non-metastatic triple-negative and HER2+ tumours. 2-[^{18}F]FDG PET/ CT is useful to detect the site and extent of recurrence when conventional imaging methods are equivocal and when there is clinical and/or laboratorial suspicion of relapse. Recent developments are promising."[xvii]

Overall, the authors concluded: "2-[^{18}F]FDG PET/CT is extremely useful in BC management, as supported by extensive evidence of its utility compared to other imaging modalities in several clinical scenarios."[xviii]

Will FAPI replace FDG?

Molecular imaging is evolving constantly, hence, EANM maintains that the latest guidelines should be viewed as a dynamic document rather than a definitive document. In the field of tracers, some radiopharmaceuticals have been around for more than 50 years, and new tracers are being developed and tested at the same time. One especially promising tracer being FAPI. Preliminary results using the FAP-targeted PET tracer FAPI in BC patients showed significantly higher tracer uptake compared with 2-[^{18}F]FDG in the primary tumour as well as in the metastatic disease. It might be particularly useful in the detection of brain metastatic lesions, due to the low physiologic uptake of [^{68}Ga]FAPI,[xix] which is a beacon of hope and will need further investigations.

Cornelia Wels-Maug,
December 14, 2024

REFERENCES

[i] https://www.who.int/news-room/fact-sheets/detail/breast-cancer

[ii] Current and future burden of breast cancer: Global statistics for 2020 and 2040, Breast. 2022 Sep 2;66:15–23. doi:10.1016/j.breast.2022.08.010, https://pmc.ncbi.nlm.nih.gov/articles/PMC9465273/#:~:text=With%20over%202.3%20million%20new,most%20commonly%20diagnosed%20cancer%20worldwide.&text=Most%20cases%20occur%20in%20transitioned,share%20of%20breast%20cancer%20deaths.

[iii] https://www.who.int/news-room/fact-sheets/detail/breast-cancer

[iv] https://gco.iarc.who.int/tomorrow/en/dataviz/isotype?years=2040&cancers=20&single_unit=100000

[v] https://www.who.int/news-room/fact-sheets/detail/breast-cancer

[vi] DePolo Jamie, Molecular Subtypes of Breast Cancer, https://www.breastcancer.org/types/molecular-subtypes

[vii]See Musket A, Davern S, Elam BM, Musich PR, Moorman JP and Jiang Y (2024) The application of radionuclide therapy for breast cancer. Front. Nucl. Med. 3:1323514. doi: 10.3389/fnume.2023.1323514

[viii]See Musket A, Davern S, Elam BM, Musich PR, Moorman JP and Jiang Y (2024) The application of radionuclide therapy for breast cancer. Front. Nucl. Med. 3:1323514. doi: 10.3389/fnume.2023.1323514

[ix]Musket A, Davern S, Elam BM, Musich PR, Moorman JP and Jiang Y (2024) The application of radionuclide therapy for breast cancer. Front. Nucl. Med. 3:1323514. doi: 10.3389/fnume.2023.1323514

[x]Musket A, Davern S, Elam BM, Musich PR, Moorman JP and Jiang Y (2024) The application of radionuclide therapy for breast cancer. Front. Nucl. Med. 3:1323514. doi: 10.3389/fnume.2023.1323514

[xi]Vaz, S.C., Woll, J.P.P., Cardoso, F. et al. Joint EANM-SNMMI guideline on the role of 2-[^{18}F]FDG PET/CT in no special type breast cancer. Eur J Nucl Med Mol Imaging 51, 2706–2732 (2024). https://doi.org/10.1007/s00259-024-06696-9 https://link.springer.com/article/10.1007/s00259-024-06696-9#citeas

[xii]See Vaz, S.C., Woll, J.P.P., Cardoso, F. et al. Joint EANM-SNMMI guideline on the role of 2-[^{18}F]FDG PET/CT in no special type breast cancer. Eur J Nucl Med Mol Imaging 51, 2706–2732 (2024). https://doi.org/10.1007/s00259-024-06696-9 https://link.springer.com/article/10.1007/s00259-024-06696-9#citeas

[xiii]Vaz, S.C., Woll, J.P.P., Cardoso, F. et al. Joint EANM-SNMMI guideline on the role of 2-[^{18}F]FDG PET/CT in no special type breast cancer. Eur J Nucl Med Mol Imaging 51, 2706–2732 (2024). https://doi.org/10.1007/s00259-024-06696-9 https://link.springer.com/article/10.1007/s00259-024-06696-9#citeas

[xiv]See Vaz, S.C., Woll, J.P.P., Cardoso, F. et al. Joint EANM-SNMMI guideline on the role of 2-[^{18}F]FDG PET/CT in no special type breast cancer. Eur J Nucl Med Mol Imaging 51, 2706–2732 (2024). https://doi.org/10.1007/s00259-024-06696-9 https://link.springer.com/article/10.1007/s00259-024-06696-9#citeas

[xv]Vaz, S.C., Woll, J.P.P., Cardoso, F. et al. Joint EANM-SNMMI guideline on the role of 2-[^{18}F]FDG PET/CT in no special type breast cancer. Eur J Nucl Med Mol Imaging 51, 2706–2732 (2024). https://doi.org/10.1007/s00259-024-06696-9 https://link.springer.com/article/10.1007/s00259-024-06696-9#citeas

[xvi]Vaz, S.C., Woll, J.P.P., Cardoso, F. et al. Joint EANM-SNMMI guideline on the role of 2-[^{18}F]FDG PET/CT in no special type breast cancer. Eur J Nucl Med Mol Imaging 51, 2706–2732 (2024). https://doi.org/10.1007/s00259-024-06696-9 https://link.springer.com/article/10.1007/s00259-024-06696-9#citeas

[xvii]Vaz, S.C., Woll, J.P.P., Cardoso, F. et al. Joint EANM-SNMMI guideline on the role of 2-[^{18}F]FDG PET/CT in no special type breast cancer. Eur J Nucl Med Mol Imaging 51, 2706–2732 (2024). https://doi.org/10.1007/s00259-024-06696-9 https://link.springer.com/article/10.1007/s00259-024-06696-9#citeas

[xviii]Vaz, S.C., Woll, J.P.P., Cardoso, F. et al. Joint EANM-SNMMI guideline on the role of 2-[^{18}F]FDG PET/CT in no special type breast cancer. Eur J Nucl Med Mol Imaging 51, 2706–2732 (2024). https://doi.org/10.1007/s00259-024-06696-9 https://link.springer.com/article/10.1007/s00259-024-06696-9#citeas

[xix]Vaz, S.C., Woll, J.P.P., Cardoso, F. et al. Joint EANM-SNMMI guideline on the role of 2-[^{18}F]FDG PET/CT in no special type breast cancer. Eur J Nucl Med Mol Imaging 51, 2706–2732 (2024). https://doi.org/10.1007/s00259-024-06696-9 https://link.springer.com/article/10.1007/s00259-024-06696-9#citeas

4 | THE ONGOING QUEST OF NUCLEAR MEDICINE TO BETTER DIAGNOSE INFECTIONS

Infectious diseases are on the rise worldwide and are one of the leading causes of morbidity and mortality. Globally they accounted for **7.7 million deaths in 2019**, representing 14% of the 55 million people who died that year. Infections are caused by pathogenic microorganisms, such as bacteria, viruses, parasites or fungi. Alongside well-known infections such as tuberculosis, HIV, pneumonia or malaria, there are new infectious diseases emerging, with COVID-19 being the most prominent case in point in recent years. To start the appropriate treatment, it is crucial to diagnose infectious diseases at an early stage and to evaluate treatment efficacy as soon as possible to avoid more suffering, transmission and resistance. However, a major challenge for their diagnoses is to differentiate infection from inflammation and cancer. Further developments both in imaging devices as well as in pathogen-specific infection and inflammation tracers will be needed to achieve this goal.

