Why Nuclear Imaging and Radiotherapy?

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Fundamentals

What Is Nuclear Medicine?

Nuclear medicine is classically defined as the application of radionuclides to medicine [1]. Nuclear medicine takes advantage of the unique properties of radioactive elements, which have significantly different physical properties compared to stable elements but identical chemical behavior. More specifically, radionuclides decay at a characteristic rate (*i.e.* half-life) via the emission of particles or electromagnetic radiation (*e.g.* positrons, gamma rays, *etc.*). These emissions can be harnessed to facilitate the imaging or therapy of disease. Radiolabeled molecules, termed "radiopharmaceuticals," are an essential element in the medical subspecialty of nuclear medicine [2]. As such, radiopharmaceutical chemistry—the branch of chemistry dedicated to the synthesis, characterization, and evaluation of radiopharmaceuticals—is a fundamental and critical component of nuclear medicine.

Why Nuclear Imaging?

Nuclear imaging is predicated on the fact that essentially none of the biomolecules within the body are radioactive. As a result, radiopharmaceuticals can be distinguished easily from native molecules, providing nearly infinite contrast for imaging. This represents a dramatic departure from other imaging modalities—such as computer tomography (CT)—in which *all* tissues produce a signal and differences in the intensity of the signal between different tissues provide image contrast. In principle, every molecule of a diagnostic radiopharmaceutical can be detected over its lifetime, providing extraordinary sensitivity for imaging [3, 4]. In practice, however, several factors—including the limits of detection devices, the absorption of emissions before they leave the body (attenuation), and the need to limit radiation exposure to patients—all impose limits on imaging the emissions from a radiopharmaceutical. That said, it is possible to generate high-quality images using radioactivity doses as low as 30–600 MBq, values which correspond to as little as nanomoles of the compound or less, depending upon the half-life of the radionuclide [5–7] (see Table 1 for a representative calculation). This unique property allows radiopharmaceuticals to behave as true molecular tracers without perturbing the native biochemistry of the system, following the tracer principle of De Hevesy [2].

Why Nuclear Radiotherapy?

Nuclear radiotherapy (also called radionuclide therapy) is predicated on the use of radiopharmaceuticals to deliver therapeutic radiation to a target within the body [8–10]. For example, diphosphonates—which are commonly labeled with the gamma-emitting radionuclide ^{99m}Tc to enable the imaging of bone mineralization——can also be labeled with a beta particle-emitting radionuclide such as ^{153}Sm to deliver therapeutic radiation to sites of new bone formation, most typically for the treatment of cancer metastases [11]. Nuclear radiotherapy offers some significant advantages over traditional systemic therapy with nonradioactive drugs (*e.g.* chemotherapy) and external beam radiotherapy. Unlike traditional chemotherapeutics, radiopharmaceuticals can deliver potent therapeutic doses that are not limited by the biochemical action of the drug on the target. Radiopharmaceuticals are administered at low molecular doses and therefore do not generate the nonspecific off-target biochemical effects that can be seen at higher doses of chemotherapeutics. Compared to external beam radiotherapy, molecularly targeted radiopharmaceuticals are typically able to deliver radiation to tissues more selectively than

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Table 1 Example of the nuclear medicine tracer principle based on radiopharmaceutical radioactivity dose and theoretical mass limits

The following illustrates the tracer principle of nuclear imaging in the case of the radiopharmaceutical [^{18}F]fluoroestradiol (FES), an analog of estradiol used for the visualization of the regional expression of the estrogen receptor (ER) in breast cancer [5, 6]
Calculation of the molecular quantity of FES needed to image regional ER expression
Radioactivity needed to generate an image, balancing radiation dose and imaging quality: 185 MBq (5 mCi)
Typical specific activity of FES at the time of injection: 37 GBq/μmol (1 Ci/μmole)
The molar dose associated with this dose of radioactivity: 5 nmol
Expected peak concentration after the infusion of FES for a typical 5 L distribution volume: 1 nM
Physiologic range for the concentration of circulating estradiol: as low as 1 nM in menopausal patients
Thus—at transient peak concentrations—the molecular concentration of FES is at or below the lower limits of physiologic concentrations of estradiol, permitting PET imaging of FES-ER binding without perturbing the biology of native estrogen

spatially-targeted external beam radiotherapy. For example, nuclear radiotherapy of thyroid cancer with Na^{131}I can deliver up to 10–15 Gy to thyroid cancer cells without disturbing most adjacent neck tissues. In contrast, only 5–7 Gy can be deposited in the thyroid cancer cells during external beam radiotherapy due to concerns surrounding the toxicity to normal tissues [12]. Yet nuclear radiotherapy is not perfect, of course. Indeed, nuclear radiotherapy is limited by the specificity of the probe for the targeted disease—typically cancer or endocrine disorders—and by the toxicity to organs involved in the absorption, transport, and clearance of the radiopharmaceuticals.

Why Nuclear Medicine Vis-a-Vis Alternatives?

