

Chapter 21

Back to the Future: Nuclear Medicine Rediscovered Its Therapeutic Roots

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Abstract Before the advent of diagnostic imaging, nuclear medicine was a treatment modality. The first therapeutic application of radioisotopes was almost contemporaneous with the discovery of radioactivity. P-32 became one of the first effective therapies for a range of malignant blood disorders; I-131 was established as the benchmark for the treatment of metastatic thyroid cancer; Sr-89 was recognised to provide palliative benefit in advanced prostate cancer. The development of tomographic imaging with SPECT and PET, further enhanced by hybrid CT or MRI devices, has recently focussed the speciality of nuclear medicine on the diagnostic use of isotopes. Against this trend there has been renewed awareness on the ability of radiotracers to identify potential therapeutic targets and to use this information to select patients for and to monitor the efficacy of targeted therapies using radioisotopes. This process has been termed “theranostics”. A significant factor in the rebirth of therapeutic nuclear medicine has been the development of peptides labelled with Ga-68 and Lu-177. Ga-68 DOTA-octreotate PET/CT and Lu-177 DOTA-octreotate peptide receptor radionuclide therapy (PRRT) provides the modern prototype of the theranostic paradigm. Experience with PRRT has, however, emphasised the need for a more rigorous scientific approach to radionuclide therapy. The future holds promise of wide range of therapeutic options based on diagnostic/therapeutic pairs including I-124/I-131 and Cu-64/Cu-67. Quantitative SPECT/CT and PET/CT will be key platform technologies for planning and monitoring such therapy and will realise the true promise of molecular imaging in characterising rather than just finding disease.

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21.1 Introduction

Many current practitioners working in nuclear medicine are unaware of its rich history as a therapeutic modality. For interested readers, a delightful series of anecdotes and historical vignettes are contained in Marshall Brucer's "A Chronology of Nuclear Medicine" (Publisher: Robert R Butaine (September 1990) ISBN-10: 096256740X, ISBN-13: 978-0962567407). To summarise this fascinating tale of discovery, serendipity and human sacrifice are beyond the scope of this paper but I will try to cover its key events in order to provide a background to current advances in nuclear medicine practice that I believe will be fundamental to its future evolution.

21.2 Radioisotopes Become Therapeutic Tools

Shortly after the discovery of radioactivity in naturally occurring elements by Henri Becquerel in 1896 and the subsequent isolation of radium by Marie and Pierre Curie in 1898, Pierre Curie became aware of the potential of radioactive elements to damage cells, when he himself sustained a very slow healing radiation ulcer on his chest after carrying a sample of radium to a lecture at the Sorbonne in Paris. Louis Pasteur opined that chance favours the prepared mind. In this case, this simultaneously unfortunate but fortuitous event led Pierre Curie to ponder whether radium might have potential therapeutic application in the treatment of malignant skin lesions. In a seminal example of translational research, he discussed this with a medical colleague, Henri-Alexandre Danlos, who successfully treated patients with aggressive squamous cell and basal cell cancers. This quickly led to the dissemination of radium throughout the world for treatment, first of skin cancers and, later, of all manner of malignancies. Intra-tumoural administration of radium was a forerunner of modern brachytherapy. However, it soon became clear that despite, at times, dramatic therapeutic effects, this treatment, particularly when administered systemically, could have significant side effects, including death but, particularly, haematological disorders and, in the case of radium, osteosarcoma. Marie Curie herself died of aplastic anaemia. Although this has been attributed to her exposure to radioisotopes, she also would have received substantial radiation while using unshielded X-rays while operating a field ambulance service in World War 1.

