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THE FUTURE OF NUCLEAR MEDICINE IMAGING OF NEUROENDOCRINE TUMORS BY USING ^{68}Ga

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Abstract:

Positron emission computed tomography (PET) has become an established technique in clinical routine because it provides an increased spatial resolution and higher sensitivity compared to single photon emission computed tomography (SPECT). Therefore, it is of critical importance to develop ^{68}Ga radiotracers suitable for PET imaging. This review article updates on the design, preparation and pre-clinical investigation of ^{68}Ga derivatives for radio labeling with radioisotopes for PET. Among those the most relevant radionuclide of gallium-68 (t1/2: 68 min, Eav β+: 830 keV).

Keywords: PET, SPECT, ^{68}Ga, Cancer & Image

Introduction:

Medical imaging is one of the fastest growing disciplines in medicine. The development of innovative new imaging modalities and radiopharmaceuticals has improved the ability to study biological structures and functions in health and disease, and continues to contribute to the evolution of medical care. Besides the routine use of X-rays, the most common imaging techniques in current clinical practice are: *computed tomography* (CT or CAT), *magnetic resonance imaging* (MRI), *ultrasound* (US), *planar scintigraphy (gamma camera)* and *single photon emission computed tomography* (SPECT). The use of *Positron emission tomography* (PET) is less common, but is growing fast. CT and MRI scanners, ultrasound units and gamma cameras are now an essential part of clinical practice. PET and magnetic resonance spectroscopy (MRS) are also increasingly used in the management of patients with cancer and neurological disorders. Planar scintigraphy, CT, SPECT and PET make use of ionizing radiation, and except for CT, these nuclear imaging modalities make use of medical radioisotopes. SPECT/CT and PET/CT perform better than SPECT and PET respectively. Therefore the share of these hybrid modalities is increasing rapidly.

Artificially made radioisotopes, among which those for medical use, are mainly produced by research reactors. Currently more than 80% of the medical radioisotopes are produced by research reactors. The remaining isotopes are made by particle accelerators, mostly with circular accelerators (cyclotrons) and sometimes with linear accelerators (linacs), or by other methods. Production of medical isotopes is used by the nuclear industry as public relation for nuclear research reactors. The production of medical isotopes is seen as the sole purpose of the planned replacement of the Dutch High Flux reactor by the Pallas reactor, although 50 percent of reactor-time will be used for nuclear related research. Actually, such research reactors are not necessary at all for the production of isotopes. Radioisotopes production with cyclotrons offers many advantages over a nuclear reactor. Firstly, the volume of radioactive waste produced by cyclotrons is far less and much less hazardous than the radioactive waste of research reactors. Secondly, the production is decentralized. Cyclotrons are located hospital-based, by which the delivery of pharmaceuticals to patients is much more secured. In addition the risk of transport accidents is practically zero. Thirdly, there are no risks

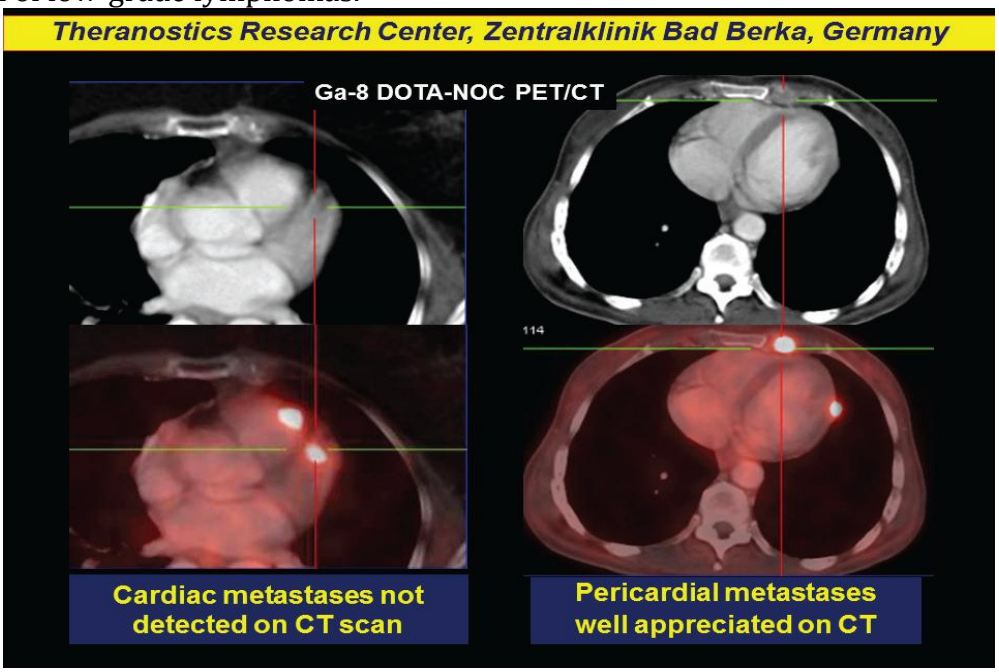
due to nuclear-power accidents, because there is no need for controlled chain reactions. Fourthly, there is no nuclear proliferation risk.

