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EDITORIAL

Highlights of the 34th EANM Annual Congress 2021, 2nd virtual edition: "FROM HAMBURG WITH LOVE"

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Introduction

The 34th Annual Congress of the European Association of Nuclear Medicine (EANM) was planned to take place in Hamburg, Germany. However, due to the persisting SARS-CoV-2 pandemic, the second virtual edition took place from the 20th to the 23rd of October under the chairmanship of Professor Fanti. Despite the hope of the organizers, as well as the participants to be able to have a real "face-to-face" meeting again, everybody was dedicated to generate scientifically outstanding content, with over 1200 submitted abstracts from 59 different countries. The ease of accessibility allowed 2810 participants to join the congress from anywhere globally (from 110 countries), reaching more than 175,000 hits on the virtual platform during the 3.5 congress days. Some of the popular sessions were viewed over 3100 times; furthermore, the continued availability to view the educational contents and CME sessions allowed prolonged access to the high-quality lectures and was still frequently used in the first week of December. Overall, among the 1272 submitted abstracts, 1088 (1034 scientific, 54 technologists) were accepted with 623 abstracts considered for oral presentations and 313 rated as potential highlights by the reviewers of the respective subcommittees. Like last year, EU countries including Italy (13%), Spain (9.6%), Germany (8.8%), and France (7.3%) submitted the greatest number of abstracts. The non-EU country contributing most abstracts this year was Turkey (6%) (Fig. 1).

The Congress program offered scientific sessions and a variety of lectures such as plenary lectures including the Marie Curie Lecture held by Prof. Rodney Hicks (Peter MacCallum Cancer Center, Melbourne, Australia) about "Other New Theranostics," joint symposia, CME sessions, pitfalls & artifacts sessions, and dedicated teaching sessions covering all relevant fields of nuclear medicine.

This review gives a summary of our personal choice among the most notable scientific contributions of this year's conference, presented in the Highlights session of the Annual congress of the EANM 2021.

Preclinical developments

There were 34 preclinical abstracts rated as potential highlights for this year's conference, showing that innovative concepts for constant improving of targeting and efficacy are at the core of nuclear medicine. But not only novel radiopharmaceuticals have been in the focus, but also more technical approaches to assess the distribution for [^{18}F]FDG in head and neck tumors. Debacker et al. showed a combination of micro PET/CT of the specimen after head and neck surgery, in parallel to autoradiography and histopathology to visualize the intratumoral heterogeneity of the [^{18}F]F-FDG accumulation with exact coregistration to the different tissues. This might also be a technology to improve the assessment of surgical margins in selected head and neck tumors [1].

A large focus of this year's conference was around improvements for the detection and efficacy of therapy in prostate cancer. Belissant et al. investigated four different cell lines with four different tracers in tumor-bearing mice. They could show that [^{64}Cu]Cu-DOTHA$_2$-FAPI-04 had an intense uptake in all cell lines (LNCaP, PC3, NCI-H660), while [^{68} Ga]Ga-PSMA-617 was negative in the small cell

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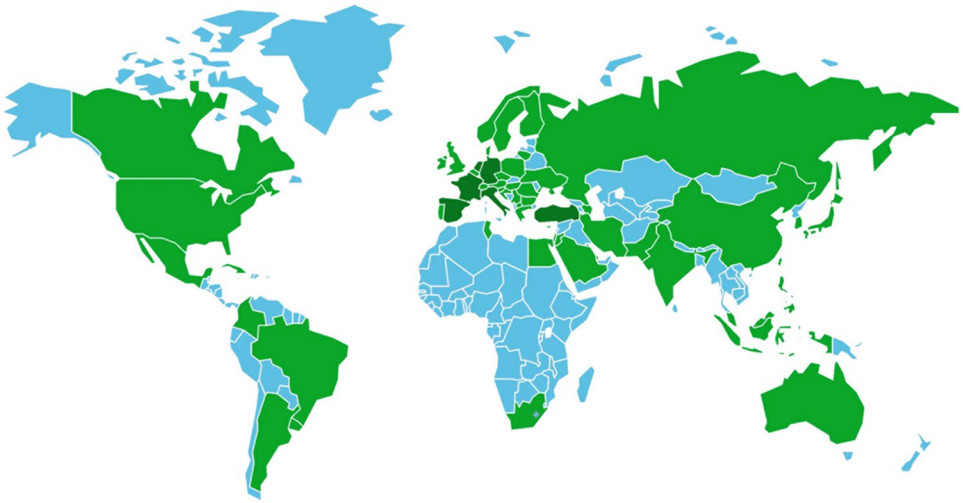