The development of the cyclotron by Ernest O. Lawrence provided a range of new isotopes [1]. One of these, P-32, was found to suppress blood counts, and again in a serendipitous manner, Lawrence's brother was a haematologist and decided to try this agent for the treatment of a patient. This patient was, in fact, a medical

student, with chronic myeloid leukaemia. The dramatic benefit from this treatment led to its use in a range of other blood malignancies. P-32 remains a useful treatment for myeloproliferative syndromes, especially in the elderly who tolerate chemotherapy poorly. In studying calcium metabolism using Sr-89, a Belgian by the name of Charles Pecher believed he had discovered a cure for metastatic prostate cancer following dramatic and complete pain relief in a patient suffering from advanced stages of this disease. Although this discovery was lost for a period of time due to a combination of the untimely death by suicide of Pecher and suppression of information about the American nuclear weapons program, it was “rediscovered” in the 1970s and was the first of a range of bone-seeking radiopharmaceuticals that came into widespread use in the 1980s and 1990s [2]. In studying thyroid function using I-130 in the 1930s, the development of hypothyroidism was recognised and leveraged for the treatment of thyrotoxicosis. Subsequently, Glenn Seaborg and John Livingood made I-131 and Sam Seidlin applied it to the treatment of metastatic thyroid cancer in the 1940s [3]. It has since become an integral part of the management of thyroid cancer. The ability to iodinate biologically relevant molecules was translated into other therapies including I-131 metaiodobenzylguanidine. I was privileged to be trained in therapeutic nuclear medicine at the University of Michigan by some of the pioneers of this therapy, James Sisson and Brahm Shapiro [4]. This treatment remains an important therapeutic option for the treatment of metastatic pheochromocytoma and paraganglioma and also in refractory neuroblastoma [5]. While these therapeutic techniques have continued to be used by nuclear medicine physicians, with the exception of I-131 therapy of thyroid cancer, they are often seen as the treatment of last resort after surgery, chemotherapy, targeted agents and radiotherapy have failed.

21.3 The Rise and Rise of Imaging

In evaluating the uptake and retention of I-131 in thyroid cancer metastases, Sam Seidlin used a Geiger-Muller counter since nuclear imaging hadn't been conceived. It wasn't until the advent of the rectilinear scanner, conceived by Benedict Cassen, that it became possible to image the internal distribution of radiopharmaceuticals. In the first of many seminal contributions to the field of nuclear medicine, David Kuhl combined photographic film to the rectilinear scanner to create the photoscanner [6]. He subsequently developed the principles of tomographic imaging while being a resident in the Radiology Department of the University of Pennsylvania [7]. Using an Am-245 source, he created the first transmission scan, a forerunner of X-ray computed tomography [8], and also performed emission tomography, the forerunner of single-photon emission computed tomography (SPECT) [9]. Gordon Brownell developed coincidence detection to acquire multiplanar images from positron-emitting radionuclides, and Michael Phelps and Ed Hoffman adopted this approach and combined it with the tomographic method developed by Kuhl to create positron emission tomography (PET). The first human

scanner was released in 1976 [10]. The real revolution in PET came with the development of the glucose analogue F-18 fluorodeoxyglucose (FDG) [11]. It was both fortunate and tragic that FDG was one of the first PET tracers to become available. Its excellent performance for evaluating diseases of the heart [12] and brain [13] and more recently cancer has stifled the clinical application of other PET tracers. Even its lack of specificity in whole-body imaging mode has found application for the imaging of infection and inflammation.

Throughout the world FDG PET/CT has become the dominant molecular imaging technique for evaluating cancer with demonstrated effectiveness in diagnosis, staging, therapeutic response assessment and restaging. Further, it provides information of about the biological aggressiveness of tumours. With the addition of anatomical landmarks from CT, some see FDG as the ideal “contrast agent” for cancer detection and has encouraged many to consider nuclear medicine as a diagnostic imaging technique that should be integrated into radiology. This view has been strengthened by the development of hybrid PET-MRI scanners, which have a particular strength in localisation of disease sites.

The wider availability of PET/CT scanners has, however, made positron-emitting radiopharmaceuticals that were developed and used in the era of rectilinear scanners but which fell out of favour with the introduction of the gamma camera, attractive again. F-18 sodium fluoride (NaF) was formerly a widely used agent for bone scanning but was replaced by Tc-99 m bisphosphonates in routine nuclear medicine practice as the gamma camera replaced rectilinear scanners. NaF PET/CT is, however, clearly superior to Tc-99 m MDP SPECT/CT in terms of spatial and contrast resolution, enhancing both sensitivity and specificity [14]. Gallium-68 is another example of an old radionuclide being seen in a new light and will be addressed later.