Challenges in diagnosing infections

Traditionally, the diagnosis and treatment evaluation of an infectious disease are based on clinical findings, histological and/or microbiological results and laboratory parameters. At the recent EANM'24 Congress in Hamburg, Prof. Sanjay K. Jain, MD, Director Center for Infection and Inflammation Imaging Research, Johns Hopkins University School of Medicine, US, epitomised the challenges of using clinical samples and the limitations they entail: "The fundamental problem in infectious diseases is that despite the massive explosion of molecular tests, which have completely revolutionised how we diagnose infections, we still need clinical samples." And the latter come with drawbacks as clinical constitutional symptoms and laboratory parameters are often non-specific and biopsies may not always be feasible or come at the risk of an invasive procedure and contamination. Moreover, there is the likelihood of a sampling bias to occur as no view on the whole organ respectively body of the disease is available. In view of these shortcomings Jain proposed: "So, why not take a picture instead?"

Nuclear imaging techniques overcome the limitations of structural imaging techniques

Diagnosing infectious diseases with structural imaging modalities like radiography, sonography, computed tomography (CT) and magnetic resonance imaging (MRI) have come to play an important clinical role. However, for diseases that do not have structural anatomic abnormalities or only manifest in later stages, these modalities do not provide sufficient diagnostic information.

Advanced diagnostics of infections with the help of PET and PET/CT

Nuclear medicine (NM) imaging techniques can complement structural modalities and overcome their deficiencies to a certain extend. Positron emission tomography (PET), which detects functional changes even at an early stage, has proved particularly helpful in diagnosing infections and in evaluating treatment responses after a few days or weeks. Jain pointed out that the advantage of PET over traditional diagnostic approaches in relation to infection is its speed, sensitivity and whole-body analysis capabilities. Moreover, integrating PET and CT into a PET/CT scanner allows to simultaneously image functional and anatomical changes without moving the patient and perform a more accurate localising of lesions.

PET tracers: Limitations and new approaches

PET scans use radiotracers injected into the patient prior to the scan to visualise blood flow and metabolic and biochemical activities in diseased and healthy tissues. Fludeoxyglucose ^{18}F (^{18}F-FDG) is the most

universal used PET tracer.[i] After injection into the body, it is distributed in the tissue and taken up by cells that have a high sugar turnover.

The tracer ^{18}F-FDG also has limitations, especially the lack of specificity of its uptake: Infectious and inflammatory conditions show increased ^{18}F-FDG uptake and so do immune cells and cancer cells. This makes the differentiation between infection and inflammation respectively infection and cancer difficult and, therefore, complicates the diagnoses. Another complication is the physiological uptake of ^{18}F-FDG especially in the brain, the intestines and the urinary tract. This confines the chances to detect infection in those organs/tissues. Also, diagnosing an infection shortly after surgery or radiation therapy can be problematic as cells involved in the wound healing process and granulation tissue have a potentially higher tracer uptake. Further limitations concern the reactive uptake due to foreign body material that can occur in, e.g., vascular grafts, orthopaedic implants or prosthetic heart valves, as well as cases where the intake of some medications, including antibiotics, in combination with ^{18}F-FDG can deter from diagnosing an infection.[ii] Jain exemplified: "The biggest challenge is to enrol patients in our studies early on when they have not received a lot of antibiotics, but it is very hard to find these patients as there is a high likelihood for them to be already on a course of antibiotics to improve their condition."

New horizons: developments in imaging devices and pathogen-specific tracers

The field of NM has developed fast over recent years. This resulted in progress made in the creation of new radiopharmaceuticals that allow to move closer to an unambiguous diagnosis of infections and in the sphere of imaging systems – resulting in higher sensitivity.

Development of pathogen-specific tracers

NM has led to a better understanding of the tumour biology,[iii] including insights on how to target cell subpopulations and molecules involved in infectious and inflammatory lesions. This knowledge has been used to try to overcome the shortcomings of ^{18}F-FDG. Jain illustrated how his lab had started a decade ago to develop bacteria-specific imaging tracers approaches that targeted small molecules that are metabolised preferentially and could be used as tracers for:

- Specific detection and localisation of all bacterial classes, e.g., para-aminobenzoic acid (PABA)
- Identify a specific bacterial class causing infection in situ, e.g., fluorodeoxysorbitol
- Rapidly detect therapeutic failures that could be associated with drug-resistant organisms.

So far, the first-in-human ^{11}C-PABA PET studies at Johns Hopkins proved it was safe, well-tolerated and had a favourable biodistribution, with low background activity in the lungs, muscles and brain. Therefore, this technology has potential for clinical translation to detect and localise a broad range of bacteria. ^{18}F-Fluorodeoxysorbitol (^{18}F-FDS) has also been tested in humans and shown to be safe. Additionally, ^{18}F-FDS PET was also able to detect and localize infections in patients and differentiate them from cancer or non-infectious inflammatory diseases.

Although there is substantial interest in developing pathogen-specific tracers for bacteria and fungi, clinical studies are needed to validate the preclinical studies to test the sensitivity and specificity of the new approaches and to evaluate how they change clinical practice: "If an approach isn't practical or too expensive or only available to very few, it doesn't help," concludes Jain.

So far, a lot of work with these tracers has been done in the animal domain, but only a limited number of tracers have been tested on humans. Jain urges to move things form the preclinical world to the clinical world and encourages the European audience to do so: "It is very critical that we take these tracers into the clinic and I think it might be easier done in Europe than in the US."

In a next step, NM could not only be able to determine that there is an infection but also, which bacteria is causing it (Gram positive or Gram negative). This would enable a swift start of an effective antibiotic treatment early on.

PET/MRI scans

The fully integrated whole-body PET/MRI system was introduced for research purposes in 2010 and approved for clinical applications shortly after. The indications for PET/MRI have emerged in areas where PET and MRI were already commonly employed as complementary imaging techniques. As of 15 April 2023, there were 47 scanners installed in a total of 18 countries, the majority located in Europe and particularly in Germany and France, explained Prof. Dr. Martina Sollini, Associate Professor in Diagnostic Imaging and Radiotherapy, Faculty of Medicine and Surgery, Vita-Salute San Raffaele University, Milan, Italy.

Based on the number of research papers published between 2018 and 2022, Sollini pointed out that the use of PET/MRI for research purposes has been mainly in the field of inflammation. Only one sixth of the overall publication in that timeframe focused on infection. Overall, all papers included in the review centred on diagnosing infections with the help of the ^{18}F-FDG tracer. Between 2022 and 2024, seven additional studies were published, primarily focusing on bone and joint infections, with some exploring new radiopharmaceuticals.

Overall, Sollini's metastudy showed a high diagnostic performance of PET/MRI in infection, with bone & joint being the main field of application and SUV-based ratios been proven helpful. So far, there is insufficient data to mention PET/MRI in guidelines and no data on paediatric population exists. Also, no biomarkers could be identified that would add metabolic information to perfusion, diffusion or other signals. Despite its high diagnostic performance in infection, it has still limited clinical use. The high price of a PET/MRI scanner, its complexity and the long scanning time have until now confined it as a research tool. In the future, faster scanners, in addition to new clinical settings plus quantitative hybrid biomarkers and artificial intelligence will make it more suited for the clinical routine.

More recent advances in nuclear imaging – LAFOV PET/CT

The latest development in the field of scanners is the long axial field-of-view (LAFOV) PET/CT scanner. It shows a substantial increase in sensitivity, enables faster scanning with a significant reduction in injected activity, and, hence, a lower administered radiotracer dose. Prof. Dr. Andor Glaudemans, Professor in MultiModality Imaging of Infections and Inflammatory Diseases, University Medical Center Groningen, the Netherlands, emphasizes the high sensitivity of the scanner: "The sensitivity increase is up to 40 times over that of a conventional PET." It remains to be seen, how many bacterial colonies can be detected with it, said Glaudemans.

