Future Challenges of Multimodality Imaging

30

Diego Alfonso López-Mora, Luis Alarcón Lagos, Montserrat Estorch, and Ignasi Carrio

Contents

30.1 Introduction

To understand genetics of cancer and its proliferative nature remains the main objective of current cancer research. Improved knowledge of cancer pathogenesis results in an array of biomarkers to be used for diagnosis and treatment of the disease. Molecular imaging is the visualization, characterization, and measurement of biological processes at the molecular and cellular levels in a living system. Molecular imaging techniques using radiotracers allow the demonstration of functional or phenotypic changes associated with pathology in vivo, and the characterization of both genotypic and phenotypic tumoral signatures.

D. A. López-Mora · M. Estorch · I. Carrio (✉)
Nuclear Medicine Department, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain
e-mail: i.carrio@santpau.cat

L. A. Lagos
Nuclear Medicine Department, Hospital Dr. Gustavo Fricke, Viña del Mar, Valparaíso, Chile

O. Schober et al. (eds.), *Molecular Imaging in Oncology*,
Recent Results in Cancer Research 216,
https://doi.org/10.1007/978-3-030-42618-7_30

Positron emission tomography/computed tomography (PET/CT) and single-photon emission computed tomography/computed tomography (SPECT/CT) have procured advances in research and clinical application of fusion imaging unthinkable before, due to its simultaneous developments of new technologies, acquisition and reconstruction parameters, and advanced quantitative methods to measure absolute concentration of radiotracers related to the severity and/or progression of cancer.

The introduction of new hybrid imaging systems such as the digital PET/CT and PET/MRI opened horizons for multimodality molecular imaging, more precise, with simultaneous morphologic, functional, and molecular information of a living system. Moreover, the combinations of anatomic and functional imaging modalities hold further promise in basic medical research or in clinical medicine, especially in the field of staging/restaging and follow-up of oncological diseases. These developments are paralleled by advances of biomolecules and particles that will provide new agents useful for more than one imaging modality and will facilitate the study of the same target by different imaging devices.

30.2 Technology and Probe Design

After the introduction of multimodality systems combining CT with SPECT and PET that changed significantly the capabilities of stand-alone SPECT and PET, fused functional and anatomic images have gained wide acceptance, becoming a powerful clinical tool especially in oncology. With multimodality imaging the research efforts were mostly focused on the integration of MRI with PET and SPECT [46]. The recent introduction of digital detectors in PET/CT systems may change the paradigm in hybrid imaging and may improve the diagnostic performance in oncological and non-oncological diseases, such as neurodegenerative and inflammatory processes [23, 40, 45].

30.2.1 SPECT/CT

New technologies have improved the performance of SPECT and SPECT/CT beyond the technology invented by Hal Anger in 1957 [1]. The initial primary goal of simultaneous SPECT and CT studies was to improve sensitivity and specificity by the combination of coregistered anatomical and functional images and to facilitate lesion localization and attenuation correction [39]. With the incorporation of diagnostic CT, the clinical information from SPECT/CT has been significantly improved. In consequence, guidelines of clinical practice and a number of clinical protocols in cancer, especially in neuroendocrine and thyroid tumors, incorporate SPECT/CT to facilitate precise diagnosis.

Involuntary motions because of cardiac contraction, respiration, or bowel movement are common technical problems encountered in SPECT/CT. Respiratory

motion results in inaccuracy of attenuation correction for lung tumors because of eventual misregistration between emission and transmission data. Research efforts developed methods for correction of respiratory motion effects, such as external or internal devices that make possible to estimate respiratory motion gating emission data and the adequate matching to CT cine data, or the use of modeling motion and matching of CT data from a single CT and a respiratory-gated emission study. Additionally, the development of new technologies such as dose modulation and iterative reconstruction methods can help to reduce radiation dose [39].

The adoption of cadmium zinc telluride (CZT) detectors has impacted the design of new SPECT/CT technologies, such as the adoption of solid-state reading systems. This includes pin diodes (PD), avalanche photodiodes (APD) including position-sensitive devices (PSAPD), silicon photomultipliers (SiPM), and silicon drift detectors (SDD) [31]. The collimator continues to be the main barrier to SPECT/CT progress. Multipinhole collimators in combination with high intrinsic resolution have demonstrated greater potential [31].