The major focus of much PET radiopharmaceutical development has, however, been on compounds labelled with fluorine-18. This is a radionuclide that is easily produced in small cyclotrons in abundant quantities after a relatively short period of target irradiation. Its physical half-life is attractive both for distribution and imaging. In my own department we chose to establish fluorinated PET tracers in addressing areas in which FDG has demonstrable weaknesses and the alternative SPECT agents are also suboptimal. As a result, the amino acid analogue, F-18 fluoro-ethyl-tyrosine (FET), which has low uptake in normal brain tissue but enhanced transport into brain tumours, has replaced both FDG PET and Tl-201 SPECT brain tumour imaging in our facility [15], as it has in many other centres [16]. Similarly, the proliferation tracer, F-18 fluorothymidine (FLT) provides a conceptually more robust evaluation of the status of bone marrow function than does a range of techniques previously used to assess this using a gamma camera. Whereas we previously utilised either radiolabelled white blood cells or Tc-99 m antimony colloid scanning, we now exclusively use FLT to assess bone marrow reserves [17] or to assess unexplained cytopenias. Preliminary data suggests a potential role of this agent for assessing leukaemias [18]. Similarly, agents such as F-18 fluoro-methyl-choline (FCH) have also found a clinical role in the evaluation of cancers that tend to have low uptake of the conventional oncological PET tracer,

Table 21.1 Fluorinated tracers used clinically at the Peter MacCallum Cancer Centre

Agent	Abbreviation	Process	Clinical use
¹⁸ F-fluoro-deoxyglucose	FDG	Glycolytic metabolism	Most cancers Neutropaenic sepsis
¹⁸ F-fluoro-thymidine	FLT	Cell proliferation	Marrow status Tumour proliferation
¹⁸ F-sodium fluoride	NaF	Bone formation	Prostate cancer, breast cancer, osteosarcoma etc.
¹⁸ F-fluoro-methyl-choline	FCH	Membrane synthesis	Prostate cancer, lobular breast cancer
¹⁸ F-fluoro-ethyl-tyrosine	FET	Amino acid transport	Brain tumours
¹⁸ F-fluoro-azomycin-aribinoside	FAZA	Hypoxia	Assessment for hypoxia cytotoxins

FDG [19]. Prostate cancer and lobular breast cancer are notable examples [20]. Table 21.1 provides a list of fluorinated agents routinely used in my department for oncological indications. We have a range of other F-18-labelled agents that are still being evaluated in clinical trials. These include an agent with high specificity for melanin, an attractive target for imaging malignant melanoma.

Despite the attraction of F-18, there remained many aspects of oncological imaging practice that were still best served by single-photon-emitting radionuclides. This situation has more recently been addressed by development of gallium-68-based tracers. The germanium-gallium-68 generator has reintroduced a radionuclide that was first described more than 50 years ago. Providing an alternative to the technetium-99 m generator, Ga-68 provides the option of centres without immediate access to a cyclotron, or even those with access to cyclotron products, to a potentially wide array of radiotracers that can replace existing nuclear medicine techniques.

The most established of these tracers are the somatostatin analogues, which have significantly impacted the management of patients with a range of neuroendocrine tumour (NET) [21]. Where available, these Ga-68 agents have largely replaced the conventional nuclear medicine imaging technique of In-111 DTPA-octreotide scintigraphy due to a combination of significantly enhanced diagnostic accuracy, greater patient convenience and more favourable radiation dosimetry. However, there is a range of other agents that could rapidly enter into routine nuclear medicine practice. These include agents for renal scanning [22] and ventilation-perfusion imaging [23]. Table 21.2 provides a list of Ga-68-labelled agents that are used clinically in my department.