The higher sensitivity of the LAFOV PET/CT results in an increased lesion detectability, while it renders delayed scanning of satisfying diagnostic accuracy possible. Furthermore, for the first time, whole-body dynamic imaging becomes possible, which helps to better differentiate between infection and inflammation. Glaudemans explained that if the ^{18}F-FDG uptake increases in time, it is an infection, whereas a stable tracer uptake indicates an inflammation.

He concludes that LAFOV/PET/CT scanners offer several unique advantages for the imaging of infections and inflammations and that the best protocol in terms of level of activity, scanning time and use of dynamic imaging must be tailored to the patient. However, on the roadmap for its implementation, the largest hurdle will be to convince decision makers as to why they should purchase such an expensive system. Other considerations will include the adaption of the infrastructure in the hospital in such a way that it takes into account the need for more waiting rooms.

Taking all this into consideration, Gaudemans concluded at the EANM'24 Congress: "The holy grail for inflammation & infection imaging is within our reach!" This is a big step forward.

Cornelia Wels-Maug,
November 19, 2024

REFERENCES

[i] See https://www.mdpi.com/2075-4418/13/12/2018 as seen on 28.10.24

[ii] See for more details: https://www.frontiersin.org/journals/medicine/articles/10.3389/fmed.2023.1149925/full as seen on 24.10.2024

[iii] See https://www.mdpi.com/2075-4418/13/12/2018 as seen on 28.10.2024

5 | NUCLEAR CARDIOLOGY – A NUCLEAR PERSPECTIVE ON MATTERS OF THE HEART

Nuclear imaging modalities for quantifying myocardial blood flow

Nuclear cardiology is a specialised field in nuclear medicine that evaluates the heart function to help diagnosing conditions such as coronary artery disease and to assess treatment efficacy, whilst minimising invasive procedures like biopsies. More recently, clinicians have increasingly opted for nuclear imaging over endomyocardial biopsy to diagnose cardiac amyloidosis, allowing for earlier detection of the disease. Myocardial perfusion imaging (MPI), essential in assessing blood flow to the heart muscle, plays a critical role in identifying coronary artery disease and requires scans for accurate diagnosis. While positron emission tomography (PET) is the gold standard for myocardial blood flow (MBF) quantification, the limited availability of PET scanners has led to growing interest in single-photon emission computed tomography (SPECT) as a viable alternative, though further validation and standardisation are necessary. The future of nuclear cardiology looks promising with advancements in radiopharmaceuticals, such as the recently FDA-approved F^{18}-Flurpiridaz, and the integration of artificial intelligence to streamline quantitative assessments in cardiac PET-MPI.

What is nuclear in cardiology?

Nuclear cardiology is a subspeciality of general cardiology that evaluates how organs function. Unlike conventional imaging methods like X-rays, magnetic resonance imaging (MRI) or computed tomography (CT), which primarily visualise the physical structure of tissues and organs, it captures a wide range of metabolic processes.

Using radioactive substances that are administered in extremely small quantities and, as a rule, hardly differ from the substances naturally occurring in the organism, the function of organs, tissues and bones examined is practically not affected, but only observed. Nuclear cardiology can help to evaluate, diagnose and treat heart conditions in a noninvasive way and therefore avoids potential risks associated with a biopsy.

Nuclear cardiology imaging tests are used to determine respectively monitor:

- whether a patient's heart-related symptoms are due to coronary artery disease or atherosclerosis
- if there is adequate blood flow to the heart muscle during stress versus rest. A restricted blood flow from the left ventricle to the aorta, for example, can lead to increased pressure in the heart and reduced oxygen supply to the body. This is called an aortic valve stenosis, a medical condition characterised by the narrowing of the aortic valve opening
- whether a person is at risk of a heart attack and needs angioplasty or coronary artery bypass graft (CABG) surgery
- a patient's condition after CABG surgery or a cardiac catheterisation procedure
- establish the presence along with the severity of prior heart attacks (size and location) as well as the risk of future heart attacks
- evaluate how well a heart is pumping, which could indicate cardiomyopathy, heart injury or an infection
- the effects of chemotherapy or medications on a patient's heart.

This information will help clinicians to decide more accurately on the most appropriate treatment options to take.

Nuclear imaging challenges endomyocardial biopsy

Nuclear imaging as an alternative diagnostic approach has become more popular among clinicians who suspect cardiac amyloidosis in their patients rather

than performing an endomyocardial biopsy (EMB).[i] Cardiac amyloidosis is a protein-folding disorder that can result in heart failure. Amyloid can be formed from many different precursor proteins, with the most common ones in the cardiac field being immunoglobulin-derived light chains – causing AL amyloidosis – and transthyretin (TTR) proteins – causing ATTR amyloidosis.[ii] Differentiating these two forms of cardiac amyloid is vital in determining prognosis and treatment of the disease. Doing so with nuclear imaging scans has led to earlier detection of the disease.

Until recently, endomyocardial biopsy was "considered the gold standard for diagnosing cardiac amyloidosis and differentiating amyloid subtypes, but its use is limited because of the invasive nature of the procedure, with risks for complications and the need for specialized training and centers to perform the procedure. Radionuclide cardiac imaging has recently become the most commonly performed test for the diagnosis of ATTR amyloidosis but is of limited value for the diagnosis of AL amyloidosis," are the findings of a 2021 publication that investigated the role of nuclear imaging for the diagnosis of cardiac amyloidosis. The authors of the study expect that diagnosing cardiac amyloidosis with PET will expand in the future, supported by imaging protocols being under refinement to achieve better quantification of the disease burden and prediction of prognosis.

Myocardial perfusion imaging at the core of nuclear cardiology

MPI, also known as a nuclear stress test, is the most widely performed procedure in the field of nuclear cardiology. It assesses how well the blood flows to the heart muscle to diagnose and evaluate coronary artery disease (CAD). The latter occurs when the arteries supplying blood to the heart become narrowed or blocked. This clinically important assessment of cardiac function and amount of heart muscle at risk allows cardiologists to identify patients who need further testing or require medical procedures.

A myocardial perfusion scan is performed, for example, after a heart attack to identify areas of damaged heart muscle. Typically, MPI requires two scans — one at rest and one during exercise (walking on a treadmill or riding a stationary bike). Patients with mobility issues can be given an infusion of an intravenous pharmacological stressing agent like regadenoson, dipyridamole or adenosine. The scans reveal, which regions of the heart are healthy or injured: Areas that have absorbed the tracer are considered healthy, whereas those that have not absorbed the tracer can be regarded as damaged or lacking in good blood flow. In this context, Prof Tim P. van de Hoef, MD, PhD, Interventional Cardiologist, University Medical Centre Utrecht, the Netherlands, pointed out at EANM'24 the results of recent studies assessing the physiology of myocardial blood flow using pharmacological agents to stress the coronary system: "We know from extensive studies in animal experiments and more recently in human studies that using those dilaters substances creates different physiological responses than during exercise during which most patients actually experience their symptoms. More research needs to go into this."

Physiological aspects of myocardial blood flow

Van de Hoef also shared some helpful background on the physiology of MBF: "The metabolic demand of the heart increases when we exercise, primarily via an increase in the heart rate; with the rise in metabolic demand primarily accommodated through an increase in myocardial blood flow." This increase in blood flow is primarily generated through a decrease in microvascular resistance, he said. Van de Hoef pointed out a healthy heart's ability of autoregulation, which he described as the "ability of the heart to maintain a constant flow in the face of a change in perfusion pressure whilst the myocardial metabolism remains unchanged." Van de Hoef added: "Eighty percent of increase in oxygen supply to the heart muscle upon exercise is determined by an increase in coronary flow and only 20% in increase in oxygen extraction." Referring to a meta-study that included 59,740 individuals, van de Hoef emphasised that a reduction in coronary flow reserve was strongly associated with an increase in mortality and a rise in major adverse cardiovascular events. He remarked: "Pathological changes in all compartments of the coronary circulation can lead to depletion of reserve vasodilator capacity."

Quantifying myocardial blood flow with PET or SPECT?