30.2.2 PET/CT

The introduction of combined PET/CT in 2001 opened a new era in the field of nuclear and molecular imaging, improving the sensitivity and specificity of clinical PET, and facilitating clinical acceptance and implementation of multimodality imaging [6]. The combination of PET and CT into a single gantry has provided the paradigm for multimodality imaging and has improved and simplified clinical management of patients. Currently, PET/CT is a critical component in the diagnosis and treatment management of oncologic and non-oncological diseases, being a well-known useful in vivo noninvasive imaging tool to measure disease burden [43, 55, 75].

Continuing advances in PET technology include detectors with improved spatial resolution, increased axial field of view (aFOV) with subsequent improvement of sensitivity, faster and more efficient iterative reconstruction algorithms, and improved signal-to-noise ratio by incorporating time-of-flight (TOF) information. Additionally, on the CT field, the development of faster scanner multislice detectors allows the implementation of new acquisition protocols. These evolution advances also include significant changes in reconstruction softwares, integrating resolution recovery with advance iterative techniques [62].

Recently, the introduction of the new generation of PET/CT based on the use of digital detectors may improve detectability and result in enhanced diagnostic performance. The higher detectability of the digital system lies in the different scintillator element coupling technology. Until now, the conventional (analog) PET/CT scanners have been mainly based on multiple scintillation crystals coupled to multiple detectors, while in the digital PET/CT scanners each scintillation crystal is coupled to a single detector. This 1:1 counting coupling of the digital systems provides an enhanced time of flight (TOF) and lower dead time, as well as higher timing and spatial resolution [17, 22, 47, 62]. These advantages of the digital

system improve localization of the annihilation events, significantly influence image quality, diagnostic confidence, and detection/characterization of small lesions (subcentimeter) [23, 40]. Additionally, the smaller volume definition and the improved lesion conspicuity and sharpness of digital system allow more accurate tumor rendering over the analog PET/CT, facilitating radiotherapy planning, prognostication, and treatment monitoring [45]. Therefore, clinical implementation of digital PET/CT opens new perspectives in the assessment of tumor quantification and characterization [40, 55].

In this scenario, digital PET/CT may bring new opportunities for personalized nuclear medicine, as enhanced image quality can be used to optimize administered radioactivity and/or scan duration. In clinical practice, such factors should be considered especially in pediatric (low-dose radiation) or unstable patients (from intensive care units) who cannot sustain long scanning periods [35, 42, 59]. Further developments may include advances in timing resolution and the construction of the first total-body PET/CT with an increase of the geometric coverage to encompass the whole body, which may increase sensitivity by a factor of about 40 for entire body and a factor of about 4–5 for a single organ [16, 55].

As it happens in SPECT/CT, motion between or during PET/CT studies poses technical problems, with remaining uncertainties in the registration process. The correction of respiratory motion effects, which may result in inaccuracy in attenuation correction for lung tumors, represents a challenge for PET/CT. Methods to reduce the effect of respiratory motion include breath-hold during treatment, "gating" in which the beam is turned on or off in synchrony with the respiratory cycle and "tracking" in which the beam follows the tumor based on imaging technology [7, 12, 14]. It has been shown that respiratory gating PET/CT is a valid approach not only to improve quantification, detectability, and definition of radiotherapy of moving lesions and organs, but to be applied routinely in most PET/CT scans [26].

Accurate definition of the boundaries of active disease is of clinical relevance in guiding biopsy sites and in planning surgery and radiotherapy fields. PET/CT studies facilitate the correct anatomical delineation of 18F-FDG uptake optimizing biopsy and improving the planning of surgical procedures [2, 25]. The better delineation of tumor tissue by PET/CT has supported the implementation of this multimodality system in radiation therapy planning of various tumors as non-small cell lung carcinomas, head and neck tumors, and lymphoma [20, 27, 64].

30.2.3 SPECT/MRI and PET/MRI

Over the years, numerous working prototypes of PET/MRI systems have been described and introduced [8, 33, 56, 62]. The combination of SPECT and PET with MRI can be important in areas where this technique is the preferred anatomic imaging modality. There are clear synergies between these modalities in areas where, beyond anatomic landmarking, MRI can detect organ-specific abnormalities and pathologies by spectroscopic quantification of concentrations of molecules.

Moreover, the expected radiation dose for SPECT and PET/MRI is significantly less than that for SPECT and PET/CT, which may be of importance in oncologic patients that are followed with multiple studies to monitor disease progression and response to therapy.