There has also been a move to replace I-131, which has unfavourable imaging and radiation dose characteristics with I-123 for SPECT/CT diagnostic imaging. We clearly preferred this agent to I-131, but when comparing it to FDG, the technical differences between the scans often limited comparison of tracer avidity, particularly for small lesions. Accordingly, we have moved to using I-124, particularly in patients likely to come to I-131-based therapy. The treatment of metastatic thyroid cancer, pheochromocytoma/paraganglioma, neuroblastoma and

Table 21.2 Gallium-68 tracers used clinically at the Peter MacCallum Cancer Centre

Agent	Abbreviation	Process	Clinical use
⁶⁸ Ga-DOTA-octreotate	GaTate	SSTR	NET Phaeo/PGL
⁶⁸ Ga-DOTA-exendin-4	Ga-GLP-1	GLP-1 receptor	Insulinoma/MTC
⁶⁸ Ga-nano-aerosol	Galligas	Ventilation	VQ scanning
⁶⁸ Ga-macro-aggregated albumin	Ga-MAA	Lung perfusion	VQ scanning
⁶⁸ Ga-EDTA	Ga-EDTA	Renal filtration	Renal scanning
⁶⁸ Ga-HBED-PSMA	Ga-PSMA	PSMA cell surface expression	Prostate cancer Renal cancer
⁶⁸ Ga-nano-colloid	Ga-colloid	Phagocytosis	SLN imaging
⁶⁸ Ga-tropolone	Ga-RBC	Blood products	Blood pool imaging

SSTR somatostatin receptor, *NET* neuroendocrine tumour, *Phaeo/PGL* phaeochromocytoma/paraganglioma, *SNL* sentinel lymph node, *RBC* red blood cell

Table 21.3 Iodine-124 tracers used clinically at the Peter MacCallum Cancer Centre

Agent	Abbreviation	Process	Clinical use
¹²⁴ I-iodide	I-124	NaI symporter	Thyroid cancer
¹²⁴ I-meta-iodo-benzylguanidine	I-124 MIBG	Catecholamine transporter	Phaeo/PGL Neuroblastoma

Phaeo/PGL phaeochromocytoma/paraganglioma

lymphoma with iodinated products has opened the way for the “theranostic” application of I-124-labelled tracers. Table 21.3 provides a list of I-124 compounds used clinically in my department.

In addition to these tracers, we are involved in developing further agents for clinical PET scanning or validating agents that have been developed elsewhere. These include agents labelled with Cu-64 and Zr-89. These agents will play, we believe, an important role in further advancing the safety and efficacy of radionuclide therapy as well as putting it on a solid scientific footing. Table 21.4 provides a list of agents that are being evaluated prior to moving into routine clinical use.

This catalogue of tracers is not limited by opportunities for further relevant clinical applications but rather by the challenges posed by producing such a large array of tracers in an academic department, particularly in the context of increasingly stringent requirements for product to comply with good manufacturing practice (GMP). We have partly overcome these issues by partnering with a commercial supplier of PET tracers who have helped to transition tracers from the research domain into routine clinical practice by producing and distributing GMP-certified agents more widely. By achieving economies of scale not feasible in a hospital-based radiopharmacy, tracers like FLT, FET and NaF are now readily available to other PET facilities in our region. As experience with these tracers has grown, the role of PET has become ever more enthusiastically embraced by medical

Table 21.4 Other tracers being evaluated at the Peter MacCallum Cancer Centre

Agent	Abbreviation	Process	Clinical use
¹⁸ F-Fluoronicotinamide	MEL-50	Melanin	Melanoma
⁶⁴ Cu-SAT-octreotate	CuSARTATE	SSTR	NET
⁷⁹ Zr-trastuzumab	Zr-CEPTIN	HER-2 receptor	Breast cancer
¹²⁴ I-metomidate	I-124 rituxan	Cortisol synthesis	Adrenocortical cancer

SSTR somatostatin receptor, *NET* neuroendocrine tumour

and radiation oncologists as well as by surgeons. There are, in many countries, impediments to dissemination of these techniques as a result of health technology assessment regimes that require a significantly higher level of evidence than existed for older technologies prior to allowing their use and, particularly, reimbursing their cost. Notwithstanding these limitations, it seems inevitable that hybrid PET devices will become the preferred diagnostic imaging technique in cancer at least [24].