Radioisotopes Used in Imaging:

Radioisotopes used in cancer imaging of the many different radionuclides used in diagnostic procedures, only a few are valuable in diagnosing cancer. PET/CT is currently accepted to be the most accurate way to stage and monitor many types of cancer. It is used routinely in detecting tumors of thyroid and primary or metastatic tumors of the bone, brain and liver or spleen. Globally, the vast majority of these investigations are performed using the glucose analogue, ^{18}F-FDG. This radiotracer allows cancers to be seen as 'hot spots' on the PET scan. ^{18}F-FDG PET is emerging as a useful tool in the treatment of breast, colorectal, esophageal, head and neck, lung, pancreatic, and thyroid cancer; lymphoma, melanoma, and sarcoma; and unknown primary tumor. Gallium-68 (^{68}Ga) has been used experimentally in the staging of lymphoma and shows a great deal of promise in bone scanning. Though PET and PET/CT imaging is becoming a dominant modality in cancer imaging, SPECT isotopes, such as technetium-99 (99mTc) and iodine-123 (^{123}I) are more common for use in cancer imaging. Other isotopes used in cancer imaging are: chromium-51 (^{51}Cr), gold-198 (^{198}Au), indium-113m (113mIn), iodine-125 (^{125}I), iodine-131 (^{131}I), mercury- 197 (^{197}Hg), mercury-203 (^{203}Hg), selenium-75 (^{75}Se), and Ytterbium-169 (^{169}Yb). Except ^{123}I, all of these radioisotopes are currently produced by research reactors.

Radioisotopes Used iIn Cardiac Imaging by Using ^{68}Ga:

It is thought that PET imaging may be able to overcome the limitations of the currently used perfusion tracers thallium-201 (^{201}Tl) and technetium-99m (99mTc) in SPECT. Gallium-68 (^{68}Ga) and copper-64 (^{64}Cu) are named as potentially attractive PET tracers for this purpose. Other perfusion agents are: ^{11}C (in CO_2), ^{15}O, ^{13}N (in NH_3) and rubidium-82 (^{82}Rb). Thallium-201 (^{201}Tl), used in cardiac scintigraphy and SPECT, is also used for diagnosis of other heart conditions such as heart muscle death and for location of low-grade lymphomas.



Radioisotopes Used in Thyroid Imaging:

Thyroid imaging tests are used to diagnose or monitor thyroid conditions such as hyperthyroidism, thyroid nodules, thyroid cancer, enlarged thyroid gland (goiter) and

thyroiditis. These tests can help a physician to determine the most effective treatment approach for a patient's condition. Types of thyroid imaging tests include isotope imaging with PET and SPECT. PET uses iodine-124 (^{124}I), gallium-68 (^{68}Ga) and fluorine-18 (^{18}F) and shows better results than the more commonly used gamma camera with iodine-131 (^{131}I) or indium-111 (^{111}In) and SPECT with ^{201}Tl and ^{131}I.29 The iodine-isotopes ^{123}I and ^{131}I remain the most frequently used radionuclides for thyroid imaging in the diagnosis and treatment of well-differentiated thyroid carcinomas (WDTC), which account for almost 90% of thyroid cancers. Although ^{131}I is superior to ^{201}Tl in the detection of lung metastasis, ^{201}Tl may detect metastases not visualized with ^{131}I, and the sensitivity of planar ^{201}Tl may be improved with SPECT from 60 to 85% sensitivity. Imaging with ^{201}Tl has been of value when ^{131}I scans are negative in the presence of known thyroid cancer. ^{201}I has been shown to be useful in patients with WDTC and elevated thyroglobulin levels, despite a negative ^{131}I scan.