Multiple nuclear imaging modalities may be used to perform an MPI. They all have in common that they are preventative and minimal invasive techniques used to diagnose and assess heart conditions. Using nuclear stress tests to determine the medical condition of a heart is an essential step to take before deciding which method of medical treatment is indicated. However, the nuclear stress test can be performed using different nuclear imaging modalities. At EANM'24 in Hamburg, a particular focus was around the performance of PET/CT and SPECT for performing MPI. Both PET/CT and SPECT are effective in evaluating blood flow. However, PET is still regarded as the reference standard for flow quantification, said Dr Laetitia Imbert, PhD, Medical Physicist, University Hospital CHRU Nancy, France. However, the number of PET scanners in Europe is not sufficient to cover the request for PET scans, remarked Prof Wanda Acampa, Assistant Professor, Federico II University Hospital, Naples, Italy. She also added that this could be a crucial driver for a shift from PET to SPECT for clinical use in nuclear cardiology as PET scanners are hardly used for cardiological imaging, but rather for oncological scans.

Given the limited capacity of doing PET-MPI scans in Europe, especially in the field of cardiology, researchers explore the role of SPECT-MPI as an alternative, an area Imbert has been working on: "The quantification of myocardial blood flow with PET it is already well validated with the cardiac PET tracers 82Rb,13N, 15O-water. But there are some potential advantages of SPECT imaging, including the better availability of SPECT cameras in comparison to PET cameras." Imbert also said, tracers for PET perfusion were expensive and not widely available unlike the tracers used for SPECT that also come at lower costs. "It is more and more interesting to try to quantify the myocardial blood flow using SPECT systems. SPECT is more widely used for myocardial perfusion imaging", Imbert remarked.

The quantification of MBF with SPECT could be potentially useful, especially for patients with severe coronary artery disease. For performing dynamic SPECT imaging, it needs multidetector systems with fast acquisition of dynamic data in 5-10 sec, but also a tracer with a high enough myocardial flow extraction fraction at high flow rate, as well as advanced reconstruction methods. "With the dynamic acquisition and dynamic reconstruction, we will have many frames with a short time acquisition, and this will increase the noise in the reconstruction. The development of models, algorithms and data processing methods will become increasingly important to enable dynamic SPECT with a good kinetics analysis but also to obtain accurate results," Imbert explained. She also added that for the quantification of MBF with SPECT, the focus had switched to cadmium zinc telluride (CZT) solid- state systems with dedicated cameras to perform cardiac investigations and more recently to whole-body 360-degree CZT systems. These CZT cameras facilitate the determination of MBF due to their higher sensitivity compared to the conventional SPECT, resulting in higher image quality and an enhancement in the spatial resolution (which is linked to the pixelated size of pixelated detectors). Imbert concluded: "PET is still the reference standard for flow quantification, but CZT SPECT is an alternative for flow quantification although further validation work is required before full clinical acceptance." She pointed to the large variability among dynamic cardiac SPECT imaging in the literature with regards to variations in the acquisition duration and temporal framing, algorithms used for the image correction and reconstruction in addition to some discrepancies related to the post-processing. She urged: "Standardisation is required to achieve reproducible and accurate quantification."

Outlook

The expected growth of radiopharmaceutical options for PET in the near future promises to rapidly expand access options to PET-MPI and likely reduce the costs of PET-MPI.

The introduction of the novel PET-MPI agent F^{18}-Flurpiridaz, which recently gained approval by the U.S. Food and Drug Administration (FDA), is seen as a positive sign for the growth of PET-MPI. It is the first new radiotracer for nuclear cardiology for use in adult patients with known or suspected coronary artery disease to evaluate for myocardial ischemia and infarction in nearly three decades.

Furthermore, many of the challenging quantitative tasks for cardiac PET-MPI will continue to be simplified and automated by using artificial intelligence.

Cornelia Wels-Maug,
January 15, 2025

REFERENCES

[i]See Li W, Uppal D, Wang YC, Xu X, Kokkinidis DG, Travin MI, Tauras JM. Nuclear Imaging for the Diagnosis of Cardiac Amyloidosis in 2021. Diagnostics (Basel). 2021 May 30;11(6):996. doi: 10.3390/diagnostics11060996. PMID: 34070853; PMCID: PMC8228334. https://pmc.ncbi.nlm.nih.gov/articles/PMC8228334/

[ii]See Li W, Uppal D, Wang YC, Xu X, Kokkinidis DG, Travin MI, Tauras JM. Nuclear Imaging for the Diagnosis of Cardiac Amyloidosis in 2021. Diagnostics (Basel). 2021 May 30;11(6):996. doi: 10.3390/diagnostics11060996. PMID: 34070853; PMCID: PMC8228334. https://pmc.ncbi.nlm.nih.gov/articles/PMC8228334/

6 | PATIENT-CENTRED CARE IN STEP WITH THE UNFOLDING ROLE OF NUCLEAR MEDICINE

Patient-centred care (PCC), sometimes also referred to as both people-centred and person-centred care, is recognised as a central element to improve the quality of healthcare. It is based on the principle of actively involving patients in their own care and decisions affecting both diagnostic and therapeutic options. However, to enable such shared decision-making, a step change in the relationship between healthcare providers and patients is required: the former need to support the latter with relevant information tailored to different patient groups and the opportunity of dialogue between patients and clinicians. This development is in tune with the unfolding role of nuclear medicine (NM) physicians as their gamut of expertise is evolving from mainly offering diagnostic imaging services to also treating patients. So far, there are only few studies on the effects of implementing PCC in the field of NM, but the documented benefits are encouraging.

The heart of patient-centricity

PCC strives to integrate "preferences, values, and beliefs of the person into the process of decision-making, producing a treatment plan that is both appropriate and meaningful for the patient. It supports the role of patients making informed and active choices, rather than remaining passive recipients of their care."[i]

The concept of PCC has implications for the patient-doctor relationship with physicians now designing a care path that is more tailored to the patient's preferences. The success of a treatment no longer hinges only upon the accuracy of the diagnostic tests and the effectiveness of the administered treatment, but also on the quality of patient experience and the cooperation of the patient with the healthcare team.

At the EANM'24 congress, Dr Erik Briers, MS PhD, Vice Chairman Europa Uomo, The European Prostate Cancer Coalition, provided the patient perspective on PCC: "Patient-centred nuclear medicine from the patient's view requires treating persons with dignity and respect and involving them in all decisions about their health." He emphasised how important it is for clinicians to find out what the patient wants. As NM physicians mainly treat cancer patients, a cure might not always be in the realm of the possible. In these cases, patients want to have control over the progression of their disease and wish for a good quality of life, full well knowing, "that they cannot have their old life back," explained Briers. Under these constrained circumstances, Briers, thriving for an optimal quality of life implies the choice of an evidenced-based treatment plan that delivers maximum benefits at minimum side effects and is accessible, available, and affordable for the patient. This also includes quality at the end of life.

Shared decision-making needs informed patients

For patients to be involved in deciding on their treatment, they need to have a certain level of understanding of their disease, the available diagnostic and therapeutic options and the associated risks and benefits. To this end, Dr Glenn Flux, Head of Radioisotope Physics, The Royal Marsden and The Institute of Cancer Research, UK, shared his experience with patient education strategies at the EANM'24 congress. He described how the Royal Marsden had been exploring a communication approach to interact with patients during a clinical trial. This included the creation of patient information material addressing relevant aspects of NM for diverse levels of comprehension, including information sheets for patient advocacy groups ("What is Radiation?", "Types of ionising radiation"): flux felt that many complex patient information sheets that accompany clinical trials are often too "long and turgid" – and that many information booklets are aimed at a low reading age. Patient information was supported by the opportunity for personal discussion (face to face or by phone) which he thought essential for informing and educating patients. Flux also pointed out that asking

patients for feedback on the helpfulness of those educational texts and how they experienced the treatment had been crucial to make informed changes of the trial protocol to strike a better balance between scientific validation and patients' preferences. In one clinical trial, it led to exposing patients to less radiation.