Nuclear imaging and radiotherapy gain their principal advantages over competing approaches from the "tracer principle." The essence of "tracer principle" is that radiopharmaceuticals are administered at such low molar masses that they can create high-contrast images or deliver therapeutic doses without perturbing native biochemistry whatsoever. As such, nuclear medicine approaches hold their greatest advantages over other forms of imaging and therapy in molecularly sensitive processes—*i.e.* those that are most readily affected by low doses of exogenous molecules—including metabolism, receptor binding, and cellular transport [2, 13, 14]. More specifically, glucose metabolism [13, 15], binding to neuroendocrine and steroid receptors [5], and amino acid transport [16, 17] are three clinically important examples of biologic processes that are well served by radiopharmaceutical-based strategies. Nonetheless, nuclear medicine approaches inevitably have some disadvantages compared to other imaging and therapeutic modalities:

- Nuclear medicine offers limited spatial resolution compared to modalities such as X-ray or CT.
- Nuclear medicine involves exposure to radiation, unlike modalities such as MRI or ultrasound.
- Nuclear medicine requires patient-specific radiation safety precautions for treatments, unlike chemotherapy and external beam radiotherapy.

Ultimately, the advantages of nuclear approaches outweigh their disadvantages when applied to diseases associated with molecular targets that can be targeted by diagnostic or therapeutic radiopharmaceuticals. This has led to the considerable use of radiopharmaceuticals in both clinical practice and clinical research for oncology, endocrinology, neuropsychiatry, cardiology, and several other diseases, as outlined later in the chapter.

Details

Clinical Applications for Nuclear Imaging

Nuclear imaging is a key tool for clinical diagnosis that is used thousands of time each day around the world. It is most commonly used to detect and quantify organ function and/or abnormal physiology and molecular biochemistry in a variety of disorders [1]. The need to trace a particular physiologic process or molecular pathway is a common trait of many current clinical applications. Below is a non-exhaustive list of common clinical situations in which nuclear imaging is applied, in rough order of frequency. One or more examples of radiopharmaceuticals used for each application are provided as well.

- *To detect cancer and/or document its spread:*
  - By imaging aberrant glucose metabolism using [^{18}F]fluorodeoxyglucose (FDG) [15] (Fig. 1)
  - By imaging abnormal amino acid transport using [^{18}F]fluciclovine [16, 17] (FACBC)
  - By imaging the expression of cancer-specific biomarkers using ^{18}F- and ^{68}Ga-labeled small-molecule ligands that target prostate-specific membrane antigen [18]
  - By imaging new bone formation associated with cancer metastases using [^{99m}Tc]methylene diphosphonate (MDP) or [^{18}F]NaF [19] (Fig. 2)
- *To identify and quantify endocrine disorders:*
  - By characterizing and quantifying the basis of hyperthyroidism indicated by the uptake and retention of iodine using [^{123}I]NaI [20]
  - By localizing abnormal catecholamine-producing tumors such as pheochromocytomas and neuroblastomas using [^{123}I]metaiodobenzylguanidine (mIBG) [21]