Radioisotopes Used in Renal Imaging:

There are two types of commonly used scintigraphies to assess the kidney function. Cortical Renal Scintigraphy, an exam used to measure and evaluate the functioning kidney tissue, and Diuretic Renal Scintigraphy, an exam used to detect blockages in the kidney. For these purposes and renal SPECT imaging 99 mTc is the most widely used radioisotope. The main advantage of PET is that images provide quantitative information on tracer kinetics. Kinetic parameters that correlate with biologically defined processes can be calculated for the entire renal cortex or as pixel-based parametric images. Renal PET studies can be classified as functional (metabolic) imaging studies. Such as determinations of renal blood flow studies with ^{15}O labeled water, ^{13}N labeled ammonia, ^{64}Cu and ^{82}Rb pharmaceuticals. Other isotopes used in renal function imaging are: ^{55}Co and ^{68}Ga

Cancer Treatment with Radio Immunotherapy and PET:

^{68}Ga-PET is not only employed for imaging in the management of neuroendocrine tumors and neural crest tumors, but also for therapeutic use, where it complements present radiologic and scintigraphic procedures. Diagnosis and radiotherapy treatment planning for meningiomas (the second most common primary tumor of the central nervous system) in pertinent clinical setting is another potential use of ^{68}Ga-PET. Therefore, current experience tends to open a new horizon for the clinical utility of ^{68}Ga- PET imaging in future. Immuno-PET as a quantitative imaging procedure before or concomitant with radioimmunotherapy is an attractive option to improve confirmation of tumor targeting and especially assessment of radiation dose delivery to both tumor and normal tissues. Immuno- PET combines the high resolution and quantitative aspects of PET with the high specificity and selectivity of monoclonal antibodies. This makes immuno-PET an attractive imaging modality for tumor detection. Moreover, immuno-PET has the potential to supersede gamma-camera imaging in combination with radioimmunotherapy, because it enables the sensitive confirmation of tumor targeting and a more reliable estimation of radiation dose delivery to both tumor and normal tissues. Because PET is believed to be superior to SPECT with respect to quantification, several PET radioisotopes have been suggested as substitutes for gamma-emitting radionuclides used in radioimmunoscintigraphy. Theoretically, this could enable easy conversion from a SPECT to a PET procedure. Examples of PET/SPECT radioisotope pairs are 94mTc/99mTc, ^{67}Ga/^{68}Ga, and ^{124}I/^{123}I, and examples of PET/radioimmunotherapy radioisotope pairs are ^{64}Cu/^{67}Cu, ^{86}Y/^{90}Y, and ^{124}I/^{131}I. ^{68}Ga can be produced – such as 99mTc - from a generator system with the parent radionuclide Germanium-68. ^{68}Ga has a long half-life of 271 days which allows

the production of long-lived, potentially very costeffective generator systems. ^{67}Ga en ^{68}Ga has the same medical applications, whereas ^{67}Ga is used with SPECT/CT and ^{68}Ga with PET/CT.

Molecular Imaging Using Radioisotopes:

Knowledge of the molecular profile of a tumor not only guides clinical decisions for optimal treatment but can be harnessed also to monitor treatment response objectively. In this respect, theranostic approaches for the diagnosis and treatment of a variety of tumor types are rapidly gaining momentum. By combining diagnostic imaging modalities with therapeutic interventions directed against the same molecular target, theranostics enables selection of patients more likely to respond to a specific therapy and consequently improves the therapeutic/toxicity ratio while avoiding unnecessary treatment [1].

Molecular imaging using radioisotopes is now commonly used for non-invasive detection of specific tumor targets. By replacing the imaging isotope (i.e., gamma or positron emitters) with alpha, beta or auger-electron emitters, a specific probe is turned into a powerful therapeutic agent. Interestingly, using diagnostic/therapeutic pairs is not a new concept in the nuclear medicine field. For more than 60 years. ^{123}I/ ^{131} has been employed for the diagnosis and radionuclide therapy of well-diferentiated thyroid cancers. More recently this principle has been applied to neuroendocrine tumors using compounds specifically targeting somatostatin receptors (SSRT) for both imaging and peptide receptor radionuclide therapy (PRRT) [2]. The nuclear medicine community has enthusiastically embraced the use of the pair ^{68}GaDOTATATE (PET imaging)/ ^{177}Lu-DOTA-octreotate (PRRT) which proved successful in multiple nuclear medicine centres [2, 3].