Fig. 1 Countries with abstract contributions for EANM 2021 (green), with the 6 countries with the highest numbers of submitted abstracts in dark green

neuroendocrine variant of prostate cancer. These are promising results and may help to overcome the limitations due to tumor heterogeneity in prostate cancer [4]. Improving the bio-distribution of [^{177}Lu]Lu-PSMA to increase tumor control was the aim of Tschan et al.; by modification of PSMA-617 with the addition of ibuprofen, they could increase the tumor uptake by 40%. [^{177}Lu]Lu-Ibu-DAB-PSMA significantly reduced tumor growth compared to [^{177}Lu]Lu-PSMA-617 and improved survival, with most mice still alive after 84 days after one injection of 5 or 10 MBq [^{177}Lu]Lu-Ibu-DAB-PSMA [2] (Fig. 2). This contribution was recognized with the Marie Curie Award 2021.

The increasing success of internal radiotherapy is also rising the questions about optimal combination therapy. Grzmil et al. investigated a combination of mTORC1 inhibition (RAD001/everolimus) and a [^{177}Lu]-labeled minigastrin analogue [^{177}Lu]Lu-PP-F11N. The increase in cholecystokinin B receptor (CCKBR) 3–5 days after injection of everolimus significantly reduced tumor growth in A431/CCKBR tumor-bearing nude mice after additional injection of [^{177}Lu]Lu-PP-F11N [3].

Developments in instrumentation

The introduction of long-axial FOV scanners with SiPM-based PET technology has enabled high temporal and spatial resolution imaging with increased sensitivity, thus opening new frontiers in dynamic total-body PET imaging. Sari et al. explored the feasibility of parametric image generation on [^{18}F]FDG PET datasets acquired using a long-axial FOV PET/CT system [4]. The authors reported that direct Patlak reconstruction provided superior noise properties with higher TBR contrast than conventional SUV images. Influx images from 2TC models were vulnerable to motion effects and should be interpreted carefully, as this method uses the whole 65-min acquisition data.

During the past 5 years, the number of yearly published studies investigating the value of radiomics has increased more than tenfold. However, the comparability between different scanners and centers is still an issue, as radiomic features are notoriously sensitive to imaging factors variability such as scanner model, acquisition protocols, and reconstruction algorithms. Harmonization strategies are therefore strongly needed to ensure reproducibility of data and to utilize radiomic features as clinical biomarkers. Da-ano et al. compared two approaches for the analysis of [^{18}F]FDG PET and MRI data of three different centers: first by pre-selecting features based on their robustness across centers and second by ComBat a posteriori harmonization [4]. In their study, the use of harmonized features yielded indeed systematically better results than the pre-selection of highly robust features only. In another study, Orlhac and colleagues reported that the composition of the training cohort has an impact on the performance of a radiomic model [4]. The authors suggest that a radiomic model trained by most "typical" patients for a certain diagnosis may yield better results and may be more generalizable when applied to external databases, which may improve their transportability.

An interesting and pragmatic application of a radionuclide has been tested by Laudicella et al. in their interventional "hot needles" study [4]. In this prospective proof of mechanism study, prostate cancer patients underwent a low-dose [^{18}F]F-PSMA-1007 PET/CT followed by PET/CT guided biopsy 110 min after tracer injection. The measured counts in malignant biopsies allowed a quick confirmation of accurate sampling of