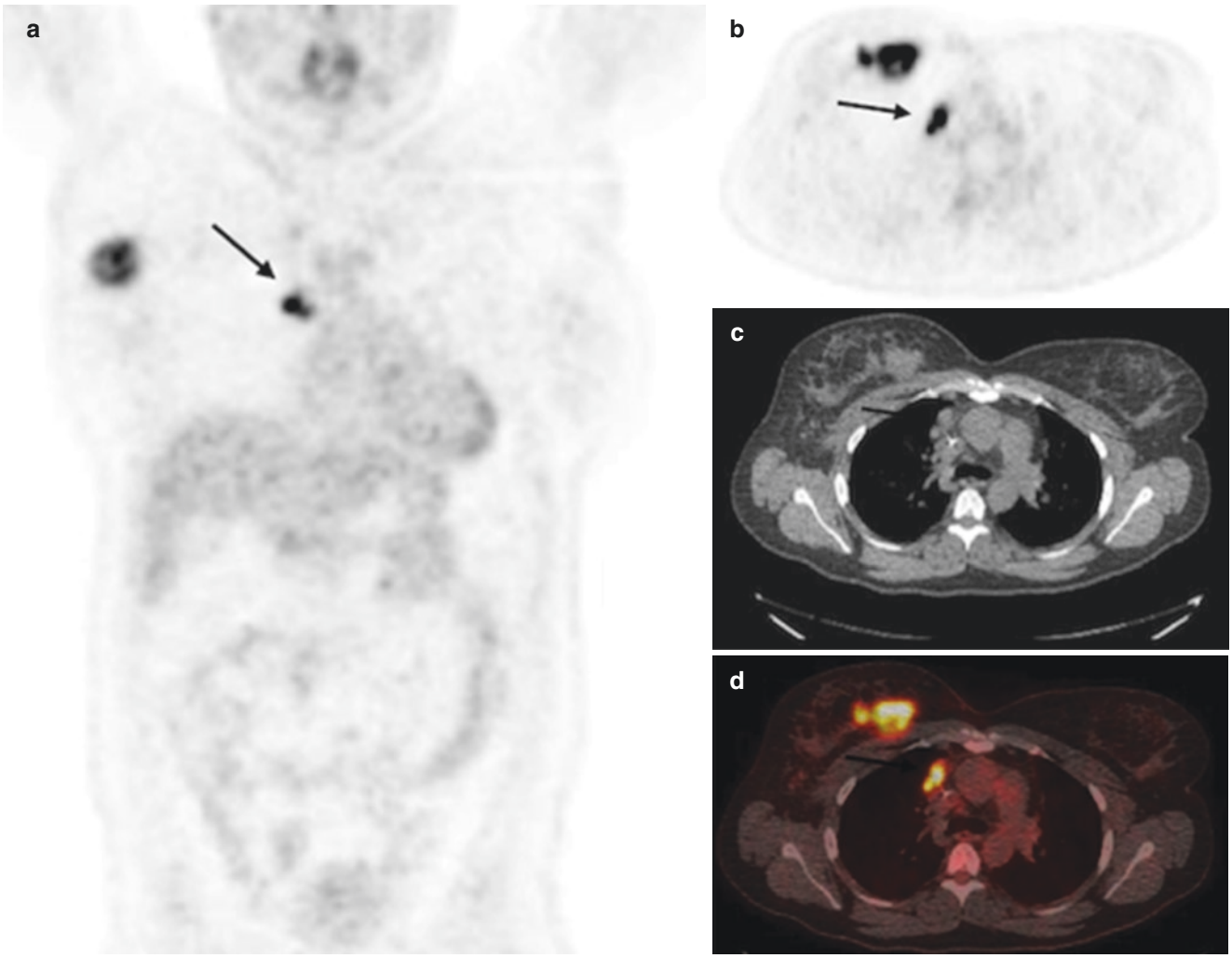

Fig. 1 [^{18}F]fluorodeoxyglucose ([^{18}F]FDG) PET/CT of breast cancer demonstrates the spread of the disease to small mediastinal nodes that are not detected by CT (*arrows*). Image **a** is a coronal PET image of the regional retention of FDG; on the right, axial PET images (**b**) have been combined with CT in the images (**c**) to yield fused images overlaying PET and CT images (**d**)

  - By localizing neuroendocrine tumors on the basis of somatostatin receptor expression using [^{111}In]pentetreotide or [^{68}Ga]-DOTATATE [21] (Fig. 3)
- *To detect and monitor cardiovascular disease:*
  - By identifying significant coronary artery disease on the basis of the delivery of perfusion agents retained in myocardium using [^{99m}Tc]sestamibi or [^{82}Rb]RbCl [22, 23]
  - By measuring aberrant presynaptic cardiac innervation in heart failure and arrhythmias using [^{123}I]mIBG [24]
- *To identify patterns associated with specific neurologic and psychiatric diseases:*
  - By identifying seizure foci on the basis of aberrant perfusion and/or glucose metabolism using [^{99m}Tc]ECD or [^{18}F]FDG, respectively [25]
  - By diagnosing Alzheimer's dementia on the basis of the deposition of amyloid in neural plaques using [^{11}C] Pittsburgh compound B (PIB) or ^{18}F-labeled analogs [26] (Fig. 4)
- *To document normal and abnormal function of excretory organs:*
  - By determining the causes of renal dysfunction by tracing the clearance of renal substrates using [^{99m}Tc] MAG3 [27]
  - By documenting cholecystitis and biliary dyskinesia by tracking biliary excretion using [^{99m}Tc]mebrofenin [28]
- *To identify regional tissue damage due to infection, trauma, etc.:*
  - By localizing bone trauma and infection on the basis reactive new bone formation using [^{99m}Tc]MDP [19]
  - By localizing infection using white blood cells (WBCs) labeled using [^{111}In]oxime [29]