To further ease the spread of information Flux also proposed to the audience to consider exploring, e.g., the use of social media whilst not replacing human interactions; involving all care team members into the PCC model and to stratify educational material into six to eight layers of complexity so that patients can choose for themselves.

Another means of informing patients is the opportunity to learn from other patients' experience. This can be achieved via the involvement of patient advocacy organisations. At EANM'24, Cybil Nielsen, MBA, CNMT, FSNMMI-TS, nuclear medicine educator at Gurnick Academy of Medical Arts, USA, 2024-25 president-elect for the Society of Nuclear Medicine and Molecular Imaging Technologist Section (SNMMI-TS), highlighted the benefits of patient advocacy groups: "By partnering with different medical societies, patient advocacy groups assist with writing guidelines, serve as a support and education network for patients, help joint research initiatives, advance reimbursement and access to care issues." She emphasised the significance of incorporating patients' voices: "A patient's word has a huge impact; it is more powerful than that of a physician or an industry group."

Leading healthcare organisations endorse PCC

The World Health Organisation (WHO) has been encouraging healthcare providers to implement the concept of PCC into their medical practice and other leading healthcare organisations like the National Institute for Health and Clinical Excellence and the American Heart Association have done the same.[ii] In a 2015 strategy paper, the WHO endorsed the principles of PCC: "Developing more integrated people-centred care systems has the potential to generate significant benefits to the health and health care of all people, including improved access to care, improved health and clinical outcomes, better health literacy and self-care, increased satisfaction with care, improved job satisfaction, improved efficiency of services, and reduced overall costs."[iii]

Although there is no consensus as to exactly which parameters should be included in the definition of PCC – which makes it more difficult to assess the effects of implementing PCC into clinical practice on a larger scale – PCC is associated with more engaged patients, improved patient experience whilst cutting the number of admissions, readmissions and the length of hospital stay. Additionally, it not only results in professional improvements but also in higher patient loyalty, better disease control, heightened treatment adherence, reduced patients' anxiety and increased organisational efficiency.[iv]

The benefits of patient-centred care in nuclear medicine – patient experience soars

Nevertheless, so far, few studies have evaluated the application of PCC in the field of NM. According to a 2024 publication, "A scoping review of person-centred care strategies in diagnostic Nuclear Medicine," this type of research is missing. A part of the review analysed a subgroup of 39 relevant papers that focused on patients only and for those the authors concluded that applying PCC in the field of NM resulted in improved patient experience (76%), growth both in patient comfort (13.2%) and patient knowledge (5.7%) as well as a decrease in patient anxiety (9.4%) and waiting/scan time (3.8%).

In 2005, Renee M. Moadel, MD, MSc, Associate Professor of Radiology and Director for the Nuclear Medicine Residency Program, Montefiore Medical Center New, York, USA, started a patient consultation programme in the NM department which was built around PCC principles. The programme involves directly meeting patients ahead of their initial treatments to explain the care plan, address any concerns and questions and ensure that the patients are "mentally, physically, and emotionally"[vi] prepared to undergo the treatment. A 2018 evaluation of this programme measured the radiologists' impact on patients understanding of radiology procedures, nuclear medicine in general as well as patients' knowledge and feelings regarding their condition and therapy. The results of the review are encouraging as patients are more prepared for

treatment, have a better understanding of their care plan and are less anxious after speaking directly with a NM physician. For example, 32% of surveyed patients reported prior to the consultation to be anxious about their upcoming treatment whereas afterwards almost 90% of them related that they felt "generally" or "perfectly" calm.[vii] Overall, the programme has been a success: "[…] the consultations resulted in a smoother, less stressful treatment process for patients and physicians and quickly became the standard of care at Montefiore for thyroid cancer therapy as well as other nuclear medicine treatments."[viii]

The unfolding role of nuclear medicine physicians

That the topic of PPC made it onto the agenda of the EANM'24 congress is a testimony to the changing role of NM in the treatment of patients – a point referred to many times throughout the event. The growing relevance of theranostics, where NM physicians are not only diagnosing and monitoring patients but also treating them, has greatly impacted the way they engage with patients. They are not just providing medical imaging services ordered by an oncologist (in most cases) but are stepping into a new role that needs defining yet where NM physicians evolve into 'NM oncologists' who co-navigate the patient journey with the patient and other clinical specialists, including the 'traditional' oncologists. In one of the discussions at the congress, an unnamed NM radiologist poignantly said: "We need to embrace that we do not only handle imaging, but we are treating physicians, who need to embrace oncology."

Briers also took up this point when he asked: "Will nuclear medicine opt for a role of dispenser of complex medicines in a special environment or will it engage into cancer care and opt for a more independent role?"

Whichever way NM will evolve, involving patients will be essential in each scenario.

Cornelia Wels-Maug,
November 28, 2024

REFERENCES

[i] E.M. Langberg et al., Development of the concept of patient-centredness - a systematic review
Patient Educ Couns (2019), In: https://www.sciencedirect.com/science/article/abs/pii/S0738399121007254 as seen on 7 November 2024

[ii] See https://www.sciencedirect.com/science/article/abs/pii/S0738399121007254 as seen on 7 November 2024

[iii] WHO global strategy on integrated people-centred health services 2016-2026 Executive Summary, https://interprofessional.global/wp-content/uploads/2019/11/WHO-2015-Global-strategy-on-integrated-people-centred-health-services-2016-2026.pdf

[iv] See https://www.sciencedirect.com/science/article/abs/pii/S0738399121007254 as seen on 7 November 2024

[v] A scoping review of person-centred care strategies used in diagnostic Nuclear Medicine. Radiography, Volume 30, Issue 2, March 2024, Pages 448-456. Author links open overlay panel. M. Champendal a j, K. Borg Grima b j, P. Costa c j, C. Andersson d j, C. Baun e j, R.G. Gorga f j, S. Murphy g j, A. Kedves h k, A.Santos i k, A. Geao https://www.sciencedirect.com/science/article/abs/pii/S1078817423002511

[vi] Laying Out a Plan. A consultation appointment helps patients arrive at their nuclear medicine treatment more prepared and comfortable. November 13, 2020. https://www.acr.org/Practice-Management-Quality-Informatics/Imaging-3/Case-Studies/Patient-Engagement/Laying-Out-a-Planas seen on 7 Nov 2024.

[vii] Quantifying the Impact of Patient-Centered Care by Emily Paulsen, November 2020, American College of Radiology. https://www.acr.org/-/media/ACR/Files/Case-Studies/V2_Montefiore-Sidebar.pdf as seen on 8 November 2020

[viii] Laying Out a Plan. A consultation appointment helps patients arrive at their nuclear medicine treatment more prepared and comfortable. November 13, 2020. https://www.acr.org/Practice-Management-Quality-Informatics/Imaging-3/Case-Studies/Patient-Engagement/Laying-Out-a-Planas seen on 7 Nov 2024

7 | RADIOLIGAND THERAPY: ERADICATING CANCER CELLS WITH HIGH PRECISION AND MINIMAL EFFECTS ON HEALTHY CELLS TO MAKE PATIENTS BETTER

Despite the progress in cancer care, caring for patients whose cancers have spread to other parts of the body, who are resistant to treatments or suffer from rare cancers has remained difficult. Radioligand therapy (RTL) is an emerging type of treatment that has given cause for hope as it can enhance the quality of life and improve the length of survival. This has been especially the case for those with castration-resistant prostate cancer that has spread to the bone and neuroendocrine cancers. RLT can play an important role in personalised, targeted treatment. Currently, RLT is used as an ultimate treatment option when all other options are exhausted. However, trials are exploring its effectiveness when used in earlier stages of prostate cancer, with different combinations of radionuclides and ligands. A lot more research is needed in this field to relieve suffering.