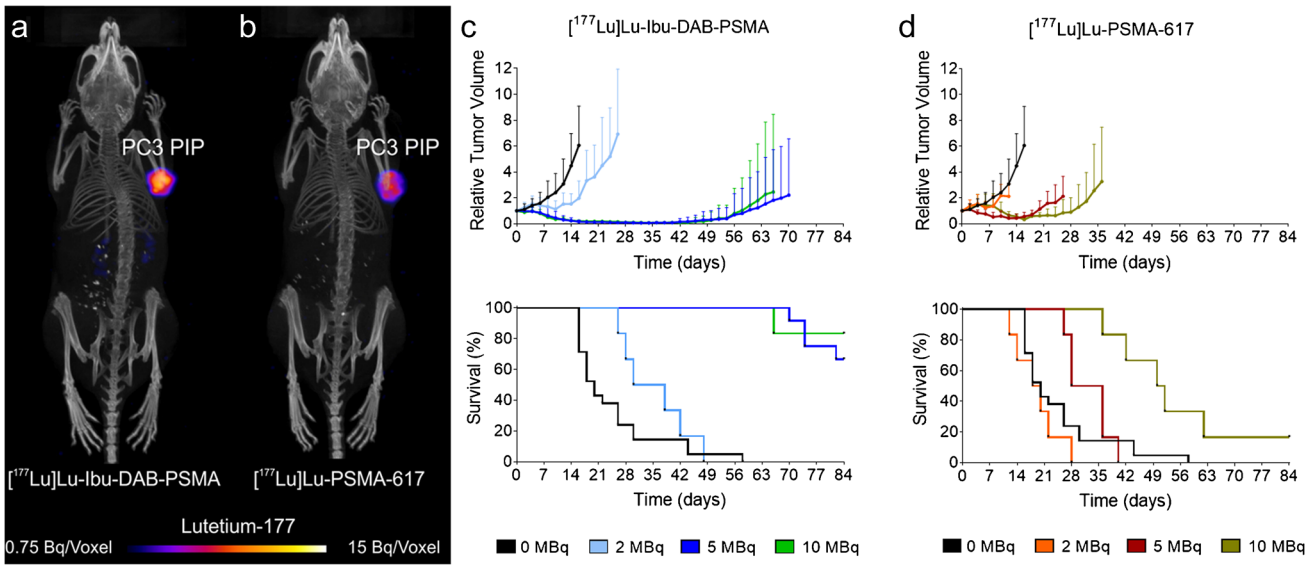

Fig. 2 **A**, **b** SPECT/CT images of PC-3 PIP tumor-bearing mice 24 h after injection of **a** [^{177}Lu]Lu-Ibu-DAB-PSMA and **b**[^{177}Lu]Lu-PSMA-617. Tumor growth and survival curves of control mice (median survival: 20 days) and mice treated with 2 MBq, 5 MBq, or 10 MBq of the respective radioligand. **c** [^{177}Lu]Lu-Ibu-DAB-PSMA (median survival: 34 days, > > 84 days and > > 84 days, respectively); **d** [^{177}Lu]Lu-PSMA-617 (median survival: 19 days, 32 days and 51 days, respectively) (Figure courtesy C. Müller/V. Tschan)

the malignant tissue, which might help to improve the confidence in imaging-based biopsy guidance and reduce the need for saturation biopsy [4].

Clinical developments: cardiovascular

The detection of an acute myocarditis, which is in most cases related to viral infections, may become even more relevant in the context of the actual pandemic. In a pilot study with patients with acute myocarditis, Boursier et al. performed gated [^{68}Ga]DOTATOC digital PET at early and later stages with encouraging results, suggesting a high sensitivity of [^{68}Ga]DOTATOC PET for the detection of acute and subacute myocarditis [4]. In another pilot study by Hugenberg and colleagues, the novel glycoprotein IIb/IIIa receptor-targeted PET tracer [^{18}F]GP1 was investigated for visualization of prosthetic valve thrombosis [4]. In their proof of concept study, [^{18}F]GP1 PET/CT showed high focal uptake of the thrombus at baseline in all three patients. A total of 12–16 weeks after oral anticoagulation [^{18}F]GP1 PET/CT revealed complete thrombus resolution without tracer uptake in one patient and persisting residual tracer uptake in the two remaining patients, suggestive of ongoing platelet aggregation. Whether [^{18}F]GP1 PET/CT may serve as novel sensitive tool for detecting and monitoring prosthetic valve thrombosis needs to be evaluated in future studies.