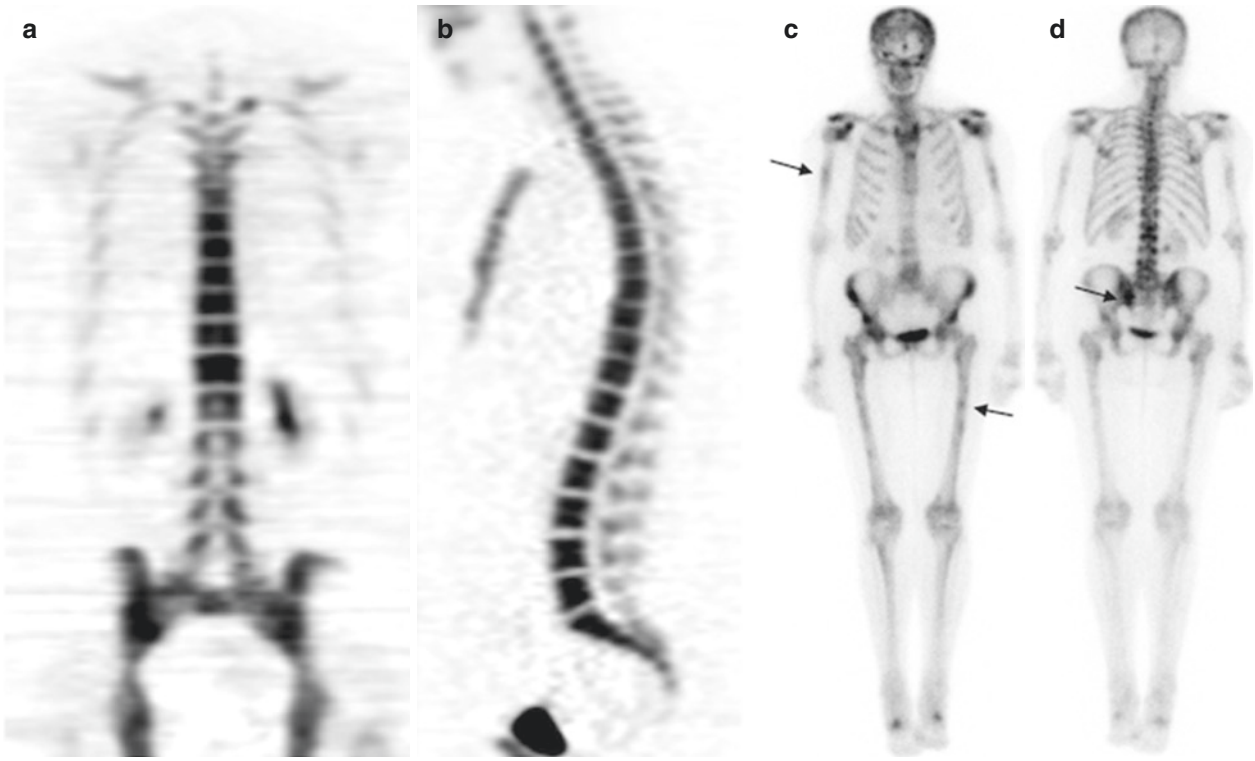

Fig. 2 Bone imaging using [^{18}F]NaF (PET imaging, **a** and **b**) [^{99m}Tc] methylene diphosphonate (MDP, single-photon imaging, **c** and **d**). The FDG PET scan shows the normal distribution of the tracer from the skull base to the pelvis in coronal (**a**) and sagittal tomographic views (**b**). The MDP bone scan shows anterior (**c**) and posterior (**d**) planar images that demonstrate multiple bone metastases, including sites in the left femur, right humerus, and left sacrum (*arrows*)

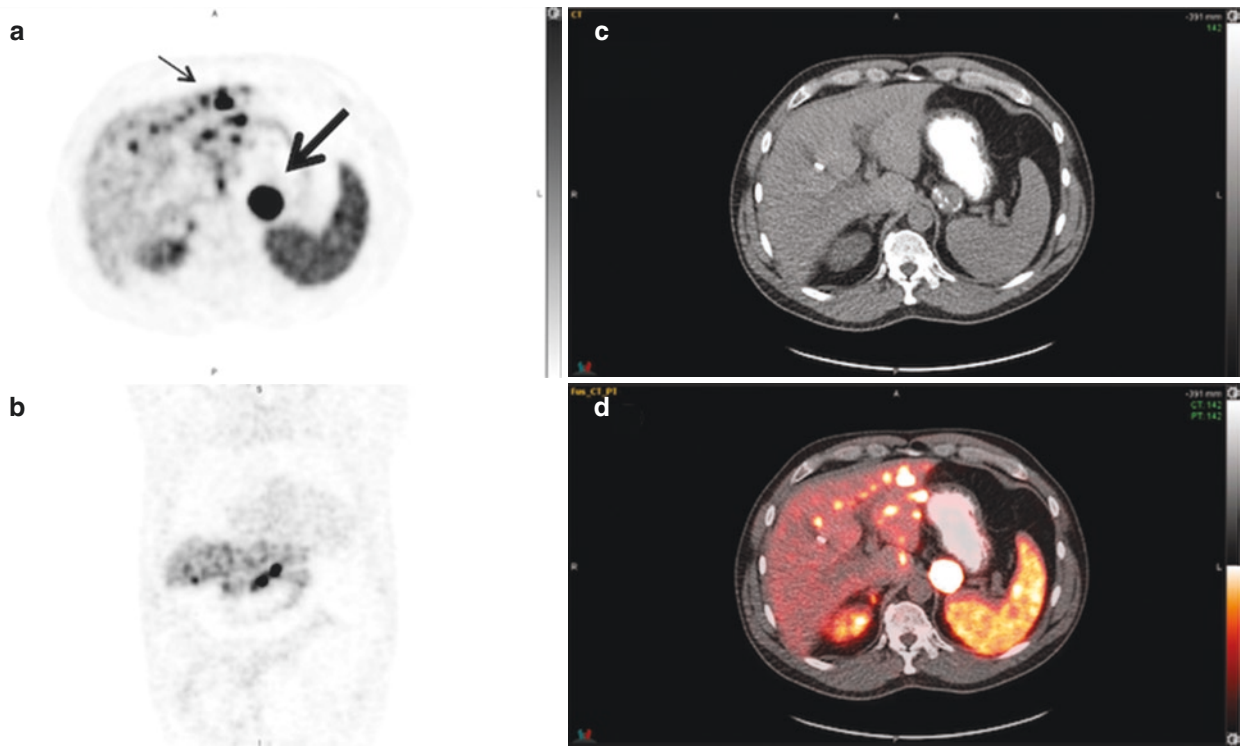

Fig. 3 The staging of neuroendocrine tumors using [^{68}Ga]DOTATE PET/CT. These images demonstrate the feasibility of imaging somatostatin receptor-expressing carcinoid tumor deposits on the emission PET scans (axial view, **a**, coronal view, **b**) and relate the localization of sites of radiopharmaceutical uptake to anatomic sites indicated by the accompanying CT (**c**) and depicted on fused PET and CT images (**d**). Images depict a low-grade neuroendocrine tumor presenting as a perigastric mass (thick arrow) with numerous liver metastases (*thin arrow*)