21.4 The Slow Rebirth of Radionuclide Therapy

Many hoped that small-molecule kinase inhibitors that target specific mutations in cancer cells would be the final solution in cancer therapy. The dramatic metabolic responses seen in gastrointestinal stromal tumours (GISTs) provided great excitement, as this was a disease previously without effective therapies. The use of BRAF inhibitors to combat the most common mutation in malignant melanoma was similarly ground-breaking and again accompanied by marked and early metabolic response in FDG PET [25]. However, it has become very clear that resistance to such agents develops almost universally, sometimes after only a brief response. This resistance arises due to genomic heterogeneity and evolution of tumours under the selective pressure of signal transduction blockade. If cells lack the specific therapeutic target or develop a means of bypassing its role in promoting tumour growth, the therapy ceases to work. Similarly, if delivery of the drug to the tumour is impaired, inadequate drug levels may allow cells to survive. While radionuclide therapy also relies on target expression, it is possible to measure the expression of any given target in individual lesions serially over time and on a whole-body scale. Thus, the task of selecting patients for radionuclide therapy and predicting which lesions will respond, and those that are unlikely to, is significantly easier than it is for targeted therapies where treatment selection is typically made on the basis of a tiny piece of biopsy material, which is assumed to be representative of all sites of disease. Furthermore, unlike drugs that require each cell to express the target, the particle range of many therapeutic isotopes means that a cell with high uptake can lethally irradiate nearby cancer cells that might themselves either lack the target or take up insufficient of the agent to have a direct toxic effect. The recognition of microscopic tissue heterogeneity within tumours provides a strong rational basis for

radionuclide therapy with crossfire effect overcoming spatial heterogeneity of target expression, at least at the microscopic scale.

While the old war horses, I-131 and Y-90, remain important therapeutic radionuclides, the renaissance of radionuclide therapy has been driven by the development of Lu-177. The physical characteristics of this isotope make it highly attractive for therapy. Although it has sufficient gamma emissions to allow reasonably high-quality post-therapy imaging, they are not so abundant to pose a major external radiation hazard allowing treatment to usually be performed on an outpatient basis. The decay rate delivers radiation over several weeks but the beta-particle range of only 1–2 mm means that relatively little radiation is delivered to normal cells close to tumour deposits. This is especially beneficial for treating patients with rather heavy infiltration of the liver or bone marrow. Recent studies have also indicated the potential of alpha-particle-emitting radionuclides such as Ra-223 [26], which deliver radiation over only a few cell diameters.

Lu-177 DOTA-octreotate (LuTate) has revolutionised our treatment of NET. Building on the pioneering work of the Erasmus Medical Center in Rotterdam, Holland, we added radiosensitising chemotherapy to the therapeutic regimen [27] and have achieved excellent progression-free and overall survival rates even in patients who would be considered to have a poor prognosis based on the presence of high FDG avidity [28]. The key to achieving such outcomes has, however, been ensuring that there are no lesions with FDG uptake that lack sufficient somatostatin receptor to deliver effective radiation [29]. Again, this reflects a cogent example of the theranostic paradigm wherein personalised selection of treatment can be based on “if you can see it, you can treat it”.

Another example of this approach has been the development of PSMA-binding ligands that are labelled with either I-131 [30] or Lu-177 [31]. Although preliminary, the results look impressive in patients with advanced castrate-resistant prostate cancer. As is often the case, the patients referred for such trials have often been heavily pretreated with several lines of therapy and have large burdens of disease. Our own “compassionate use” eligibility criteria similarly allowed treatment of patients who would almost certainly be ineligible for most industry-sponsored trials of novel chemotherapy or targeted agents.

Herein lies a major future issue for nuclear medicine. We see patients who are often at death’s door; we usually referred them only when another oncologist has effectively abandoned the patient’s care for lack of any other options and has little incentive to ever see the patient again. We see the wonderful benefit that some, indeed many, patients derive, but this is usually reported in case series that lack rigorous prospective design, defined eligibility criteria or standardised response and toxicity assessment. Accordingly, the medical community often view these trials as being flawed at best and anecdotal at worst.

If we are going to have radionuclide therapy assume the respectability it deserves as a cancer therapy, we need to adopt the trial methodology used by drug companies and stick to clearly defined protocols. There are certainly encouraging moves in this direction with both industry-funded and cooperative group trials being developed that integrate radionuclide therapy.