Several preclinical proof-of-concept studies have now validated extracellular melanin as a suitable target for imaging and radioimmunotherapy (RIT) [4]. In a recent phase Ia/Ib clinical trial, the melanin-binding ^{188}Re-6D$_2$ monoclonal antibody was well tolerated, showed only mild haematological toxicity and improved patient survival [5]. Cell permeable benzamide derivatives such as ^{18}F-MEL050 may further improve imaging of pigmented melanoma since they recognize both intra- and extracellular melanin. Early preclinical work evaluating benzamide derivatives diagnostic/therapeutic pairs in mouse melanoma models is promising [6, 7] but further clinical trials are required to assess whether these could improve clinical outcome in patients with pigmented melanoma.

Toxicity to Normal Organs Observed With Radionuclide Therapy:

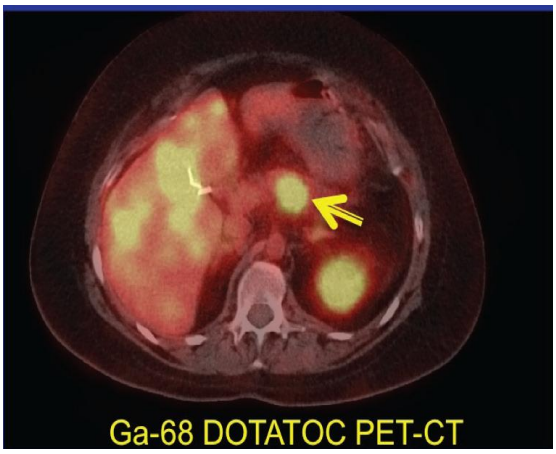
The toxicity to normal organs observed with radionuclide therapy highlights the importance of accurate dosimetry. Here again, major advances have been made with the introduction of PET radionuclides with long half-lives such as ^{64}Cu (12.7 hours) that, unlike radionuclides with short half-life (^{68}Ga, 68 minutes), allows long term dosimetry. For individualized patient dosimetry, the same element should be used for imaging and therapy to better reflect the biodistribution of the therapeutic radiotracer. Development of simplified chemistry for the synthesis of more stable ^{64}Cu/^{67}Cu-labeled imaging and therapeutic radiotracers will most likely facilitate their translation to the clinic [13].

The genetic and phenotypic heterogeneity of tumours and the activation of alternative signalling pathways in response to targeted therapies all contribute to the development of drug resistance and treatment failure. While in theory this approach is powerful, clinical evidence indicates that drug resistance to targeted therapy almost inevitably occurs (e.g. BRAF inhibitors for the treatment of melanoma or Tamoxifen for

the treatment of ER-positive breast cancer). Current clinical trends to overcome the issue of resistance are to combine inhibitors blocking multiple signalling pathways. It will be interesting to see if "combination theranostics" utilising radionuclides directed towards multiple molecular targets will be suficient to prevent the emergence of resistance. If so, the next challenge will be to identify the best combination therapies and optimisation of treatment regimens.

The Novel Receptor Targets Utilizing Innovative Radio Pharmaceuticals:

Strategies to advance current techniques the development of an efficient and reproducible SSR-based molecular imaging procedure is a strategic necessity to ensure clinical acceptance of current and future techniques. The recent assignment by FDA/EMA of orphan drug designation to ^{68}Ga-DOTATOC and ^{68}Ga- DOTATATE is, hopefully, a step towards uniformity. A critical issue is the need to validate ^{68}Ga-SMS-RPET, especially by assuring SUV objectivity and comparability. Options include correction of the tumor maximum SUV (SUVmax) with background [21], the correction of the tumor SUVmax with the spleen, and the calculation of molecular tumor volume. Finally, in order to be predictive, the apocryphal "Rotterdam scale" needs to be objectified and adapted to PET. The collaboration of clinical and nuclear medicine societies in the process of standardization is necessary to assure adoption of a uniform process.