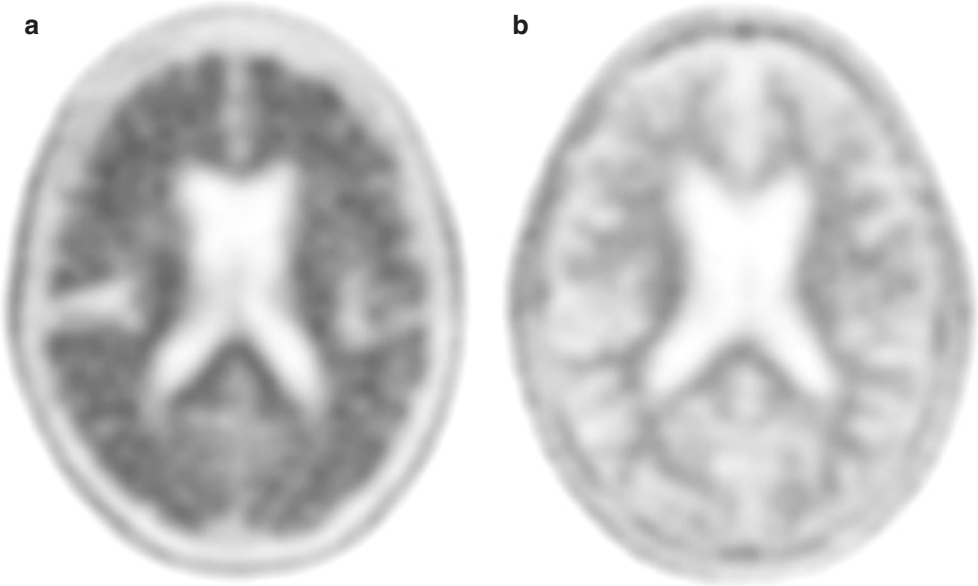

Fig. 4 Imaging amyloid deposition in Alzheimer's dementia neural plaques using [^{18}F]florbetapir. [^{18}F] florbetapir PET images from an Alzheimer's disease patient (**a**) and a normal control subject (**b**) are shown. The prominent cortical tracer binding in (**a**) indicates the presence of moderate amyloid plaques, as compared to absence of cortical binding in a negative scan (**b**). Nonspecific white matter binding is present in both the positive and negative [^{18}F] florbetapir scans

A common thread that runs through all of these applications is the need to localize and measure specific physiologic and molecular processes associated with either normal organ function or tissue dysfunction. In recent years, fundamental research in biology has led to the identification of new targets, and radiopharmaceutical chemists have leveraged this information for the creation of novel radiopharmaceuticals. This has increased the specificity of clinical diagnostic tasks through the use of imaging agents based on receptor-targeted ligands, substrates for specific transporters, and metabolic substrates specific to certain disease and tissue repair processes [14, 30, 31].

Clinical Applications of Nuclear Radiotherapy

Nuclear radiotherapy, while certainly an important clinical tool, is somewhat less commonly used than nuclear imaging. The first—and still most common—use of nuclear radiotherapy is the treatment of hyperthyroidism caused by Graves' disease and toxic nodular goiter. In this approach, modest doses of [^{131}I]NaI provide a safe and highly effective therapeutic alternative to more risky and/or toxic alternatives such as surgery or antithyroid medications. Specifically, in Graves' disease and toxic nodular goiter—in which a large fraction of ingested iodine (typically, well in excess of 30%) goes to the thyroid—thyroid tissue can be ablated by targeted radiotherapy with minimal radiation exposure to the rest of the body [32, 33].

The remaining applications of nuclear therapy largely focus on treating cancer, in which the small risk of modest radiation exposure to some normal tissues is offset by the potential for considerable therapeutic efficacy in otherwise often refractory disorders [8, 34]. The established therapeutic radiopharmaceuticals rely upon targeting either transport phenomena, metabolic pathways, or characteristic tumor biomarkers. Some examples of the established roles of nuclear radiotherapy in the treatment of cancer include:

- Thyroid cancer, using [^{131}I]NaI (typically higher doses than those needed in hyperthyroid treatments) [12] (Fig. 5)
- Painful bone metastases, using bone-targeting agents such as [^{89}Sr]$SrCl_2$, [^{223}Ra]$RaCl_2$, and [^{153}Sm]EDMP [11]
- Catecholamine-producing cancers (*i.e.* neuroblastoma and malignant pheochromocytoma), using the catecholamine transporter substrate [^{131}I]mIBG [21, 35]
- Neuroendocrine tumors, using ^{177}Lu or ^{90}Y-labeled analogs of somatostatin receptor-targeted peptides [21]

An additional type of nuclear radiotherapy is termed "radioimmunotherapy" and takes advantage of the specificity and affinity of monoclonal antibodies for molecular markers of disease. Radioimmunotherapy is predicated on the use of therapeutic radioimmunoconjugates, most commonly labeled with beta particle-emitting radionuclides such as ^{131}I or ^{90}Y [36, 37]. The application of radioimmunotherapy to B-cell lymphoma generated considerable excitement and resulted in two FDA-approved agents—Bexxar and Zevalin—which are based on anti-CD20 antibodies labeled with ^{131}I and ^{90}Y, respectively [37]. Though these were popular at the time of their introduction, advances in the application of non-labeled anti-CD20 antibodies (*e.g.* rituximab) and other drugs limited the more widespread use of these agents.