21.5 Long-Lived PET Isotopes with Therapeutic Pairs Provide the Vehicle for Improved Radionuclide Therapy Selection and Planning

One of the major impediments to establishing a scientific foundation for radionuclide therapy has been the inability to both predict and verify the radiation dose delivered to both tumour and normal tissues. Although planar imaging has been able to provide estimates of radiation to normal organs, the development of three-dimensional and quantitative capability of hybrid scanners have made it possible to use PET/CT to perform predictive dosimetry while quantitative SPECT/CT is being refined to allow dose verification.

My group has established methods for quantitative Lu-177 SPECT/CT [32]. This has taught us that while uptake of GaTate on pretreatment PET/CT provides a reasonable estimate of what radiation will be delivered to tumour deposits, it is clear that clearance kinetics of normal organs, particularly the kidneys, varies considerably between patients and cannot be adequately modelled using short-lived tracers. This is where longer-lived PET radionuclides will play an important role. For predictive dosimetry of I-131 agents, I-124 provides the ideal combination of a reasonably comparable physical half-life and excellent imaging characteristics. Cu-64 provides an interesting opportunity for predictive dosimetry of its therapeutic pair Cu-67 but could also be used as a PET surrogate for Lu-177 [33]. Zr-89 and Y-90 provide another interesting combination with respect to radioimmunotherapies.

In the future, the theranostic paradigm will hopefully change from a rather empiric approach of “see it, guess an administered activity and treat it in hope” to one that could be characterised as “see it, measure it, predict and verify therapeutic radiation delivery within tolerance of normal tissues”. As is often the case, the past can teach us useful lessons.

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References

1. Seaborg GT, Lawrence EO. Physicist, engineer, statesman of science. *Science*. 1958;128(3332):1123–4. doi:10.1126/science.128.3332.1123.
2. Robinson RG, Blake GM, Preston DF, McEwan AJ, Spicer JA, Martin NL, et al. Strontium-89: treatment results and kinetics in patients with painful metastatic prostate and breast cancer in bone. *Radiographics*. 1989;9(2):271–81. doi:10.1148/radiographics.9.2.2467331.