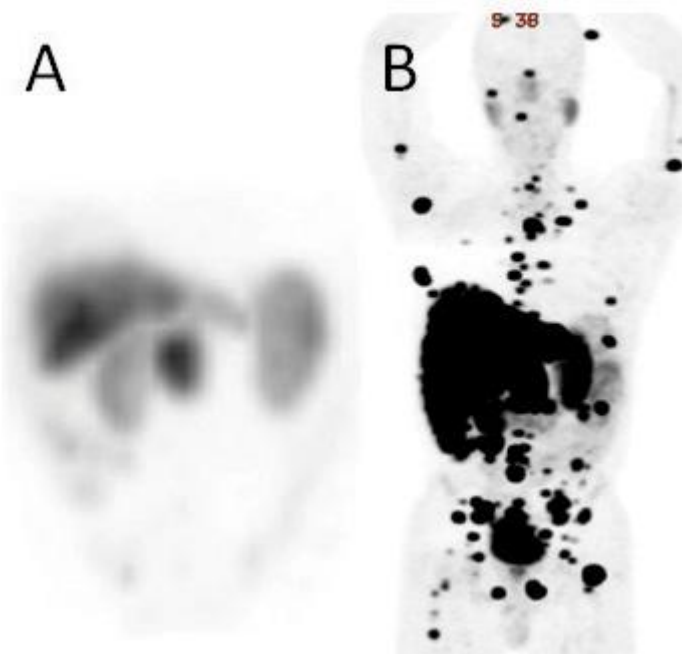


The Novel And Strategies Improvements In Current Techniques By Utilize Ga-68:

Introduction of novel techniques and strategies Improvements in current techniques that utilize Ga-68 are worthy of consideration. Thus, SSAs labeled with Cu-64 are of considerable interest, due to the excellent image quality and the spatial resolution. The 12.5-hour halflife allows later imaging compared to Ga-peptides, with stable tumor to background ratios at least 3 h after injection, thus matching more closely the tumor uptake kinetics, and the possibility of imaging at 24 h. An additional area is the development of alternative fusion imagery. Preliminary studies with fused ^{68}Ga-SMS-R-PET and magnetic resonance imaging (MRI) scan, both as diffusion-weighted and gadoxetateenhanced images, have demonstrated similar high perregion (98.9 and 97.7 %, respectively) and per-organ (95.7 and 91.3 %, respectively) sensitivity, with comparable high specificity (99.6–99.7 %).

The PET and MRI techniques provide complementary information, regarding both the anatomical detail and the functional characterization of the tissue, including the diffusion weighted imaging (DWI) parameters and the receptor mediated uptake of the ^{68}Ga-DOTA-peptide. SSAs have been the workhorse of imagery for two decades, and alternative radiopharmaceuticals that provide increased diagnostic accuracy should be identified. In this respect, the use of SSR antagonists appears to represent a highly

promising strategy. The lack of internalization and the recognition of increased binding sites represent an inversion of the current paradigm of agonists. Agents such as ^{111}In-DOTA-BASS [^{177}Lu-DOTA-pNO$_2$-Phe-c (dCys-Tyr-dTrp-Lys-Thr-Cys) dTyrNH$_2$] or ^{111}In-DOTA-JR11 (DOTA-Cpa-c[D-Cys- Aph(Hor)-D-Aph(Cbm)-Lys-Thr-Cys]-D-Tyr-NH$_2$) exhibit higher levels and longer retention rates, thereby providing a higher sensitivity compared to ^{111}Inpentetreotide. In terms of therapeutic application, in vitro studies indicate a significantly greater binding of ^{177}Lu-DOTA-BASS on neuroendocrine tumor cells than the current best agonist ^{177}Lu-DOTATATE. The clinical translation of this observation suggests a higher tumor accumulation with increased irradiation, while the lower normal tissue accumulation implies diminished exposure. Of note, however, is the observation that the somatostatin receptor affinity of such compounds can be diminished by binding to radiometals, such as Ga-68.



A comparison in the same patient between Octreoscan (A) and 68-Gallium-DOTATATE PET/CT (B)