A potential limitation of MRI in multimodality imaging systems is that this technique does not provide adequate information for attenuation correction of emission studies, being a challenge to separate air and bone, and to measure the variations of density in the lung. Attenuation correction based on MRI is an active area of research, and its developments will be key for future clinical applications of PET/MRI [30, 41, 44, 76].

To integrate SPECT and PET with MRI is a technical challenge because these systems can interfere each other. Several prototypes have been designed and are at various stages of development [48, 74]. Even if to merge the hardware of SPECT or PET and MRI into a single device is limited by space, the principal challenge derives from conventional PET detectors based on photomultiplier tubes (PMTs), which do not operate properly in presence of the magnetic field of MRI. The consequent mutual interference between both image modalities needs to be reduced at maximum to provide high-quality studies, as much PET as MRI. PET systems can interfere with MRI systems degrading the homogeneity of magnetic and radiofrequency fields resulting in a loss of image quality with presence of artifacts. On the other hand, the strong external magnetic field of MRI systems can interfere with PET systems deflecting the normal trajectory of electrons into the PMTs, and the radiofrequency field and the gradient system pulses can affect the electronic of PET producing artifacts on image. To solve mutual interference between PET and MRI, light fibers coupled to the scintillation crystals of PET detectors have been used, with only the MRI elements remaining in the magnetic field and directing the scintillations out of this field through light fibers. Scintillation crystals produce several distortion and artifacts on MRI image, due to their different magnetic susceptibilities compared with human tissue. The replacement of photomultipliers tubes by solid-state scintillation detectors has been proposed and developed [71]. These detectors, based on avalanche photodiodes, have the advantage of being insensitive to magnetic fields and can be directly connected to the scintillation crystal block within the magnetic field using a short 1–2 mm light guide. In this way, light loss is minimized and the conversion of light to electronic signals takes place inside the MRI system, avoiding the use of optical fibers. Another advantage of avalanche photodiodes is that these are smaller than PMTs allowing a design with a fully integrated PET. This design has the advantages that no metallic components are placed directly in the MRI field of view and that the short light guides lossless light. The design of compact systems using solid-state light detectors and based on superconducting magnet (split magnet) or on field cycling MRI is a challenging task [15, 61].

The integration of PET with MRI is a promising hybrid imaging tool in many aspects (including decreased radiation dose, improved motion correction, and the convenience of a combined exam), but there are many obstacles that prevent PET/MRI widespread worldwide (access, cost, speed, and familiarity). In this

scenario, clinical PET/MRI systems are still relatively rare and therefore the precise clinical patient's benefit remains unclear. However, PET/MRI seems to be promising in characterization of primary bronchogenic tumors, it fails to detect small pulmonary nodules [29, 52, 53] as well as the determination of their extent and metastases [52, 53, 57]. In the same line, PET/MRI seems also to be promising in non-traumatic neurological disease (dysplasias, tuberous sclerosis, and temporal lobe epilepsy) [9, 13, 50], detection and characterization of hepatic lesions [34], and head and neck tumors [49]. Overall, PET/CT scanners are unlikely to be replaced by PET/MRI in a short-term period [19].

30.3 Tracers

The clinical use of PET for diagnosis, staging, and characterization of tumors is based on the assessment of increased metabolism as an important hallmark of cancer. As most tumors display considerably increased glycolytic activity, uptake and accumulation of 18F-FDG have been widely employed for tumor localization and characterization and have been approved for clinical use in suspected or existing cancers by most international health care regulatory agencies [73].

However, 18F-FDG has some disadvantages and limitations. Increased glycolytic activity is a relatively nonspecific and sometimes imprecise indicator of malignancy mainly because increased 18F-FDG uptake is also observed in inflammatory disorders and infections. 18F-FDG PET is less suitable for brain tumors because of the high background in normal brain tissues. Relatively indolent tumors, such as prostate cancer, low-grade lung adenocarcinomas, renal cell cancers, and mucinous neoplasms, are known to have generally low 18F-FDG uptake [21]. Another tumor type with generally low uptake of 18F-FDG is the group of neuroendocrine tumors [67]. Therefore, additional PET imaging tracers have been developed, such as 68 Ga-labeled somatostatin analogs (68 Ga-SSA). Other new tracers are in development, labeled with various isotopes such as 124I. 124I is a PET isotope with a favorable half-life of 4.2 days. It offers superior imaging characteristics with enhanced spatial resolution and image sensitivity, and permits the evaluation of in vivo iodine kinetics. Therefore, 124I made it possible to detect and scan thyroid cancer lesions with high sensitivity [36, 51].