3. Seidlin SM, Marinelli LD, Oshry E. Radioactive iodine therapy; effect on functioning metastases of adenocarcinoma of the thyroid. *J Am Med Assoc.* 1946;132(14):838–47.
4. Shapiro B, Sisson JC, Eyre P, Copp JE, Dmuchowski C, Beierwaltes WH. 131I-MIBG—a new agent in diagnosis and treatment of pheochromocytoma. *Cardiology.* 1985;72 Suppl 1:137–42.
5. Shulkin BL, Shapiro B. Current concepts on the diagnostic use of MIBG in children. *J Nucl Med.* 1998;39(4):679–88.
6. Kuhl DE, Chamberlain RH, Hale J, Gorson RO. A high-contrast photographic recorder for scintillation counter scanning. *Radiology.* 1956;66(5):730–9.
7. Kuhl DE, Edwards RQ. Cylindrical and section radioisotope scanning of the liver and brain. *Radiology.* 1964;83:926–36.
8. Kuhl DE, Hale J, Eaton WL. Transmission scanning: a useful adjunct to conventional emission scanning for accurately keying isotope deposition to radiographic anatomy. *Radiology.* 1966;87(2):278–84.
9. Kuhl DE, Edwards RQ, Ricci AR, Jacob RJ, Mich TJ, Alavi A. The Mark IV system for radionuclide computed tomography of the brain. *Radiology.* 1976;121(2):405–13.
10. Phelps ME, Hoffman EJ, Huang SC, Kuhl DE. Positron tomography: “in vivo” autoradiographic approach to measurement of cerebral hemodynamics and metabolism. *Acta Neurol Scand Suppl.* 1977;64:446–7.
11. Reivich M, Kuhl D, Wolf A, Greenberg J, Phelps M, Ido T, et al. Measurement of local cerebral glucose metabolism in man with 18F-2-fluoro-2-deoxy-d-glucose. *Acta Neurol Scand Suppl.* 1977;64:190–1.
12. Phelps ME, Hoffman EJ, Selin C, Huang SC, Robinson G, MacDonald N, et al. Investigation of [18F]2-fluoro-2-deoxyglucose for the measure of myocardial glucose metabolism. *J Nucl Med.* 1978;19(12):1311–9.
13. Reivich M, Kuhl D, Wolf A, Greenberg J, Phelps M, Ido T, et al. The [18F]fluorodeoxyglucose method for the measurement of local cerebral glucose utilization in man. *Circ Res.* 1979;44(1):127–37.
14. Schirrmester H, Glatting G, Hetzel J, Nussle K, Arslanemir C, Buck AK, et al. Prospective evaluation of the clinical value of planar bone scans, SPECT, and (18)F-labeled NaF PET in newly diagnosed lung cancer. *J Nucl Med.* 2001;42(12):1800–4.
15. Lau EW, Drummond KJ, Ware RE, Drummond E, Hogg A, Ryan G, et al. Comparative PET study using F-18 FET and F-18 FDG for the evaluation of patients with suspected brain tumour. *J Clin Neurosci.* 2010;17(1):43–9. doi:[10.1016/j.jocn.2009.05.009](https://doi.org/10.1016/j.jocn.2009.05.009).
16. Popperl G, Gotz C, Rachinger W, Gildehaus FJ, Tonn JC, Tatsch K. Value of O-(2-[18F] fluoroethyl)- L-tyrosine PET for the diagnosis of recurrent glioma. *Eur J Nucl Med Mol Imaging.* 2004;31(11):1464–70.
17. Campbell BA, Callahan J, Bressel M, Simoens N, Everitt S, Hofman MS, et al. Distribution atlas of proliferating bone marrow in non-small cell lung cancer patients measured by FLT-PET/CT imaging, with potential applicability in radiation therapy planning. *Int J Radiat Oncol Biol Phys.* 2015;92(5):1035–43. doi:[10.1016/j.ijrobp.2015.04.027](https://doi.org/10.1016/j.ijrobp.2015.04.027).
18. Buck AK, Bommer M, Juweid ME, Glatting G, Stilgenbauer S, Mottaghy FM, et al. First demonstration of leukemia imaging with the proliferation marker 18F-fluorodeoxythymidine. *J Nucl Med.* 2008;49(11):1756–62. doi:[10.2967/jnumed.108.055335](https://doi.org/10.2967/jnumed.108.055335).
19. Price DT, Coleman RE, Liao RP, Robertson CN, Polascik TJ, DeGrado TR. Comparison of [18 F]fluorocholine and [18 F]fluorodeoxyglucose for positron emission tomography of androgen dependent and androgen independent prostate cancer. *J Urol.* 2002;168(1):273–80.
20. Beauregard JM, Williams SG, DeGrado TR, Roselt P, Hicks RJ. Pilot comparison of F-fluorocholine and F-fluorodeoxyglucose PET/CT with conventional imaging in prostate cancer. *J Med Imaging Radiat Oncol.* 2010;54(4):325–32. doi:[10.1111/j.1754-9485.2010.02178.x](https://doi.org/10.1111/j.1754-9485.2010.02178.x).
21. Hofman MS, Kong G, Neels OC, Eu P, Hong E, Hicks RJ. High management impact of Ga-68 DOTATATE (GaTate) PET/CT for imaging neuroendocrine and other somatostatin expressing tumours. *J Med Imaging Radiat Oncol.* 2012;56(1):40–7. doi:[10.1111/j.1754-9485.2011.02327.x](https://doi.org/10.1111/j.1754-9485.2011.02327.x).