There has been considerable recent excitement over the future of nuclear radiotherapy [34]. This optimism has been driven by two recent trends in radiopharmaceutical research:

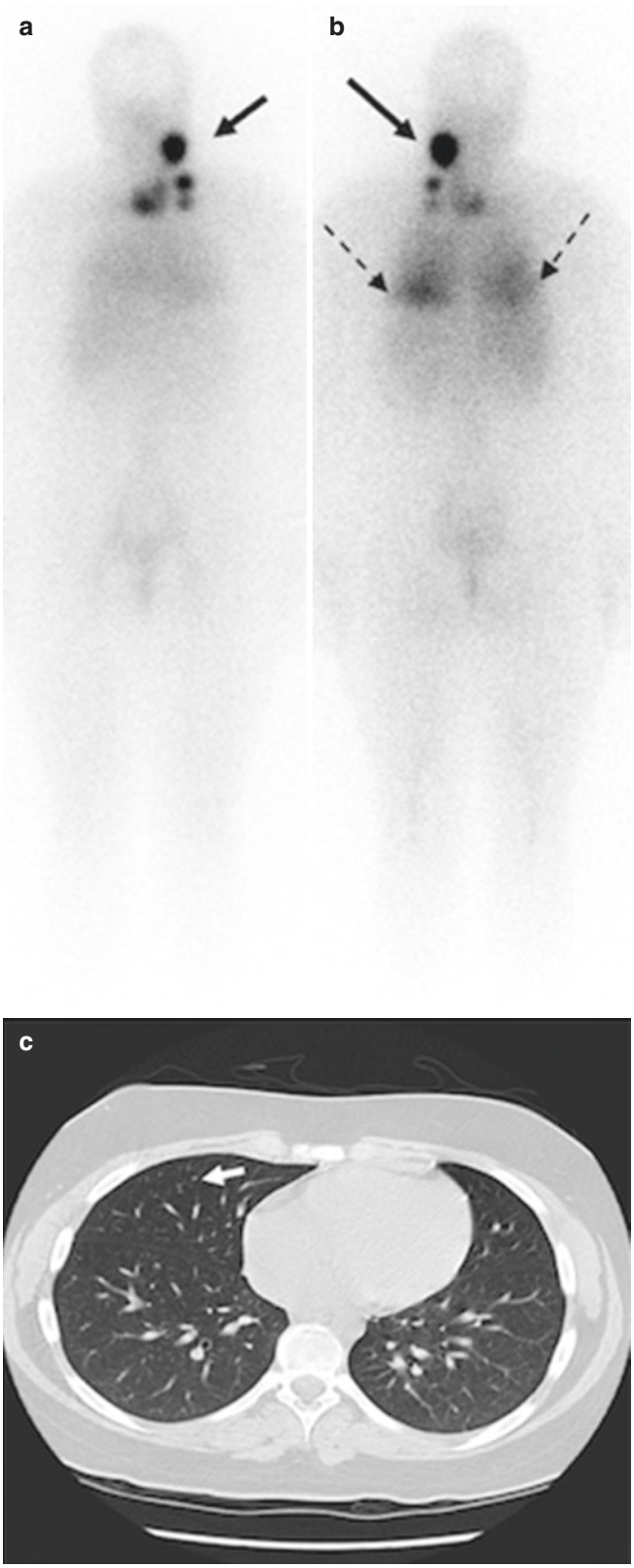

Fig. 5 Imaging with [^{123}I]NaI or low-dose [^{131}I]NaI provides a highly sensitive and specific way to detect the metastatic spread of thyroid cancer to sites of disease outside of the neck. In this case, anterior (**a**) and posterior (**b**) planar whole-body images taken 7 days after a therapeutic dose of [^{131}I]NaI demonstrate regional lymph node metastases in the neck (*solid arrow*) and distant metastatic spread to the small nodules in the lung bases (*dashed arrows*). Lung metastases were not as easily seen by CT (**c**, arrow indicates a single small nodule) but were readily apparent in the radioiodine images

1. The increased success in generating highly targeted small molecules and peptides that have high uptake and retention in cancerous tissues (*e.g.* PSMA-targeted therapeutics for prostate cancer) [18].
2. The increased potency and efficacy for therapeutic radiopharmaceuticals labeled with alpha-emitting radionuclides. For example, the recent approval of the alpha-emitting radiotherapeutic [^{223}Ra]$RaCl_2$ was heralded in clinical trials for demonstrating both highly effective pain palliation and improved survival [9]. This represents a notable departure from many years of experience with beta-emitting therapeutics which provided effective pain palliation but did not improve survival [11].

Tricks of the Trade

What Tools Do We Need?

The current and future success of nuclear imaging and therapy depends on several key technical issues:

- *Imaging instrumentation*: Over 50 years ago, the specialty of nuclear medicine was brought into the mainstream by the advent of the gamma camera, which enabled the practical collection of high-quality single-photon emitting radiopharmaceutical images in the clinic. In the 1990s and early 2000s, the advent of clinically practical positron emission tomography (PET) and PET/CT enabled clinical PET imaging to become an important and rapidly advancing part of nuclear medicine. Advances in the design of detectors and imaging systems have played a large role in the advancement of nuclear medicine [38] and have enabled the acquisition of high-quality, quantitative images with lower and lower doses of radiopharmaceuticals. Further advances in the design of hybrid imaging platforms and novel imaging devices will likely add significantly to our current capabilities [3, 4].
- *Image computing and analytics*: Advances in computational capability—enabled by advances in computing hardware and algorithms—have led to improved imaging quality at low tracer doses though sophisticated image reconstruction and post-reconstruction processing [39]. Further advances in image analysis and advanced analytics (such as machine learning-based feature extraction) will continue to maximize our ability to draw meaningful diagnostic information from nuclear imaging and guide the safer and more effective dosing in nuclear radiotherapy.

However, while instrumentation and analytics have set the pace of discovery and advancement in nuclear medicine for many years, the future of the specialty will increasingly be determined by radiopharmaceutical research and development.