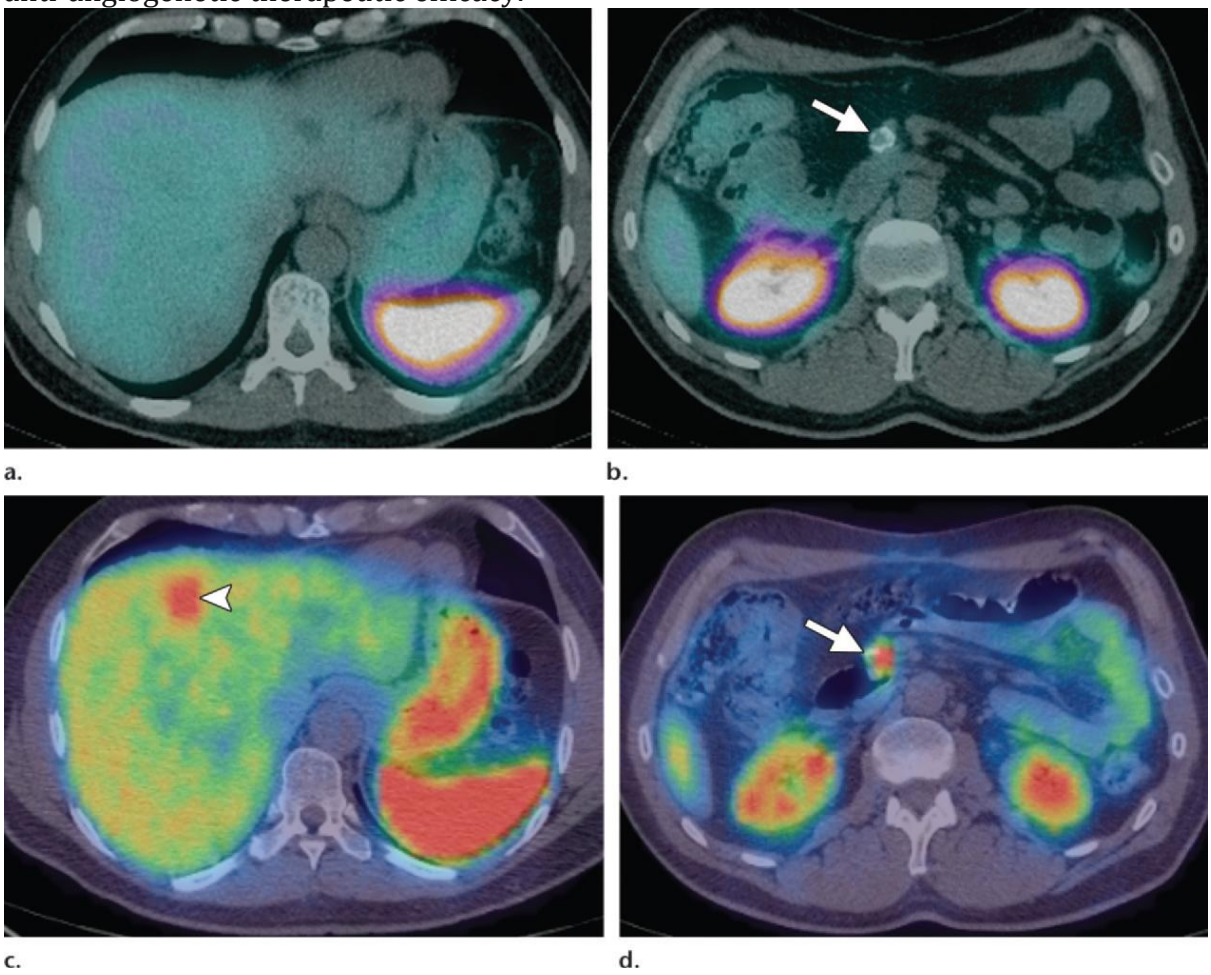
The Radiopharmaceuticals Needs Identification:

The development of novel receptor targets utilizing innovative radiopharmaceuticals needs identification. In particular, specific agents that identify a particular tumor or one with a specific secretory product need to be investigated. A number of peptides have been tested in preclinical and clinical trials. Among these, the GLP-1 receptor (GLP-R) peptides, such as ^{111}In-exendin-4 (localization of occult insulinomas), are the most advanced for clinical application. 111In-exendin-4 specifically addresses the paucity of SSRs in benign insulinomas. In this respect, GLP-R and SSR imaging demonstrate the biologically mutable aspect of insulinomas, which may be GLP-R positive and SSR negative or vice-versa, a reflection of their malignant phenotype. A ^{68}Ga-labeled exendin- 4 is the logical next step and has been tested in clinical trials. Following the same principle of the paradigm shift from agonist to antagonists, it was recently demonstrated that the 125I-BH-exendin (9–39) GLP-1 antagonist has excellent binding properties and constitutes a promising imaging agent.