22. Hofman M, Binns D, Johnston V, Siva S, Thompson M, Eu P, et al. ⁶⁸Ga-EDTA PET/CT imaging and plasma clearance for glomerular filtration rate quantification: comparison to conventional ⁵¹Cr-EDTA. *J Nucl Med.* 2015;56(3):405–9. doi:[10.2967/jnumed.114.147843](https://doi.org/10.2967/jnumed.114.147843).
23. Callahan J, Hofman MS, Siva S, Kron T, Schneider ME, Binns D, et al. High-resolution imaging of pulmonary ventilation and perfusion with ⁶⁸Ga-VQ respiratory gated (4-D) PET/CT. *Eur J Nucl Med Mol Imaging.* 2014;41(2):343–9. doi:[10.1007/s00259-013-2607-4](https://doi.org/10.1007/s00259-013-2607-4).
24. Hicks RJ, Hofman MS. Is there still a role for SPECT-CT in oncology in the PET-CT era? *Nat Rev Clin Oncol.* 2012;9(12):712–20. doi:[10.1038/nrclinonc.2012.188](https://doi.org/10.1038/nrclinonc.2012.188).
25. McArthur GA, Puzanov I, Amaravadi R, Ribas A, Chapman P, Kim KB, et al. Marked, homogeneous, and early [¹⁸F]fluorodeoxyglucose-positron emission tomography responses to vemurafenib in BRAF-mutant advanced melanoma. *J Clin Oncol.* 2012;30(14):1628–34. doi:[10.1200/JCO.2011.39.1938](https://doi.org/10.1200/JCO.2011.39.1938).
26. Parker C, Nilsson S, Heinrich D, Helle SI, O’Sullivan JM, Fosså SD, et al. Alpha emitter radium-223 and survival in metastatic prostate cancer. *N Engl J Med.* 2013;369(3):213–23. doi:[10.1056/NEJMoa1213755](https://doi.org/10.1056/NEJMoa1213755).
27. Kong G, Thompson M, Collins M, Herschtal A, Hofman MS, Johnston V, et al. Assessment of predictors of response and long-term survival of patients with neuroendocrine tumour treated with peptide receptor chemoradionuclide therapy (PRCRT). *Eur J Nucl Med Mol Imaging.* 2014;41(10):1831–44. doi:[10.1007/s00259-014-2788-5](https://doi.org/10.1007/s00259-014-2788-5).
28. Kashyap R, Hofman MS, Michael M, Kong G, Akhurst T, Eu P, et al. Favourable outcomes of (¹⁷⁷)Lu-octreotate peptide receptor chemoradionuclide therapy in patients with FDG-avid neuroendocrine tumours. *Eur J Nucl Med Mol Imaging.* 2015;42(2):176–85. doi:[10.1007/s00259-014-2906-4](https://doi.org/10.1007/s00259-014-2906-4).
29. Hofman MS, Hicks RJ. Changing paradigms with molecular imaging of neuroendocrine tumors. *Dis Med.* 2012;14(74):71–81.
30. Zechmann CM, Afshar-Oromieh A, Armor T, Stubbs JB, Mier W, Hadaschik B, et al. Radiation dosimetry and first therapy results with a (¹²⁴)I/ (¹³¹)I-labeled small molecule (MIP-1095) targeting PSMA for prostate cancer therapy. *Eur J Nucl Med Mol Imaging.* 2014;41(7):1280–92. doi:[10.1007/s00259-014-2713-y](https://doi.org/10.1007/s00259-014-2713-y).
31. Kratochwil C, Giesel FL, Eder M, Afshar-Oromieh A, Benešová M, Mier W, et al. [¹⁷⁷)Lu] Lutetium-labelled PSMA ligand-induced remission in a patient with metastatic prostate cancer. *Eur J Nucl Med Mol Imaging.* 2015;46(2):987–8.
32. Beauregard JM, Hofman MS, Pereira JM, Eu P, Hicks RJ. Quantitative (¹⁷⁷)Lu SPECT (QSPECT) imaging using a commercially available SPECT/CT system. *Cancer Imaging.* 2011;11:56–66. doi:[10.1102/1470-7330.2011.0012](https://doi.org/10.1102/1470-7330.2011.0012).
33. Paterson BM, Roselt P, Denoyer D, Cullinane C, Binns D, Noonan W, et al. PET imaging of tumours with a ⁶⁴Cu labeled macrobicyclic cage amine ligand tethered to Tyr³-octreotate. *Dalton Trans.* 2014;43(3):1386–96. doi:[10.1039/c3dt52647j](https://doi.org/10.1039/c3dt52647j).