Targeting cancer cells while minimising side effects on healthy cells

RLT is an innovative approach to treating certain types of cancers by delivering radiation to specifically targeted cancer cells or those of the tumour microenvironment, whilst minimising the damage to the surrounding healthy tissue. It is a precision cancer treatment in which an earmarked biomolecule, the so-called ligand, that can bind to the target protein on the tumour cell, is combined with a radionuclide. Once the ligand is injected into the bloodstream, it delivers the radionuclide directly to the cancer cell, where it impairs its ability to replicate and ultimately leads to the death of the cancer cell. To minimise the damage on surrounding healthy tissue the radiation is applied exactly on the tumour.

The RLT is based on the fact that some cancer cells form a specific surface structure in the body, which is recognised by the ligand. The underlying principle of RLT – combining a ligand with a radionuclide that then binds with the target protein on the tumour cell and eradicates it – can be tailored to different purposes: radioligands can be customised for diagnostic (imaging) by changing the type of radioisotope, which allows cancer cells to be visualised everywhere in the body, so that clinicians can decide on personalised therapies and track the progress of treatment. Moreover, radioligands can be adapted for therapeutic (treatment) goals by using the same or analogous ligand with a therapeutic radionuclide instead of the diagnostic radionuclide to target different types of cancer or even other diseases. RTL could potentially achieve even better treatment results in combination with conventional treatment methods such as chemotherapy or surgery. There is medical evidence that RTL can enhance a patient's quality of life as well as prolong it. This is currently being investigated in clinical trials.

Application of radioligand therapy

RLTs are well-tolerated systemic therapies used in metastasised diseases. The radioligand itself is a ready-to-use therapy for a specific day and time of administration, which is infused or injected into a peripheral vein. It is a precision medicine approach. Due to the limited time window for administration, radioligands are produced in small batches and individually ordered for a patient.

Currently, RLT is used for the treatment of selected tumour entities, especially metastasised prostate cancer and neuroendocrine tumours (NETs). A prerequisite for administering RLT is a histological diagnosis of the primary tumour and a sufficiently high expression of the target molecule – in the case of prostate cancer this is the prostate-specific membrane antigen (PSMA) and the somatostatin-receptor (SSTR) for NETs. The existence of both target molecules can be proven beforehand via a dedicated SSTR- or PSMA-ligand positron emission tomography/computed tomography

(PET/CT) scan. Moreover, a sufficient functioning of critical organs like renal function and adequate blood count is mandatory. Since the injected pharmaceutical dose is very low, radioligands tend to be well tolerated and the cumulative quantity of radiation to the critical organs is usually well below the radiation thresholds reported in the literature. However, the individual history of the patient, e.g., previous lines of chemotherapy and other patient-specific data like lab results have to be considered.

RLT consists of several cycles of treatment, which are typically administered in intervals of 2-3 months. However, the number of cycles also depends on the response to therapy, patient tolerability and estimated doses to the critical organs.

Treatment of neuroendocrine tumours

Peptides targeting the SSTR are well established for treating well to moderately differentiated NETs. This is also referred to as peptide-receptor radionuclide therapy (PRRT) and may achieve high rates of long-lasting tumour remission and stabilisation.

PET imaging of abnormal SSTR activity has largely replaced scintigraphic imaging using indium-111 pentetreotide (OctreoScan); this change has been driven by the development of a new generation of radiotracers, which has resulted in an improved sensitivity of lesion detection, lower radiation dose and shorter and more convenient study durations. The three currently available SSTR-PET radiotracers are: "^{68}Ga-DOTATATE approved by the Food and Drug Administration (FDA) in 2016, ^{68}Ga-DOTATOC approved by the European Medicines Agency in 2016 and the FDA in 2019, and ^{64}Cu-DOTATATE approved by the FDA in 2020."[i]

To promote the use of SSTR-PET imaging for NETs, the Society of Nuclear Medicine and Molecular Imaging (SNMMI) and EANM released a new practice guideline for SSTR-PET imaging of patients with NETs in February 2023. It aims "to provide clinicians with the best available evidence, to inform where robust evidence is lacking, and to help them to deliver the best possible diagnostic efficacy and study quality for their patients."[ii] The guideline offers also standardised quality control/quality assurance (QC/QA) procedures as well as imaging procedures for SSTR-PET. Furthermore, it says in the guideline: "Adequate precision, accuracy, repeatability, and reproducibility are essential for the clinical management of patients and the use of SSTR-PET within multicenter trials."[iii] This will result in a standardised imaging procedure that will help to promote the appropriate use of SSTR-PET, enhance subsequent research and facilitate the comparison of findings of multi-centre studies.

Treatment of metastasised prostate cancer

A relatively novel RLT is available for metastasised prostate cancer, using a radioligand that specifically binds to the PSMA, which is overexpressed in prostate cancer. Prof Dr Kambiz Rahbar, Attending Physician, University Hospital Münster, Department of Nuclear Medicine, Germany, explained at EANM'24 that there has been a heightened interest in PSMA ligands and radiopharmaceuticals over the last decade with many different radiotracers approved for PSMA imaging and ^{68}GA-PSMA-11PET/CT being the most common used PSMA ligand. Rahbar emphasised the benefits of PSMA imaging: "PSMA is a key biomarker in prostate cancer, it has come to stay and that's why we are here." He added, "PSMA imaging has an impact on patient management in prostate cancer, but the effects on outcomes have to be evaluated." To this end, Prof Dr Anca-Ligia Grosu, Professor and Chair, Department of Radiation Oncology, Medical Centre, University of Freiburg, stressed in her talk on the "Impact of PSMA-PET on radiation oncology planning" the need for PSMA-PET for prostate cancer in radiation oncology: "There is no doubt about this, we need nuclear medicine to have these PET scans done fast, within a week, not longer, so we can plan the treatment accordingly."

Promising results with PSMA – why not bring it forward in the treatment plan?

Currently, RLT is only used in the presence of prostate cancer metastases when other treatment options are no longer effective or are not feasible. According to the University of Jena, Germany, for example, the tolerability of RLT-PSMA is good and most patients experienced only minor side effects, which they often described as significantly less stressful compared to chemotherapy.[iv] At EANM'24, several presenters emphasised that according to current, still preliminary

data, the therapy may achieve a high rate of tumour response even in patients refractory to conventional chemotherapy.

Dr Jochen Walz, Associate Professor in Urology and Head of the Department of Urology at the Institut Paoli-Calmettes Cancer Centre, Marseille, France, cited at EANM'24 the findings of a phase 3 study that looked at the treatment with Lutetium LU-PSMA-617 as a 2nd or 3rd line situation for patients who had already received chemotherapy and were randomly selected for either standard of care versus standard of care +PSMA 617 RLT. The primary objective was overall survival, and the results were in favour of RLT. Walz said: "PSMA radioligand treatment was able to improve the overall survival in these patients who were heavily pretreated. The last option they could have had in this situation was PSMA treatment and it was effective despite the fact that a lot of modes of actions were already used. All patients benefited from the treatment with Lutetium LU-PSMA-617+ standard care in these advanced prostate cancer stages, which is very important information and a very strong sign for using PSMA RLT."

Based on this success, more research was taken out on moving PSMA RLT as the first systematic treatment for castration-resistant prostate cancer. Clinical studies to this effect showed that metastases free survival (MFS) was clearly improved after PSMA treatment and that "clinical outcomes consistently favored ^{177}Lu-PSMA-617 over a change from one androgen receptor pathway inhibitor (ARPI) to another, regardless of which ARPI patients received first."[v]

Walz added that ^{177}Lu-PSMA-617 also improved the quality of life as well as the maintenance of pain scores. He concluded: "We can see that adding Lutetium can improve the outcome and the efficacy of treatment. We have a standard of care and can clearly see that PSMA is adding efficacy and outperforms the treatment with enzalutamide in isolation. In the future, we might be able to individualise the treatment according to what the patient really needs, which depends on the information we obtain from an PSMA-PET scan before and after an initial treatment. I don't think it's one size fits all anymore."