The Multi-Receptor Expression Of Neuroendocrine Cells:

Similar evaluation of the multi-receptor expression of neuroendocrine cells has demonstrated that the cholecystokinin/gastrin ligands, such as CCK8 and minigastrin

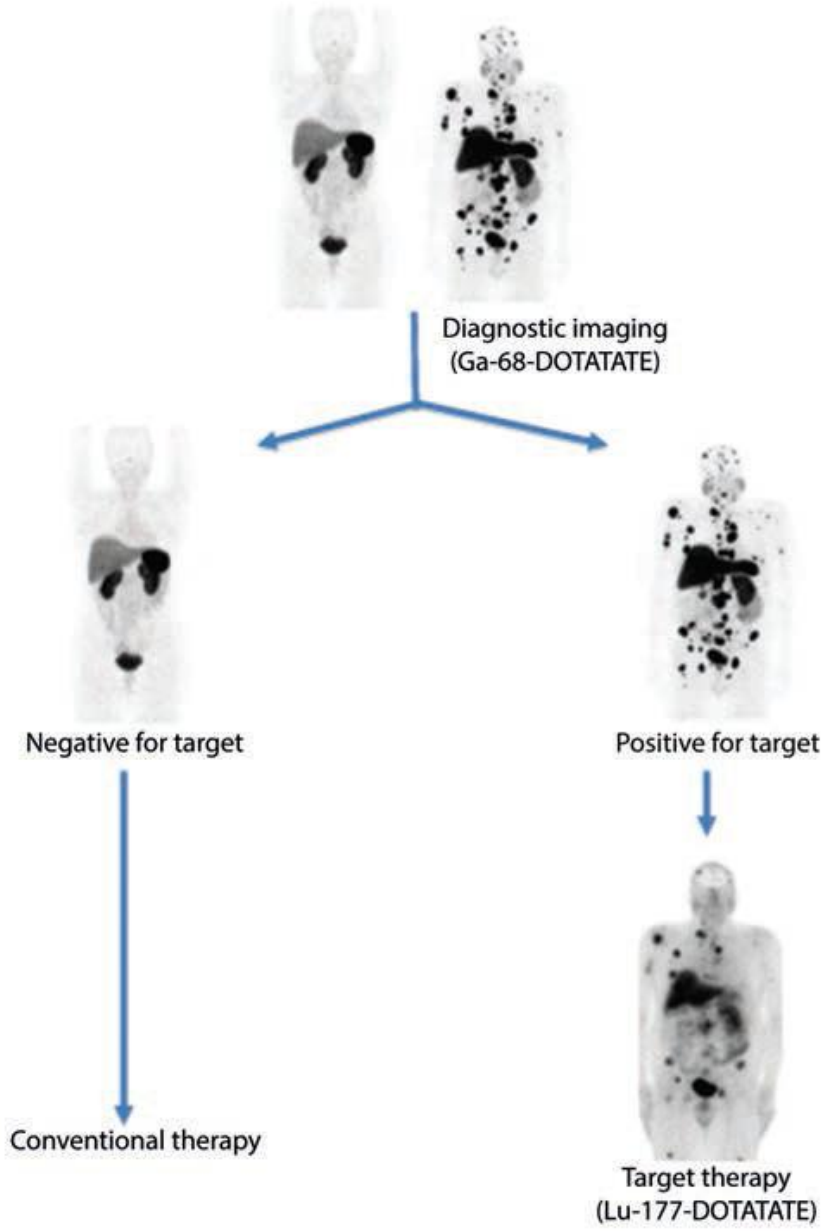
analogs labeled with 111In or 99mTc, may also have clinical utility. Other targets that have been explored for NET imaging include the bombesin receptor family, which includeGRP (gastrin-releasing peptide), NMB (neuromedin B), and BB3 (bombesin receptor subtype 3) receptors. In vitro usage to identify prostate cancer indicates positive identification in 60–100 %. Similarly, GRP and BB3 receptors have been identified in 7/10 and 2/10 gastrinomas, respectively, NMB receptors have been found in 11/27 ileal, while BB3 receptors were the predominant receptors described in 10/29 bronchial NETs. More than 40 different bombesin analogs, agonists and antagonists labeled with 99mTc or with 68Ga have been evaluated in vitro. They comprise an additional potential class of radiopharmaceuticals for NET imaging. The low plasma stability and high kidney retention have limited the application of these alternative peptides as theranostic. Nevertheless, newer, more stable molecules and the co-administration of specific enzyme inhibitors, such as the neutral endopeptidase inhibitor phosphoramidon, can be utilized to increase the bioavailability of these compounds. Adjunctive strategies of this type are likely to herald a new era in the application of receptor peptides and supplant the model of somatostatin analogs in the study of neuroendocrine tumors. Assessment of alternative components of NET biology such as angiogenesis has led to the development of promising strategies utilizing radiolabeled antibodies such as the Zr-89-labeled bevacizumab. This concept has been applied to the evaluation of a variety of NETs treated with everolimus. A decrease in the SUV led to the proposal that this technique could be of value as an early predictor of anti-angiogenetic therapeutic efficacy.