Clinical developments: neurology

Saint-Aubert et al. presented interesting insights from the interventional study dataset "MAPT," looking at cognitive changes in patients with *intermediate* amyloid load [4], which is of particular interest, as amyloid PET scans are usually rated as negative or positive and the impact of intermediate amyloid load on the clinical outcome is not yet clarified. In their study, patients with high amyloid load had a significant cognitive decline over time, while those with moderate or low amyloid remained clinically stable. Furthermore, in patients with moderate amyloid load, an improved cognitive performance could be observed after multi-domain intervention, while those without treatment showed a slight worsening. These results are important with regard to the selection of patients for treatments.

In a multicenter tau PET study, Rullmann et al. investigated the potential of the next-generation tau tracer [^{18}F]PI-2620 for in vivo Braak staging in patients with Alzheimers disease from 4 different centers worldwide and found a stage dependent positivity that widely followed the Braak scheme [4]. The authors suggested that [^{18}F]PI-2620 PET is a useful tool to perform Braak staging in vivo.

Another highly interesting study involving tau was performed by Vanderlinden et al., with the aim to describe the temporospatial association between tau pathology and synaptic density loss [4]. In a longitudinal and dual tracer PET study using [^{18}F]MK6240 and [^{11}C]UCB-J they examined

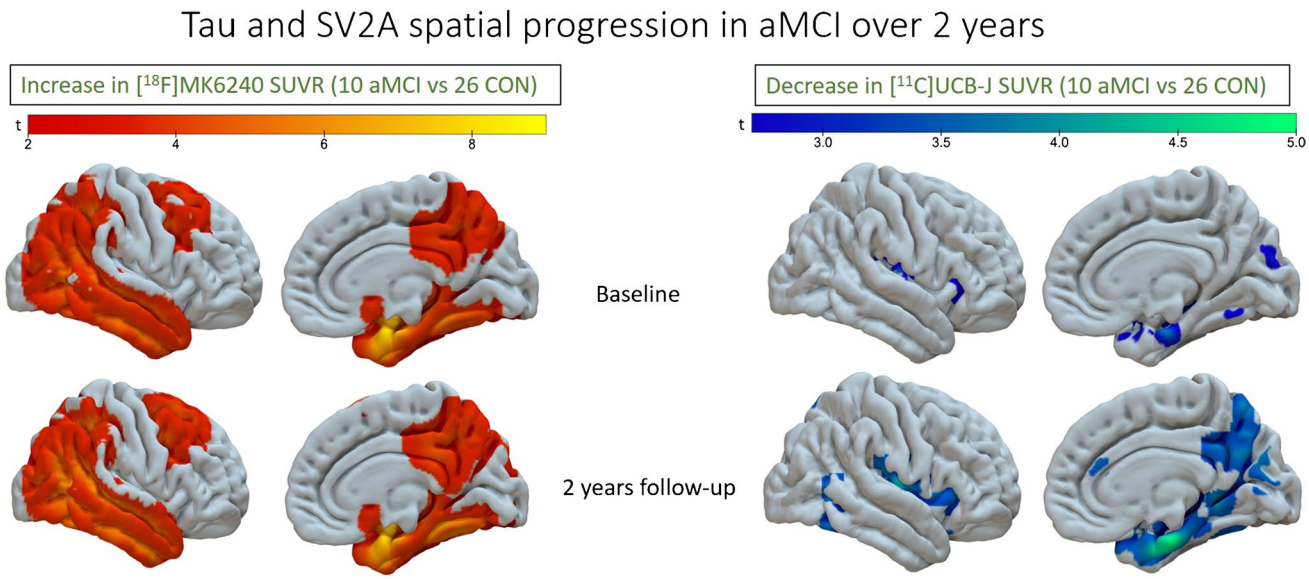

Fig. 3 Temporospatial correlation of tau PET (left) and synapse PET (right) in patients with aMCI at baseline and at 2-year follow-up shows progressive synaptic density loss in tau-positive brain areas (with courtesy from Dr. G. Vanderlinden)

amyloid positive patients with mild cognitive impairment and correlated the PET findings with clinical progression. Notably, an extensive tau increase was found at baseline, while synaptic density loss was restricted to small areas in the mesotemporal cortex only. At 2-years follow-up, however, synaptic density loss progressed and was found along the entire mesotemporal cortex, extended into the temporal cortex and the connected cingulate cortex, showing for the first time in vivo that synapse loss follows a similar progression pattern as tau accumulation (Fig. 3).