Rapid advances in our understanding of the molecular biology of health and disease underlie an increasing trend toward precision medicine using treatments guided by molecular diagnostics [14, 30, 31, 40]. As such, advances in nuclear medicine will increasingly be driven by the development of new and improved radiopharmaceuticals to guide precision medicine. The creation of paired nuclear diagnostic and therapeutic agents—known as "theranostics"—will be particularly important, as theranostics provide unparalleled opportunities with regard to the selection of patients for treatment as well as the monitoring of ongoing therapies [34]. There is therefore much reason to believe that radiopharmaceutical chemistry will increase in importance as a discipline in nuclear medicine specifically and biomedical research in general.

Controversial Issues

Will Other Imaging and Therapeutic Approaches Replace Nuclear Approaches?

The need to administer radioisotopes—and the inherent practical difficulties and need for radiation exposure—has been seen as a disadvantage of nuclear medicine since its creation. This has led many to predict the demise of the specialty over the years, especially in light of the advent of new imaging modalities such as CT and MRI. In addition, the recent development of nonnuclear probes with molecular capability—*e.g.* agents for ultrasound, optical imaging, and hyperpolarized MR—has created concerns about incremental threats to the field. Some of these concerns have been realized. For example, the use of CT to detect liver metastases replaced the nuclear liver spleen scan in the 1980s.

However, nuclear imaging procedures continue to retain significant advantages over other approaches, especially when the application is focused upon the molecular basis of the disease. For example, the aberrant glycolysis of malignant tissues compared to normal tissues reintroduced nuclear imaging as a key component of the detection of liver metastasis using [^{18}F]FDG PET/CT and now PET/MR [41]. The ongoing discovery of disease-specific biomarkers will provide an increasing basis for the use of molecular tracers for the diagnosis and treatment of disease [40]. As a result, the ongoing application of nuclear medicine for diagnosis and treatment will depend critically on radiochemistry.

The Future

What Does the Future of Nuclear Medicine Look Like?

The future of nuclear medicine will continue to exploit the unique properties of radiopharmaceuticals to exploit the tracer principle for diagnosis and treatment. Several issues within the field of radiochemistry will help drive the future of nuclear medicine [14, 30, 31]:

- *The development of precision diagnostics for precision medicine*
- *The creation of improved targeted therapeutics for cancer and other diseases*
- *The advent of paired diagnostics and therapeutics*, with nuclear imaging paired with both nuclear and non-nuclear therapeutics

The Bottom Line

- Nuclear medicine is the application of radioactive elements to medicine.
- Radiopharmaceuticals operate on the "tracer principle," namely, that radioactive tracers are administered at such low molar doses that they do not perturb the native biology of the system into which they are introduced.
- Nuclear imaging radiopharmaceuticals provide high sensitivity and molecular specificity.
- Radionuclide therapy provides a highly targeted treatment modality based upon the physical impact of radiation. It is similar to external beam radiotherapy but much more targeted.
- Radiopharmaceuticals provide a key link between basic biology and clinical practice. The future of nuclear medicine depends upon the ability of radiopharmaceutical chemists to leverage advances in molecular biology into new approaches to clinical imaging and therapy.

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References

1. Frey KA, Royal HD, Di Carli MF, Dillehay GL, Gordon L, Mankoff DA, et al. ABNM position statement: nuclear medicine professional competency and scope of practice. J Nucl Med. 2011;52(6):994–7.
2. Mankoff DA. A definition of molecular imaging. J Nucl Med. 2007;48(6):18N. 21N
3. Cherry SR, Badawi RD, Karp JS, Moses WW, Price P, Jones T. Total-body imaging: transforming the role of positron emission tomography. Sci Transl Med. 2017;9(381):pii: eaaf6169.
4. Surti S. Update on time-of-flight PET imaging. J Nucl Med. 2015;56(1):98–105.
5. Mankoff DA, Link JM, Linden HM, Sundararajan L, Krohn KA. Tumor receptor imaging. J Nucl Med. 2008;9(Suppl 2):149S–63S.
6. Peterson LM, Kurland BF, Link JM, Schubert EK, Stekhova S, Linden HM, et al. Factors influencing the uptake of