Looking ahead – much more to explore

Walz is looking positively into the future: "We have trials coming to look at PSMA in a more sophisticated manner. There are a lot of new things to come in the near future. It is certain that RLT has entered the landscape of metastatic prostate cancer, it is here to stay and there is more to come." Moreover, RLT will not just be confined to treating prostate tumours and NETs. Prof Dr Ken Herrmann, Professor for Nuclear Medicine, University Clinic Essen, Germany, told the audience at EANM'24 that there were currently about 225 trials testing the efficacy of RLT for a multitude of cancers, including breast and lung tumours.

However, the ability to provide RLT is often limited by the capacity to provide PET scans, which varies by country. Dr Ben Newton, MD, Global Head of Oncology Solutions, GE HealthCare, stressed the need for the community to understand that RTL is an important pillar of oncology that has been reinforced by the EU's Beating Cancer agenda that makes nuclear medicine a top priority. Newton reckoned: "Radioligand therapy has the potential to become an essential pillar in oncology."

Dr Oliver Sartor, MD, Medical Oncologist, Department of Oncology, Mayo Clinic, Rochester, USA, used his presentation at EANM'24 to make the audience aware of other ligands apart from PSMA that could be beneficial for RLT: "I want people to consider that there are additional PSMA ligands in development. Almost all results published today are based on work with Lu-PSMA-617 and Lu-PSMA I&T, which are very important molecules, but for some, they might be considered a first step, not even a final one, we need a lot more work." Moving forward, he urged for open-mindedness: "We have to do things a little bit differently than today. Explore earlier stages of a disease with the current ligands. There is much more to do; we need to explore more on dosage and schedules; consider combinations with hormonal therapy, external beam radiation, isotopic combos (maybe bone targeting), immunotherapies, radiation sensitizers. Precision medicine is a great path forward. I hope this large audience can explore what we need to do to make patients better, that's what we need to do."

Cornelia Wels-Maug,
January 15, 2025

REFERENCES

[i]Thomas A. Hope, Martin Allen-Auerbach, Lisa Bodei, Jeremie Calais, Magnus Dahlbom, Lisa K. Dunnwald, Michael M. Graham, Heather A. Jacene, Courtney Lawhn Heath, Erik S. Mittra, Chadwick L. Wright, Wolfgang P. Fendler, Ken Herrmann, David Taïeb and Andreas Kjaer, Journal of Nuclear Medicine February 2023, 64 (2) 204-210; DOI: https://doi.org/10.2967/jnumed.122.264860

[ii]Thomas A. Hope, Martin Allen-Auerbach, Lisa Bodei, Jeremie Calais, Magnus Dahlbom, Lisa K. Dunnwald, Michael M. Graham, Heather A. Jacene, Courtney Lawhn Heath, Erik S. Mittra, Chadwick L. Wright,Wolfgang P. Fendler, Ken Herrmann, David Taïeb and Andreas Kjaer, Journal of Nuclear Medicine February 2023, 64 (2) 204-210; DOI: https://doi.org/10.2967/jnumed.122.264860

[iii]Thomas A. Hope, Martin Allen-Auerbach, Lisa Bodei, Jeremie Calais, Magnus Dahlbom, Lisa K. Dunnwald, Michael M. Graham, Heather A. Jacene, Courtney Lawhn Heath, Erik S. Mittra, Chadwick L. Wright,Wolfgang P. Fendler, Ken Herrmann, David Taïeb and Andreas Kjaer, Journal of Nuclear Medicine February 2023, 64 (2) 204-210; DOI: https://doi.org/10.2967/jnumed.122.264860

[iv]See See https://www.uniklinikum-jena.de/nuklearmedizin/Informationen+f%C3%BCr+%C3%84rzte/Leistungsspektrum/Therapie/Radioligandentherapie+(RLT)+mit+PSMA.html

[v]Xiao X. Wei, MD, Efficacy of [^{177}Lu]Lu-PSMA-617 versus ARPI change in taxane-naive patients with metastatic castration-resistant prostate cancer by pre-randomization ARPI (PSMAfore), American Urological Association Annual Meeting Plenary, May 3, 2024

8 | THE AGE OF THERANOSTICS – IT'S ABOUT BRINGING PATIENTS HOPE

The demand for theranostics – an innovative fusion of diagnostic imaging and targeted therapy – has grown, reflecting advancements in medical technology and increasing FDA and EMA approvals. Theranostics has been notably effective in treating cancers like thyroid cancer, neuroendocrine tumours and prostate cancer, using radiopharmaceuticals that target specific disease features. While this approach does not guarantee a cure, it significantly improves patient quality of life and treatment outcomes compared to traditional therapies, though radiation exposure remains a concern. Efforts to enhance the accessibility and standardisation of theranostics are underway, including the establishment of the EARL program to certify centres and ensure high-quality care. Additionally, there is growing interest in expanding theranostics beyond cancer to other medical fields, underscoring the need for public awareness and understanding of this promising treatment modality.

Growing demand for theranostics

Recent medical advances have increased the number of theranostics procedures approved by the U.S. Food and Drug Administration (FDA) as well as the European Medicines Agency (EMA). With several key prospective phase 3 studies that have either just reported results or will do so in the near future in the U.S. and in Europe, Prof Dr Ken Herrmann, Professor for Nuclear Medicine, University Clinic Essen, Germany, concluded in his talk at EANM'24 that "theranostics has come of age." He stated a globally expanding interest in theranostics: "There is an increasing demand for this treatment and the growth of theranostics in the last five to ten years has been skyrocketing across the world. Currently, there are more than 225 trials in solid and liquid tumours. There is a need for theranostics, the demand for this new therapy is transformational and patients want it," Herrmann emphasised.

Agata Karolina Pietrzak, Chair of the EANM Technologists' Committee, Poznan University of Medical Sciences and Greater Poland Cancer Centre, Poznan, Poland, highlighted the potential of theranostics: "Nuclear medicine is a serious therapy option and the personalised, targeted approach of theranostics is the future," she said in a conversation at EANM'24. "It's about bringing patients hope and theranostics does so by enabling a better quality of life and improved outcomes," she professed. But what is theranostics and how does it work?

What is theranostics?

Theranostics is a field within nuclear medicine that combines diagnostic imaging and targeted therapy. The term "theranostics" encapsulates this innovative approach that fuses therapy and diagnostics. Contingent on the choice of radiopharmaceutical, theranostics is applied in a diagnostic or a therapeutic manner. Diagnostic radiopharmaceuticals identify patients suitable for subsequent treatment that consists of targeting specific molecular features of a disease with a radiopharmaceutical.

These radiopharmaceuticals, also referred to as radiotracers, are compounds made of chemicals that bind to a specific disease target in the body and a radioactive component. The radiotracer travels through the blood to bind to a unique, designated disease target and the radioactive component emits radiation to that specific cell to eradicate it. This dual capability of theranostics is a significant advancement in medicine, allowing for simultaneous or sequential diagnosis and treatment, which can save time and money and mitigate undesirable biological effects associated with separate strategies.

Application of theranostics

Theranostics has so far mainly been used for treating

cancer, although it can be applied to other fields of nuclear medicine as well.

Theranostics has been successfully employed in treating various cancers, prominently thyroid cancer through radioactive iodine therapies, a practice that has persisted for decades. Moreover, neuroendocrine tumours (NETs) have been treated with Lutetium-177 Dotatate (Lutathera), which has become a standard for managing NETs, particularly for carcinoid tumours.

Advancements in theranostics have also enabled more sophisticated prostate cancer treatments utilising Lutetium-177 vipivotide tetraxetan Prostate-Specific Membrane Antigen (PSMA) for patients with castration-resistant prostate cancer who have already had androgen receptor pathway inhibition and taxane-based chemotherapy.