As neuroinflammation is considered to play as key role in neurodegenerative diseases, Gnörich and colleagues investigated the impact of microglia on the metabolic connectivity on [^{18}F]FDG PET [4]. They found that the metabolic connectome was strongly decreased after pharmacological microglia depletion, while it highly increased in a mouse model with high levels of overactivated microglia, leading to the conclusion that the microglia activation status has a strong effect on the metabolic connectivity measured by [^{18}F]FDG PET. These findings relate to a recent publication showing that activated microglia substantially contribute to the [^{18}F]FDG PET signal in the brain and therefore need to be taken into account when interpreting an [^{18}F]FDG PET scan in the context of neurodegenerative diseases [5].

Pitombeira et al. performed a dual tracer PET/MR study in patients with primary progressive and relapsing remitting MS in order to evaluate the association between neuroinflammation ([^{11}C]PK11195) and myelin content ([^{11}C]PIB) with functional disability [4]. The authors found that higher disability scores were associated with low myelin content particularly in the corpus callosum, caudate, and in T2 lesions. Their findings of widespread neuroinflammation beyond T2 lesions indicate that the innate immune cell activation may contribute to functional disability in patients with MS.

Clinical developments: oncology diagnostics

The big focus in diagnostic oncology was once more understanding tumor biology and improving diagnostic accuracy with more specific approaches.

To better understand glioma heterogeneity and physiology Kaiser et al. compared amino acid PET ([^{18}F]FET), TSPO PET ([^{18}F]F-GE-180), and contrast-enhanced MRI scans voxel-by-voxel. They could show that TSPO as well as FET had a weak correlation to contrast enhancement, therefore was not just representing the blood–brain-barrier breakdown, while FET and TSPO signals were highly correlated with however some discrepant areas, which might become important in tailored therapy planning [4]. Scott et al. used ^{89}Zr-labled ifabotuzumab, an antibody targeting the tumor microenvironment, and showed high uptake in glioblastomas, with low accumulation in healthy tissue, a promising approach for future theragnostic applications [4].

Improving patient care does not necessarily need a new tracer. De Koster et al. presented data of a randomized multicenter study investigating the use of [^{18} F]FDG PET/CT in thyroid nodules with indetermined results (Bethesda III/IV) on cytology. In the group of patients referred to [^{18}F]