68 Ga-SSA include several tracers sharing a similar structure (68 Ga-DOTA-TOC, 68 Ga-DOTA-NOC, 68 Ga-DOTA-TATE) and bind, with specific affinity, to somatotropin receptors which are frequently overexpressed in neuroendocrine tumors (NETs) [5]. Other tracers available for PET/CT included choline labeled with 11C or 18F and PSMA labeled with 68 Ga or 18F for prostate cancer. Choline is a water-soluble nutrient that is incorporated into cell membranes as phosphatidylcholine. Radiolabeled choline is found in proliferating cells, such as cancer and inflammation, and therefore may be less specific demonstrating modest sensitivity [63]. PSMA is a transmembrane protein that is highly overexpressed in prostate cancer cells. The recent development of small-molecule inhibitors (i.e.,

68 Ga-PSMA-11 and 18F-labeled PSMA agents) that target the active substrate recognition site of PSMA has demonstrated superior sensitivity even at very low PSA levels with high background-to-tumor ratios [63].

PET compounds available for multimodality imaging also include those capable to target specific key biologic processes in oncogenesis, such as proliferation (18F-3-fluoro-3-deoxy-L-thymidine [18F-FLT]), hypoxia (18F-fluoromisonidazole [18F-FMISO] and 18F-fluoroazomycin arabinoside [18F-FAZA]), angiogenesis (18F-galacto-arginine-glycine-aspartic acid [18F-galacto-RGD]), and apoptosis (124I- or 64Cu-Annexin V). Imaging of these biologic targets is expected to provide meaningful information for the selection and monitoring of targeted therapy in individual cancer patients, facilitating personalized treatment of the disease.

18F-FMISO is a highly stable radiopharmaceutical directly derived from misonidazole and has been extensively studied for regional mapping of hypoxia. 18F-FMISO shows high accumulation in hypoxic tissue which is proportional to the hypoxic fraction of the tumor and allows identification of patients who may benefit from changes in their therapeutic regimen as hypoxia has been identified as a major adverse prognostic factor for tumor progression and for resistance to treatment. In addition, such mapping of hypoxia can be used to guide intensity-modulated radiotherapy [32, 65]. Clinical trials are being developed to further investigate the feasibility and safety of individualized, hypoxia-adapted, radiotherapy.

The thymidine analog 18F-FLT, derived from the cytostatic drug azidovudine, has been suggested for noninvasive assessment of cell proliferation. Hence, it should provide valuable information for response assessment to tumor therapies, and more could offer more specific tumor imaging than 18F-FDG. 18F-FLT is taken up by cell by the same mechanisms as the nucleoside thymidine. This transport step is facilitated by nucleoside transporters, especially by the human nucleoside transporter 1 (hENT1). Once within the cell, 18F-FLT is phosphorylated by the enzyme thymidine kinase 1 (TK1), which results in the intracellular accumulation of the tracer. 18F-FLT PET has still seldom been used for tumor therapy follow-up in clinical trials, in part due to limited knowledge of the factors determining 18F-FLT uptake and therapy-induced changes of its retention [54]. Labeled amino acids have been used for the diagnosis of brain tumors, like 18F-labeled fluoroethyltyrosine or 18F-fluorodihydroxyphenylalanine (DOPA) as well as 11C-methionine. 18F-fluoroestradiol has been used for the assessment of the estrogen receptor status in breast cancer [18].

One of the primary goals in cancer research is to increase knowledge on genetics of the disease and its proliferative nature. High-throughput gene-sequencing techniques of the primary tumor or its metastases will allow genetic analysis of the tumor on an individual basis. The integration of molecular imaging into clinical routine and the combination with gene-sequencing techniques should be the goal for the near future to provide a personalized medicine for most oncological patients and not only for scientific purposes [18]. Along this line, non-somatostatin receptor biomarkers overexpressed on the surface of malignant cell have been explored. These are VPAC receptors, a family of 3G protein-coupled receptors located on the plasma membrane of tumor cells that mediate the biological action of vasoactive

intestinal peptide (VIP) and pituitary adenylate cyclase-activating polypeptide (PACAP). These receptors are present on several common tumors, such as breast, prostate, bladder, and colon, and VIP and PACAP can be labeled with 99mTc, 64Cu, and 68 Ga, with opportunities to image these oncologic diseases early and specifically in the future [24, 37, 58].