MNET in a 53-year-old man. Axial images from 111In octreotide scan fused with corresponding axial CT images **(a, b)** and axial images from 68Ga PET/CT performed 1 month later **(c, d)** show that the liver metastasis (arrowhead in **c**) and mesenteric node (arrow in **b** and **d**) demonstrate increased uptake in **c** and **d**, while the findings are negative in **a** and **b**.

Utilization of Other Biologic Information to Amplify Accuracy:

It is clear that monoanalyte-derived information can never be as effective as the product of multianalyte parameters. Thus, an image alone is, by definition, limited only by the lack of additional, relevant parameters that can be integrated into an amplifiable diagnostic quotient. Inclusion of such additional material, in a mathematical probability index, or in a matrix or via a nomogram has proved of considerable added prognostic value in other disciplines. The multi-level parallel assessment of different forms of tumor/patient relevant information is mandatory to strengthen diagnostic and prognostic accuracy.



To optimally increase information gained from nuclear medicine techniques, NET images will likely require integration of tumor and blood biomarkers and the development of prognostic nomograms. A particularly informative source of information would be the integration of circulating tumor genomic data obtained from blood (simultaneous liquid biopsy) at the time of nuclear medicine image acquisition. Thus, receptor determined tumor characteristics could be combined with tumor transcript profiles, allowing for the development of a personalized predictive assessment of tumor status before, during and after treatment.

Coda The integration of functional and anatomic imaging optimizes the delineation of the status of a NET. PET, particularly with 68Ga-DOTA-peptides, is supplanting Octreo Scan®. Emerging strategies include the use of SSR-antagonists and GLP1-R peptides. However, the present lack of homogeneity and validation has limited the clinical acceptance of novel techniques. A robust and standardized basis to objectify nuclear medicine procedures is a critical requirement. The future development of multi-dimensional-algorithmic data quotients (tissue, blood and imaging) for each patient, as opposed to a mono-dimensional image-based procedure, is likely to generate information that is far more accurate than the current strategy. In this respect, the combination of a simultaneous gene transcript blood signature from the tumor as well as a functional image may provide an informative mechanism for capturing knowledge of both the biology of an individual tumor, as well as its current and future behavior.

Targeted radionuclide therapy demonstrating how theranostic systems combine diagnostic imaging (Ga-68-DOTATATE PET/CT)to detect the presence of a molecular target (somatostatin receptors) in each patient. A patient who is found to be positive for a molecular target is selected for therapeutic intervention, in this case Lu-177- Dotatate.

Conclusion:

In conclusion, medical and technological advances are rapidly changing our approach to cancer diagnosis and treatment. While the ranostics is still at an early stage of implementation, there is little doubt that over the next decades its use will become increasingly part of the standard of care for cancer patients as we move towards personalized therapy. Other challenges ahead are likely to be economic rather than scientific, due to regulatory issues and the cost of such procedures. The use of PET/CT with PET isotopes in imaging and therapy presents a better alternative than gamma camera scintigraphy and SPECT with mainly reactor produced isotopes. The share of reactor-produced medical isotopes will definitely shrink in the coming decades, while the share of PET isotopes is increasing steadily. Policy-makers can anticipate on this trend by making a choice for cyclotron-produced medical isotopes. Besides PET isotopes, this report has shown that all relevant reactor-based isotopes can be made by an accelerator. In addition, investing in cyclotrons also means investing in research for the development of new cyclotron-based pharmaceuticals, just like the current highly popular PET-pharmaceuticals.

Several studies used the short-lived ^{68}Ga isotope for radiolabeling of DOTA. The resulting PET images of tumor bearing mice were of excellent quality. A recently developed DOTA-folate conjugate comprises an albumin binding entity which is responsible for an enhanced blood circulation time and hence a better tumor-to-kidney ratio. Excellent results in terms of tumor visualization were obtained with this conjugate in combination with ^{44}Sc and ^{152}Tb whose physical half-lives matched perfectly with the slower kinetics. We believe that the FR-α is a target of critical value for nuclear imaging through use of folate-based radiotracers as it is not only expressed on several tumor types but reported to correlate with the aggressiveness of these

malignancies. Moreover, employment of folate radiopharmaceuticals for imaging of inflammatory diseases by targeting the FR-β on activated macrophages holds promise as a further field of application. The future will show which of the numerous PET folate tracers will be tested in the clinic and which one would finally evolve into the predicted useful tool in nuclear medicine.

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