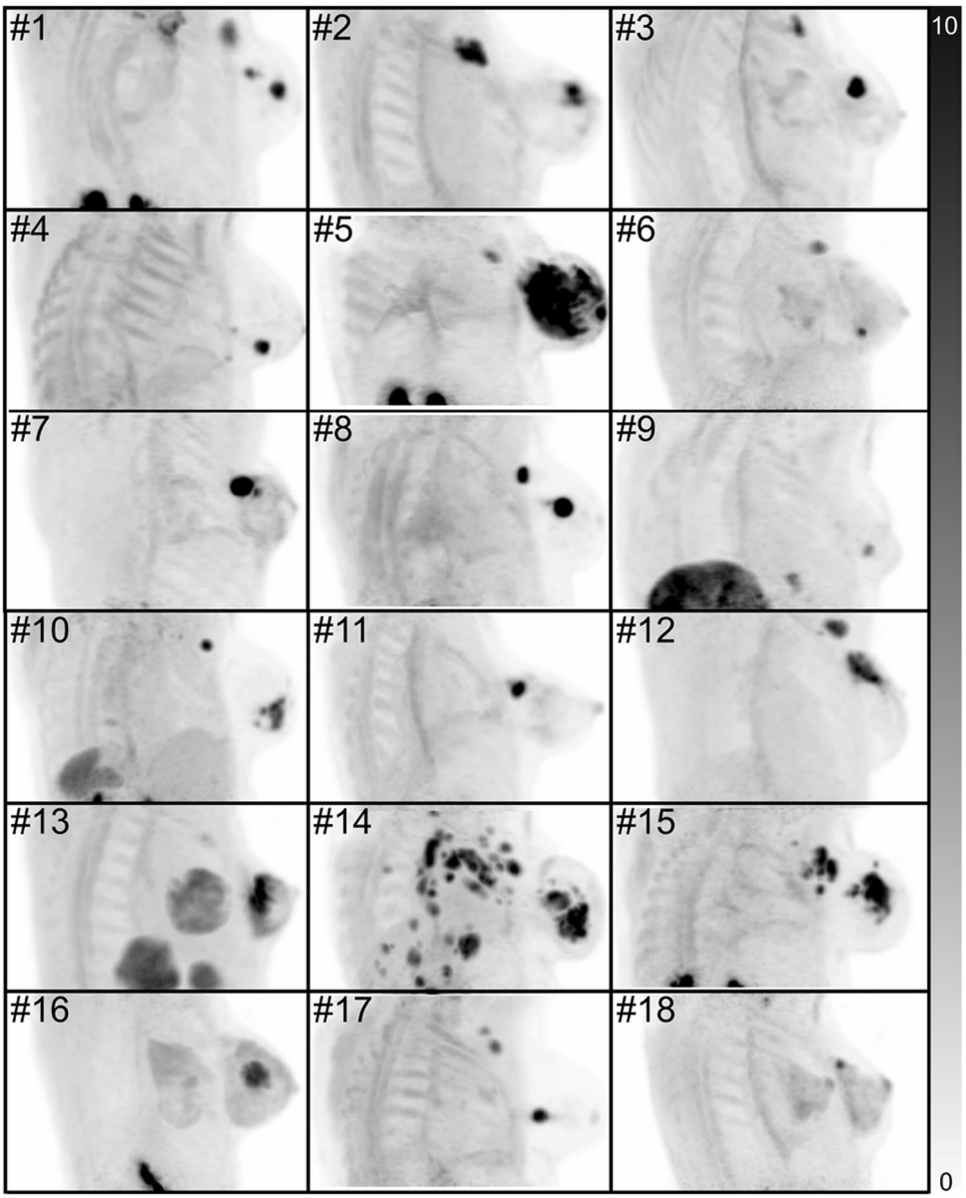

Fig. 4 Oblique MIP projections of 18 patients that underwent [^{68} Ga]Ga-FAPI-46 PET/MRI with excellent tumor to background ratios for all primary tumors and lymph node metastasis (with courtesy from Dr. P. Backhaus)

FDG PET/CT, 40% did not have increased uptake, and futile surgery could be spared [4].

A lot of enthusiasm was however generated around a novel ligand-targeting tumor-activated fibroblasts (FAP). Three abstracts using the 68Ga-labeled FAP ligands were suggested for the HL session. Chandra et al. showed a head to head comparison of [^{18}F]FDG PET/CT and [^{68}Ga]Ga-FAPI PET/CT in 25 breast cancer patients, with significantly higher tumor accumulation on [^{68}Ga]Ga-FAPI regardless of the cancer subtype [4]. This was in concordance with the results of Backhaus et al. showing high uptake in all primary tumors in 18 patients undergoing [^{68}Ga]Ga-FAPI-46 PET/MRI with intense accumulation and SUV_{max} values (13.9 ± 5.6), regardless of cancer subtypes [4] (Fig. 4).

For colorectal cancer, Lin et al. presented data for [^{68}Ga]Ga-FAPI-04 PET/CT in direct comparison to [^{18}F]FDG PET/CT in 37 patients, with a higher detection of metastasis especially in the liver, due to very low back ground and high tumor accumulation [4].

For prostate cancer imaging using the prostate-specific membrane antigen (PSMA), also interesting novel aspects were presented. De Barros et al. showed that a [^{99m}Tc]Tc-PSMA-I&T can facilitate minimal invasive salvage surgery in recurrent prostate cancer using a novel drop-in gamma probe for improved laparoscopic resection [4]. The availability of different tracers targeting PSMA is rising questions regarding the efficacy. Alberts et al. performed a Markov-chain decision analysis for [^{68}Ga]Ga-PSMA-11 versus [^{18}F]PSMA-1007 incorporating scan costs, as well as

results and further work up induced by the scan, to estimate the true costs of both imaging modalities for different health care systems. They came to the conclusion that for Switzerland, Israel, and Australia, the incremental cost efficacy ratio would be beneficial for [^{68}Ga]Ga-PSMA-11, while for Denmark, the use of [^{18}F]PSMA-1007 was favorable [4].