Another exciting and challenging goal in cancer research is the possibility to target intracellular biomarkers for diagnostic application. It has been demonstrated that oncogene expression of tumoral cells is different from their normal cohorts. Targeting specific oncogene mRNA copies with 99mTc, 64Cu, and 68Ga for SPECT or PET in dividing cells may permit imaging of oncogene expression in several tumors. This technique could be also useful to monitor effectiveness of therapy, with assessment of the upregulation or downregulation of oncogene mRNA copies and of proliferative tumoral status after treatment [10, 11, 38, 68–70, 72]. Other studies have examined the possibility to assess tumor suppressor gene p53 transcription in a cell or to determine the expression of Ki-67 protein as proliferative index of tumoral cells [60, 66]. Currently, therapeutic approaches are focused to block the division of cells, even if these approaches do not discriminate between normal and cancerous cells. To increase cell specificity, antisense technology has emerged. It is based on the sequence-specific binding of an antisense oligonucleotide to target RNA, preventing the oncogene mRNA translation and modulating the oncogene expression involved in the pathogenesis of oncologic diseases [28, 38]. Challenges to be resolved include in vivo stability, sequence length, and poor uptake in malignant cells. For new targeted therapy approaches, the identification of the correct concentration of therapeutic agent and its dose schedule has to be investigated [3, 4].

Molecular PET imaging provides diverse structural and functional information of drug development: drug distribution and concentration can be assessed using the radiolabeled compound, thereby demonstrating that the compound reaches the target and does not accumulate at sites of potential toxicities. The development of new therapeutic antibodies which have been approved for the treatment of hematologic malignancies and for solid tumors with good therapeutic results led to new attempts of radiolabeling these promising therapeutic antibodies. Such a newly developed tracer is 64Cu-DOTA-trastuzumab, which is a humanized monoclonal antibody against HER2 that is widely used for treatment of HER2-positive breast carcinomas. Another interesting newly developed tracer is Zr-89-bevacizumab, which is a recombinant humanized monoclonal antibody that blocks angiogenesis by inhibiting the VEGF-A. This approach may allow a noninvasive evaluation of the antiangiogenic therapeutic result in patients with, for example, colorectal cancer or breast cancer [18, 73].

The new technological achievements in both genomics and proteomics as well as in the bioinformatics will allow a better understanding of the molecular mechanisms of a cancer disease and will help to identify specific biomarkers for both diagnostic and therapeutic purposes. The clinical use of the new hybrid scanners together with the application of cancer-specific biomarkers will revolutionize treatment and open new ways of individual treatment.

Main existing PET tracers of 18F and of other positron-emitting radionuclides available for multimodality molecular imaging and their biochemical process, mechanism of uptake, and localization are, respectively, shown in Tables 30.1 and 30.2.

Table 30.1 PET tracers of ^{18}F: biochemical process, mechanisms of uptake and localization

Radiotracer	Biochemical process	Mechanism of uptake and localization
^{18}F-FDG	Glucose	Facilitate diffusion via glucose transporters
	Metabolism	Substrate for hexokinase in glucose metabolism
^{18}F-Fluoride	Bone metabolism	Incorporation in the hydroxyapatite crystals in bone
^{18}F-Fluorocholine	Membrane	Substrate for choline kinase in choline metabolism
	Synthesis	
^{18}F-Fluoroacetate	Lipid synthesis	Acetate is activated to acetyl-CoA in both the cytosol and mitochondria by acetyl-CoA synthetase
^{18}F-Fluorothymidine	DNA synthesis	Substrate for thymidine kinase in DNA synthesis and reflects tumor cell proliferation rate
^{18}F-FMISO	Hypoxia	Intracellular reduction and binding
^{18}F-FES	Receptor binding	Specific binding to estrogen receptors in breast cancer
^{18}F-FDOPA	AA transport and	Precursor for the synthesis of dopamine
^{18}F-FMT	Protein synthesis	Transport into the cells involves amino acid carrier protein
^{18}F-FCCA		Intracellular trapping involves protein synthesis or transmethylation
^{18}F-FB-	Angiogenesis	Integrin receptors on endothelial cells of
E[c(RGDyK)]2		Neovasculature
^{18}F-Oligonucleotide ^{18}F-FHBG	Gene expression	In vivo hybridization with mRNA Substrate to herpes virus thymidine kinase
^{18}F-labeled PSMA	Membrane antigen	Binding sites for PSMA ligands