Moreover, theranostics has been used treating patients with meningiomas, the most common primary adult intracranial tumour that show high expression of somatostatin receptors (SSTRs). These SSTRs can be targeted both with gallium-68 (Ga-68) imaging agents and therapeutic lutetium-177 (Lu-177) radiopharmaceuticals. The use of SSTR-PET imaging and therapy in meningiomas is on the rise, and new guidelines on their use can help pave the way to improve outcomes for patients. "The application of radiolabeled [somatostatin receptor] ligands is widely considered to have high potential for improved meningioma management," wrote lead author Dr. Nathalie Albert, of the Ludwig Maximilian University of Munich, and colleagues in a recently published paper.[i]

Comparison of PET tracers

Dr Friederike Eilsberger, Specialist, Department of Nuclear Medicine, Philipps University Hospital, Marburg, Germany looked in her talk "Go for GOLD – with theranostics" at EANM'24 at the PET tracers in the theranostics "toolbox": PSMA, SSTR and fibroblast activation protein inhibitors (FAPI). She concluded: "We can use all three tools and find gold in each of it. As long as our patient has a benefit of the therapy." She took the time to distinguish the initial hype around new tracers with medical evidence.

With regards to FAPI, which was highly talked about throughout EANM'24, Eilsberger offered a perhaps more impartial assessment: "When a few years ago the first publications on FAPI appeared, it was like finding the holy grail for nuclear medicine. Targeting not only the cancer cells but also those very close to the tumour cell." She looked more closely at the effects of FAPI imaging in radioiodine refractory differentiated thyroid cancer to assess whether FAPI was superior: "There are different studies; one in 2022 showed that in 87% of patients FAPI positive lesions were found. Another study on FAP-42 PET/CT in comparison with an FDG PET/CT found that the diagnostic performance of the FAPI-42 PET/CT is absolutely comparable to that of the FDG PET/CT. In some patients the FDG will have a better tumour metastases projection than the FAPI-PET."

However, Eilsberger also made the audience aware of the currently largest study regarding FAPI-PET in radioiodine refractory DTC, which compared ^{68}Ga-DOTA.SA.FAPi with ^{18}F-FDG PET/CT. The study inlcuded retrospectively a total of 117 patients and showed a superior performance of the ^{68}Ga-DOTA.SA.FAPi compared with the ^{18}F-FDG PET/CT in the detection of lymph nodal, liver, bowel and brain metastases. We will certainly see more research on the topic in the future.

Theranostics enhances quality and duration of life

While theranostics does not cure cancer, it significantly enhances the quality and duration of life for patients with challenging or resistant cancer types. The procedures are generally well tolerated, are experienced as convenient with side effects typically minimal compared to the benefits of symptom relief, an overall better quality of life, improved health outcomes and longer life compared to conventional treatment options. Herrmann confirmed these findings from his own experience: "We saw an 82% reduction in the risk of getting a progression. Theranostics translates into improved life quality."

However, potential side effects of theranostics are primarily associated with radiation exposure, which might elevate the risk of developing secondary cancers.

Theranostics workflow

Theranostics procedures are particularly suitable for patients with metastatic cancers that have shown

resistance to conventional therapies like chemotherapy. Potential candidates undergo initial positron emission tomography (PET) scans to identify the location of cancerous cells and to determine whether they can be targeted. If they are found to be widespread and suitable for therapy, patients can proceed with theranostics treatment. The procedure takes place in specialised facilities equipped to manage the particular needs of theranostics patients. In cases of localised tumours, alternative interventions like surgery or localised radiation might be more effective.

During theranostics procedures, patients initially receive an intravenous injection of the radiotracer, allowing it to absorb and bind to any present cancer cells for approximately one hour. For the diagnostic PET scan, the chosen radioactive component emits a low amount of radiation that enables to take images of the cancer cells onto which the radiotracer has latched. For the treatment part, the chemical component can remain unchanged, but the selected radioactive component will emit more radiation to destroy the cancer cell.

This approach represents a transformative 'one-two punch' against cancer that acts with precision and high efficacy. Nevertheless, despite the rising interest in theranostics, it is still a niche treatment with many patients and non-nuclear practitioners neither aware of its existence nor its benefits.

Organisational considerations around practicing theranostics

Offering theranostics procedures does also require addressing organisational issues around the availability of physical and human resources as well as workflow aspects. For example, as theranostics requires PET/CT scans after each therapy cycle, there will be a growing demand for this type of scans. However, there is a shortage of PET/CT scanners as well as technicians to operate them and clinicians to read those scans. Consequently, there is a shortage of slots for PET scans. Dr Ben Newton, MD, Global Head of Oncology Solutions, GE HealthCare, told the audience at EANM'24 that only about 20% of current patients who needed a PET scan in the UK could be scanned. To ease the bottleneck, Newton suggested to reduce the time for taking images, use existing machines in a smarter way, improve the scaling of space, deploy artificial intelligence to read the scans, augment the workflow and offer clinical decision support, amongst other measures.

EARL Theranostics Centres of Excellence programme

With the growth of theranostics also comes the need for standardising workflows to ensure comparability of results and high-quality patient care across a network of centers. EANM has been addressing this issue in the framework of its EANM Research Ltd. (EARL) initiative that looks to promote multicentre nuclear medicine and research. "Starting with the standardisation for PET imaging, and more recently SPECT, the newest thing is to certify centres to do theranostics," explained Herrmann. "We just launched the first level, the base level, of a theranostics centre in 2024. We want to give guidance as to what is necessary for each level so that each centre can work towards certification by EARL," he said. He continued, "currently, we have 50 registered centres, eventually, we aim for 500 centres at level 1 globally." Within the next 5 years he foresees to launch level 2 and level 3. Herrmann stressed the importance of transparency to allow patients, industry partners and researchers to identify the right collaborator to launch new clinical trials or therapies past approval.

Theranostics beyond cancer

While much of the current discourse around theranostics has revolved around cancer, there is an emerging interest in applying it to other fields of nuclear medicine such as neurology, cardiology and inflammatory and infectious diseases. Today, theranostics is an option available for metastatic disease that fails to respond well to established systemic therapies such as conventional chemotherapy. However, applying theranostics in conditions like Alzheimer's disease, where detecting amyloid plaques could pave the way for targeted antibody treatments, might be of great benefit on a personal and societal level.

Recently developed guidelines for the implementation of theranostics, particularly in managing brain tumours like meningiomas, signify a shift towards standardised practices and increased accessibility to these advanced therapies. Ongoing clinical trials and research will likely

further solidify the role of theranostics across various medical domains.

Offering theranostics treatment will also involve organisational considerations that need to be addressed: will patients be treated as inpatients or outpatients; will the treatment be delivered in a private versus an academic network or will it be delivered standalone or as part of an integrated cancer centre? There are many more questions to be answered.

What is the best way to bring theranostics to patients? Right now, many patients and non-nuclear practitioners are even unaware of its existence let alone its benefits for cancer care. Therefore, there needs to be more information about theranostics in the public domain.

Cornelia Wels-Maug,
January 4, 2025

REFERENCES

[i]Albert, N.L., Preusser, M., Traub-Weidinger, T. et al. Joint EANM/EANO/RANO/SNMMI practice guideline/procedure standards for diagnostics and therapy (theranostics) of meningiomas using radiolabeled somatostatin receptor ligands: version 1.0. Eur J Nucl Med Mol Imaging 51, 3662–3679 (2024). https://doi.org/10.1007/s00259-024-06783-x

SOCIAL MEDIA

@officialEANM
@officialEANM
@EANM_NucMed
@officialEANM
@eanm_NucMed
@officialEANM

USEFUL LINKS

EANM WEBSITE
https://eanm.org/

EANM'24 ABSTRACT BOOK
https://eanm24.eanm.org/abstractsubmission/abstract-book/

EANM OFFICE & IMPRINT

Executive Office

EANM Executive Office
Schmalzhofgasse 26
1060 Vienna, Austria
Phone: +43 1 890 44 27
E-mail: office@eanm.org
Website: www.eanm.org

Editors

Cornelia Wels-Maug
Healthcare IT analyst & writer

Tiphaine Trudelle
Launa Schöbinger-Hassve
EANM Executive Office

Layout & Design

Ekaterina Maslova
EANM Executive Office

DOI: https://doi.org/10.52717/XPEC8703