In children, reducing scan time might not only increase comfort but also reduce the need for sedation and therefore also costs. Therefore, Samim et al. investigated [^{18}F]F-MFBG in comparison to [^{123}I]I-MIBG for imaging neuroblastomas. Not only could they show a higher accuracy but also a significant reduction in needed anesthesia, making [^{18}F]F-MFBG a promising alternative [4].

However, molecular imaging has more to offer then a high lesion detection rate, novel tracers targeting specific pathways of existing drugs, have the potential to improve patient selection for various therapies. Therefore, Mittlmeier et al. investigated [^{68}Ga]Ga-EMP-100 as a novel PET ligand imaging the c-MET expression in renal cell cancer (RCC). C-MET is an important oncogene responsible for tumor growth and associated with worse outcome in metastatic RCC. Tyrosine kinase receptor inhibitors targeting c-MET have been approved for RCC, but with heterogeneous response rates [6]. In 12 patients, Mittlmeier et al. could show high but heterogeneous tracer accumulation of [^{68}Ga]Ga-EMP-100 in RCC metastasis, a promising approach to use this novel PET tracer for patient selection [4]. Another interesting target, recently associated with poor response to checkpoint inhibitors is LAG-3 [7]. LAG-3 is an inhibitory receptor expressed on tumor-infiltrating T cells and might be the reason why some cells escalate anti-PD-1 therapy. Miedema et al. presented first in human data on a novel tracer [^{89}Zr]Zr-BI 754111 targeting LAG-3, in patients after progression to PD-1 therapy. They could show selective uptake and high accumulation in tumors as well as saturation effects with higher mass injection [4] (Fig. 5).

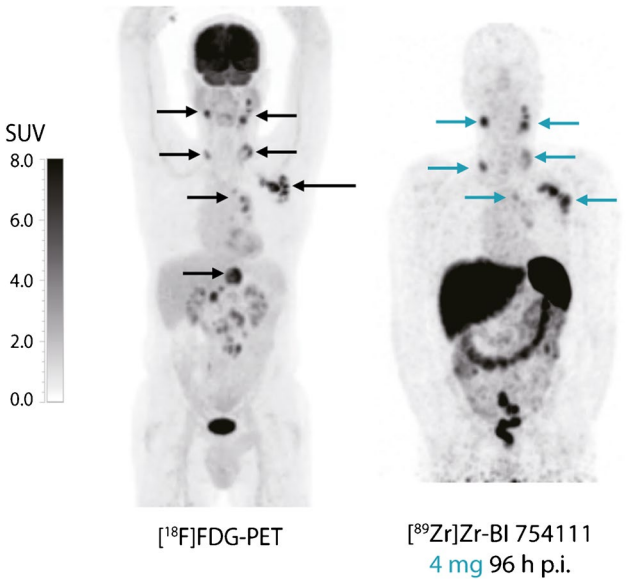

Fig. 5 LAG-3 imaging in a NSCLC patient with progression after anti-PD-1 therapy, using [^{89}Zr]Zr-BI 754111 a monoclonal antibody to image tumor-infiltrating T cells with high LAG-3 expression (with courtesy from Dr. I. Miedema)

Clinical developments: dosimetry and oncology therapy

In order to better predict response to targeted radionuclide therapy, Tamborino et al. built a simulation framework to model early radiation DNA damage induced by in vitro [^{177}Lu]Lu-DOTA-[Tyr^3]octreotate radionuclide therapy. By integrating realistic cellular and organelle geometries and their uptake with a simulation chain characterizing biological damage, they achieved to predict the number of double strand breaks per cell [4]. Another approach to understand radiobiological efficacy of PSMA-targeted radiotherapy using Ac-225 or Lu-177 in an in silico study was presented by Birindelli et al. Based on murine tissue samples, the microdosimetry and its influence on the treatment outcome for PSMA-directed radioligand therapy could be investigated, showing a more homogeneous dose distribution by Lu-177, but a higher cell-killing potency by the Ac-PSMA-ligand for the same mean irradiation dose [4].