Table 30.2 PET tracers of positron-emitting radionuclides non-^{18}F: biochemical process, mechanisms of uptake and localization

Radiotracer	Biochemical process	Mechanism of uptake and localization
^{15}O-Water	Blood flow/perfusion	Freely diffusible across membranes
^{11}C-Choline	Membrane synthesis	Substrate for choline kinase in choline metabolism
^{11}C-Thymidine	DNA synthesis	Substrate for thymidine kinase in DNA synthesis and reflects tumor cell proliferation rate

(continued)

Table 30.2 (continued)

Radiotracer	Biochemical process	Mechanism of uptake and localization
^{68}Ga-DOTATOC ^{68}Ga-DOTANOC ^{68}Ga-DOTATATE	Receptor binding	Specific binding to somatostatin receptor (SSTR-II) Specific binding to somatostatin receptor (SSTR-II, III, V) Specific binding to somatostatin receptor (SSTR-II)
^{11}C-$_{L}$-methionine	AA transport and protein synthesis	Transport into the cells involves amino acid carrier protein Intracellular trapping involves protein synthesis or transmethylation
^{124}I-^{64}Cu-^{88}Y-Labeled Antibodies	Binding to tumor antigens	Specific binding to tumor-associated antigenic binding sites
^{124}I-^{64}Cu-Annexin V	Apoptosis	Specific binding to phosphatidylserine On cell membrane
^{68}Ga-PSMA-11	Membrane antigen	Binding sites for PSMA ligands

30.4 Future and Conclusions

Molecular imaging employing multimodality systems will strongly influence the practice of medicine in the next generations. Specific imaging biomarkers will be developed to enable physicians to ensure better strategies of patient management, to stratify cancer, and to perform personalized medicine. Smarter devices, coupling different imaging modalities, with higher spatial resolution and greater sensitivity will be developed, allowing the visualization of a cluster of cells in vivo. These smart devices will use smart probes to target specific biologic phenomena that will provide a true early diagnosis and will drive the design of therapy and the assessment of its effectiveness. Even if PET/CT will ultimately replace SPECT/CT, advances in instrumentation, CT technology, and development of radiotracers have the potential to advance beyond its current level of performance. The horizon for hybrid imaging lies in the development of new tumor-specific agents that can improve oncologic clinical diagnostic and therapeutic applications.

In the near future, digital PET/CT may emerge as a powerful multimodality technique in clinical oncology, offering considerable potential for imaging applications beyond simple correlation of functional and anatomic images. Future developments should include the simultaneous acquisition of multifunctional data with quantification of PET tracer accumulation. Finally, the use of imaging as a surrogate endpoint requires demonstration of a significant relationship between imaging results and clinical outcome. Cooperation with the pharmaceutical and the instrumentation industry is needed to foster prospective randomized multicenter trials that are mandatory to demonstrate the relationship between appropriate use of multimodality imaging and better patient outcomes.