[18]F-fluoroestradiol in patients with estrogen receptor positive breast cancer. Nucl Med Biol. 2011;38(7):969–78.
7. Tu Z, Mach RH. C-11 radiochemistry in cancer imaging applications. Curr Top Med Chem. 2010;10(11):1060–95.
8. Jhanwar YS, Divgi C. Current status of therapy of solid tumors. J Nucl Med. 2005;46(Suppl 1):141S–50S.
9. Parker C, Nilsson S, Heinrich D, Helle SI, O'Sullivan JM, Fossa SD, et al. Alpha emitter radium-223 and survival in metastatic prostate cancer. N Engl J Med. 2013;369(3):213–23.
10. Schmidt M, Baum RP, Simon T, Howman-Giles R. Therapeutic nuclear medicine in pediatric malignancy. Q J Nucl Med Mol Imaging. 2010;54(4):411–28.
11. Pandit-Taskar N, Batraki M, Divgi CR. Radiopharmaceutical therapy for palliation of bone pain from osseous metastases. J Nucl Med. 2004;45(8):1358–65.
12. Pryma DA, Mandel SJ. Radioiodine therapy for thyroid cancer in the era of risk stratification and alternative targeted therapies. J Nucl Med. 2014;55(9):1485–91.
13. Cutler CS, Lewis JS, Anderson CJ. Utilization of metabolic, transport and receptor-mediated processes to deliver agents for cancer diagnosis. Adv Drug Deliv Rev. 1999;37(1–3):189–211.
14. O'Connor JP, Aboagye EO, Adams JE, Aerts HJ, Barrington SF, Beer AJ, et al. Imaging biomarker roadmap for cancer studies. Nat Rev Clin Oncol. 2017;14(3):169–86.
15. Mankoff DA, Eary JF, Link JM, Muzi M, Rajendran JG, Spence AM, et al. Tumor-specific positron emission tomography imaging in patients: [18F] fluorodeoxyglucose and beyond. Clin Cancer Res. 2007;13(12):3460–9.
16. Huang C, McConathy J. Radiolabeled amino acids for oncologic imaging. J Nucl Med. 2013;54(7):1007–10.
17. Schuster DM, Nanni C, Fanti S. Evaluation of prostate cancer with radiolabeled amino acid analogs. J Nucl Med. 2016;57(Suppl 3):61S–6S.
18. Schwarzenboeck SM, Rauscher I, Bluemel C, Fendler WP, Rowe SP, Pomper MG, et al. PSMA ligands for PET imaging of prostate cancer. J Nucl Med. 2017;58(10):1545–52.
19. Even-Sapir E. Imaging of malignant bone involvement by morphologic, scintigraphic, and hybrid modalities. J Nucl Med. 2005;46(8):1356–67.
20. Meller J, Becker W. The continuing importance of thyroid scintigraphy in the era of high-resolution ultrasound. Eur J Nucl Med Mol Imaging. 2002;29(Suppl 2):S425–38.
21. Baum RP, Kulkarni HR, Carreras C. Peptides and receptors in image-guided therapy: theranostics for neuroendocrine neoplasms. Sem Nucl Med. 2012;42(3):190–207.
22. Bravo PE, Di Carli MF, Dorbala S. Role of PET to evaluate coronary microvascular dysfunction in non-ischemic cardiomyopathies. Heart Fail Rev. 2017;22(4):455–64.
23. Dorbala S, Di Carli MF. Cardiac PET perfusion: prognosis, risk stratification, and clinical management. Sem Nucl Med. 2014;44(5):344–57.
24. Jamali HK, Waqar F, Gerson MC. Cardiac autonomic innervation. J Nucl Cardiol. 2017;24(5):1558–70.
25. Mountz JM, Patterson CM, Tamber MS. Pediatric epilepsy: neurology, functional imaging, and neurosurgery. Sem Nucl Med. 2017;47(2):170–87.
26. Nasrallah IM, Wolk DA. Multimodality imaging of Alzheimer disease and other neurodegenerative dementias. J Nucl Med. 2014;55(12):2003–11.
27. Taylor AT. Radionuclides in nephrourology, Part 2: pitfalls and diagnostic applications. J Nucl Med. 2014;55(5):786–98.
28. Ziessman HA. Hepatobiliary scintigraphy in 2014. J Nucl Med. 2014;55(6):967–75.
29. Palestro CJ. Radionuclide imaging of musculoskeletal infection: a review. J Nucl Med. 2016;57(9):1406–12.
30. Aboagye EO, Kraeber-Bodere F. Highlights lecture EANM 2016: "Embracing molecular imaging and multi-modal imaging: a smart move for nuclear medicine towards personalized medicine". Eur J Nucl Med Mol Imaging. 2017;44(9):1559–74.
31. Jaffee EM, Dang CV, Agus DB, Alexander BM, Anderson KC, Ashworth A, et al. Future cancer research priorities in the USA: a Lancet Oncology Commission. Lancet Oncol. 2017;18(11):e653–706.
32. Biersack HJ, Hotze A. The clinician and the thyroid. Eur J Nucl Med. 1991;18(9):761–78.
33. Smith TJ, Hegedus L. Graves' disease. N Engl J Med. 2016;375(16):1552–65.
34. Yordanova A, Eppard E, Kurpig S, Bundschuh RA, Schonberger S, Gonzalez-Carmona M, et al. Theranostics in nuclear medicine practice. Onco Targets Ther. 2017;10:4821–8.
35. Divgi C. Targeted systemic radiotherapy of pheochromocytoma and medullary thyroid cancer. Sem Nucl Med. 2011;41(5):369–73.
36. Larson SM, Carrasquillo JA, Cheung NK, Press OW. Radioimmunotherapy of human tumours. Nat Rev Cancer. 2015;15(6):347–60.
37. Pandit-Taskar N, Hamlin PA, Reyes S, Larson SM, Divgi CR. New strategies in radioimmunotherapy for lymphoma. Curr Oncol Rep. 2003;5(5):364–71.
38. Mankoff DA, Pryma DA. The contribution of physics to Nuclear Medicine: physicians' perspective on future directions. EJNMMI Phys. 2014;1(1):5.
39. Bhargava R, Madabhushi A. Emerging themes in image informatics and molecular analysis for digital pathology. Annu Rev Biomed Eng. 2016;18:387–412.
40. Mankoff DA, Farwell MD, Clark AS, Pryma DA. Making molecular imaging a clinical tool for precision oncology: a review. JAMA Oncol. 2017;3(5):695–701.
41. Khandani AH, Wahl RL. Applications of PET in liver imaging. Radiol Clin N Am. 2005;43(5):849–60, vii.