Even though there are still unanswered questions, around optimized dosing and exact mechanism of the radiobiology of internal radiotherapy, an important milestone could be achieved 2021. With the presentation of the VISION trial, a phase 3 study of [^{177}Lu]Lu-PSMA-617 in patients with metastatic castration-resistant prostate cancer by Krause et al. showed that [^{177}Lu]Lu-PSMA-617 increased the median overall survival from 11.3 to 15.3 months and radiographic progression free survival from 3.4 to 8.7 months [4]. In the light of previously published data with even superior response rates to [^{177}Lu]Lu-PSMA-617 was rising intense discussions around patient selection [8].

An attempt to improve patient selection was presented by Gafita et al. Based on the outcome of 270 patients treated with [^{177}Lu]Lu-PSMA-617, they collected clinical and imaging parameters and developed a nomogram using a large cohort that was treated with Lu-PSMA and investigated clinical and PSMA PET-based features to be able to predict response to therapy [4].

Also for neuroendocrine tumors, the final overall survival and long-term renal safety data for the NETTER-1 study were presented this year. Kunz et al. showed that in the final analysis, the median overall survival was superior for [^{177}Lu]Lu-DOTATATE (48 months) compared to high-dose somatostatin (36 months), despite 41 of 114 patients (36.0%)

in the control arm crossed over to radioligand therapy during long-term follow-up. Important was also that the rate of grade ≥ 3 nephrotoxicity was comparable between the therapy arm (5.4%) and the control group (3.6%) [4].

Technologists' developments

With 36%, an extraordinarily high rate of abstracts submitted to EANM 2021 by technologists was suggested for as highlights. The best oral presentation was given by Isabel Rodrigues; she presented data on multiple time point imaging with [^{18}F]FDG PET/CT to characterize the normal metabolic behavior of adrenal glands over time, an important work to improve the understanding of normal uptake at various time points [4]. Dessoubrais et al. presented data using a novel CZT 3D-ring system for dopamine transporter imaging in comparison to a conventional NaI hybrid camera. They showed that the new system is more flexible and reduced time of positioning of the patients (3 min) as well as scan time (24 vs. 30 min); furthermore, the new system was well tolerated by all patients without the need of an interruption [4]. Lemor Pereira et al. presented an innovative way to improve quality with an interactive teaching tool [4] and Rep et al. could show that image reconstruction with 2 mm instead of 4 mm can increase the detection of small parathyroid adenomas from 89 to 94% using [^{18}F]F-choline PET/CT [4].

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Declarations

Ethics approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent Not applicable.

References

1. Debacker JM, et al. High-resolution (18)F-FDG PET/CT for assessing three-dimensional intraoperative margins status in malignancies of the head and neck, a proof-of-concept. J Clin Med. 2021;10(16):3737. https://doi.org/10.3390/jcm10163737.
2. Tschan VJ, et al. Impact of the mouse model and molar amount of injected ligand on the tissue distribution profile of PSMA radioligands. Eur J Nucl Med Mol Imaging; 2021.
3. Grzmil M, et al. Pharmacological inhibition of mTORC1 increases CCKBR-specific tumor uptake of radiolabeled minigastrin analogue [(177)Lu]Lu-PP-F11N. Theranostics. 2020;10(24):10861–73.
4. European Journal of Nuclear Medicine and Molecular Imaging. 2021;48(Suppl 1):S1–S648. https://doi.org/10.1007/s00259-021-05547-1.
5. Xiang X, et al. Microglial activation states drive glucose uptake and FDG-PET alterations in neurodegenerative diseases. Sci Transl Med. 2021;13(615):eabe5640.
6. Denize T, et al. Biomarkers of angiogenesis and clinical outcomes to cabozantinib and everolimus in patients with metastatic renal cell carcinoma from the phase III METEOR trial. Clin Cancer Res; 2021.
7. Shen R, et al. LAG-3 expression on peripheral blood cells identifies patients with poorer outcomes after immune checkpoint blockade. Sci Transl Med. 2021;13(608).
8. Hofman MS, et al. [(177)Lu]Lu-PSMA-617 versus cabazitaxel in patients with metastatic castration-resistant prostate cancer (TheraP): a randomised, open-label, phase 2 trial. Lancet. 2021;397(10276):797–804.