References

1. Anger HO (1957) Scintillation camera. Rev Sci Instrum 29:27–33
2. Acuff SN, Jackson AS, Subramaniam RM, Osborne D (2018) Practical considerations for integrating PET/CT into radiation therapy planning. J Nucl Med Technol 46(4):343–348
3. Bennett CF, Swayze EE (2010) RNA targeting therapeutics: molecular mechanisms of antisense oligonucleotides as a therapeutic platform. Annu Rev Pharmacol Toxicol 50:259–293
4. Bennett CF, Baker BF, Pham N et al (2017) Pharmacology of antisense drugs. Annu Rev Pharmacol Toxicol 57:81–105
5. Bergeret S, Charbit J, Ansquer C et al (2019) Novel PET tracers: added value for endocrine disorders. Endocrine 64(1):14–30
6. Beyer T, Townsend DW, Brun T et al (2000) A combined PET/CT scanner for clinical oncology. J Nucl Med 41:1369–1379
7. Bundschuh R, Martínez-Möller A, Essler M et al (2008) Local motion correction for lung tumours in PET/CT—First results. Eur J Nucl Med Mol Imaging 35:1981–1988
8. Catana C, Procissi D, Wu YB et al (2008) Simultaneous in vivo positron emission tomography and magnetic resonance imaging. Proc Natl Acad Sci USA 105:3705–3710
9. Carne R, O'Brien T, Kilpatrick C et al (2004) MRI-negative PET-positive temporal lobe epilepsy: a distinct surgically remediable syndrome. Brain 127:2276–2285
10. Chakrabarti A, Aruva MR, Sajankila SP (2005) Synthesis of novel peptide nucleic acid-peptide chimera for non-invasive imaging of cancer. Nucleosides Nucleotides Nucleic Acids 24:409–414
11. Chakrabarti A, Zhang K, Aruva MR et al (2007) Radiohybridization PET imaging of KRAS G12D mRNA expression in human pancreas cancer xenografts with [64Cu]DO3A-peptide nucleic acid-peptide nanoparticles. Cancer Biol Ther 6:948–956
12. Chang G, Chang T, Pan T, Clark JW Jr, Mawlawi OR (2010) Implementation of an automated respiratory amplitude gating technique for PET/CT: clinical evaluation. J Nucl Med 51:16–24
13. Chandra PS, Salamon N, Huang J et al (2006) FDG-PET/MRI Coregistration and diffusion-tensor imaging distinguish epileptogenic tubers and cortex in patients with tuberous sclerosis complex: a preliminary report. Epilepsia 47:1543–1549
14. Cheng NM, Yu CT, Ho KC, Wu YC, Liu YC, Wang CW, Yen TC (2009) Respiration-averaged CT for attenuation correction in non-small-cell lung cancer. Eur J Nucl Med Mol Imaging 36:607–615
15. Cherry SR, Louie AY, Jacobs RE (2008) The integration of positron emission tomography with magnetic resonance imaging. Proc IEEE 96:416–438
16. Cherry SR, Jones T, Karp JS et al (2018) Totalbody PET: maximizing sensitivity to create new opportunities for clinical research and patient care. J Nucl Med 59:3–12
17. Degenhardt C, Prescher G, Frach T et al (2009) The digital silicon photomultiplier: a novel sensor for the detection of scintillation light. In: IEEE Nuclear Science Conference Record 2383–2386
18. Dimitrakopoulou-Strauss A (2015) PET-based molecular imaging in personalized oncology: potential of the assessment of therapeutic outcome. Future Oncol 11(7):1083–1091
19. Ehman E, Johnson G, Villanueva-Meyer J et al (2017) PET/MRI: where might it replace PET/CT? J Magn Reson Imaging 46(5):1247–1262
20. Faria SL, Menard S, Devic S, Sirois C, Souhami L, Lisbona R, Freeman CR (2008) Impact of FDG- PET/CT on radiotherapy volume delineation in non-small-cell lung cancer and correlation of imaging stage with pathologic findings. Int J Radiat Oncol Biol Phys 70:1035–1038
21. Flavell R, Naeger D, Aparici C et al (2016) Malignancies with low fluorodeoxyglucose uptake at PET/CT: pitfalls and prognostic importance: resident and fellow education feature. RadioGraphics 36:293–294

22. Frach T, Prescher G, Degenhardt C et al (2009) The digital silicon photomultiplier: principle of operation and intrinsic detector performance. In: IEEE Nuclear Science Conference Record 1959–1965
23. Fuentes-Ocampo F, López-Mora DA, Flotats A et al (2019) Digital versus analog PET/CT: intra-subject comparison of the SUVmax in target lesions and reference regions. Eur J Nucl Med Mol Imaging. In press
24. Germano PM, Le SV, Oh DS et al (2004) Differential coupling of PAC1 SV1 splice variant of human colonic tumors to the activation of intracellular cAMP but not intracellular Ca^{2+} does not activate tumor proliferation. J Mol Neurosci 22:83–92
25. Goerres GW, Stupp R, Barghouth G et al (2005) The value of PET, CT and in-line PET/CT in patients with gastrointestinal stromal tumours: long-term outcome of treatment with imatinib mesylate. Eur J Nucl Med Mol Imaging 32:153–162
26. Guerra L, Ponti E, Morzenti S et al (2017) Respiratory motion management in PET/CT: applications and clinical usefulness. Curr Radiopharm 10(2):85–92
27. Guido A, Fuccio L, Rombi B, Castellucci P, Cecconi A, Bunkheila F, Fuccio C, Spezi E, Angelini AL, Barbieri E (2009) Combined 18F-FDG-PET/CT imaging in radiotherapy target delineation for head-and-neck cancer. Int J Radiat Oncol Biol Phys 73:759–763
28. Hersey P, Bastholt L, Chiarion-Sileni V, Cinat G, Dummer R, Eggermont AM, Espinosa E, Hauschild A, Quirt I, Robert C, Schadendorf D (2009) Small molecules and targeted therapies in distant metastatic disease. Ann Oncol 20(Suppl6):vi35–vi40
29. Heusch P, Buchbender C, Kohler J et al (2013) Correlation of the apparent diffusion coefficient (ADC) with the standardized uptake value (SUV) in hybrid 18F-FDG PET/MRI in non-small cell lung cancer (NSCLC) lesions: initial results RoFo 185:1056–1062
30. Hofmann M, Steinke F, Scheel V et al (2008) MRI-based attenuation correction for PET/MRI: a novel approach combining pattern recognition and atlas registration. J Nucl Med 49:1875–1883
31. Hutton BF (2014) The origin of SPECT and SPECT/CT. Eur J Nucl Med Mol Imaging 41 (Suppl 1):S3–S16
32. Inobushi M, Tatsumi M, Yamamoto Y et al (2018) European research trends in nuclear medicine. Ann Nucl Med 32:579–582
33. Judenhofer MS, Wehrl HF, Newport DF et al (2008) Simultaneous PET-MRI: a new approach for functional and morphological imaging. Nat Med 14:459–465
34. Kang B, Lee JM, Song YS et al (2016) Added value of integrated whole-body PET/MRI for evaluation of colorectal cancer: comparison with contrast-enhanced MDCT. AJR Am J Roentgenol 206:W10–W20
35. Koopman D, Groot Koerkamp M, Jager PL et al (2017) Digital PET compliance to EARL accreditation specifications. EJNMMI Phys 4:9. https://doi.org/10.1186/s40658-017-0176-5
36. Kuker R, Sztejnberg M, Gulec S (2017) I-124 imaging and dosimetry. Mol Imaging Radionucl Ther 26(suppl 1):66–73
37. Kumar P, Tripathi SK, Chen CP et al (2019) Evaluating Ga-68 peptide conjugates for targeting VPAC receptors: stability and pharmacokinetics. Mol Imaging Biol 21(1):130–139
38. Lendvai G, Estrada S, Bergström M (2009) Radiolabelled oligonucleotides for imaging of gene expression with PET. Curr Med Chem 16:4445–4461
39. Ljungberg M, Preterius H (2018) SPET/CT: an update on technological developments and clinical applications. Br J Radiol 90:20160402
40. Lopez-Mora DA, Flotats A, Fuentes-Ocampo F et al (2019) Comparison of image quality and lesion detection between digital and analog PET/CT. Eur J Nucl Med Mol Imaging 46 (6):1383–1390
41. Mehranian A, Arabi H, Zaidi H (2016) Vision 20/20: magnetic resonance imaging-guided attenuation correction in PET/MRI: challenges, solutions, and opportunities. Med Phys 43 (3):1130–1155. https://doi.org/10.1118/1.4941014
42. Messerli M, Stolzmann P, Egger-Sigg M et al (2018) Impact of a Bayesian penalized likelihood reconstruction algorithm on image quality in novel digital PET/CT: clinical

implications for the assessment of lung tumors. EJNMMI Phys 5:27. https://doi.org/10.1186/s40658-018-0223-x
43. Mittra E, Quon A (2009) Positron emission tomography/computed tomography: the current technology and applications. Radiol Clin N Am 47:147–160
44. Mollet P, Keereman Vincent, Bini J et al (2014) Improvement of attenuation correction in time-of-flight PET/MR imaging with a positron-emitting source. J Nucl Med 55(2):329–336
45. Nguyen N, Vercher-Conejero JL, Sattar A et al (2015) Image quality and diagnostic performance of a digital PET prototype in patients with oncologic diseases: initial experience and comparison with analog PET. J Nucl Med 56:1378–1385
46. Patton JA, Townsend DW, Hutton BF (2009) Hybrid imaging technology: from dreams and vision to clinical devices. Semin Nucl Med 39:247–263
47. Rausch I, Ruiz A, Valverde-Pascual I et al (2018) Performance evaluation of the Philips Vereos PET/CT system according to the NEMA NU2-2012 standard. J Nucl Med 60(4):561–567
48. Raylman RR, Majewski S, Lemieux SK et al (2006) Simultaneous MRI and PET imaging of a rat brain. Phys Med Biol 51:6371–6379
49. Ruhlmann V, Ruhlmann M, Bellendorf A et al (2016) Hybrid imaging for detection of carcinoma of unknown primary: a preliminary comparison trial of whole-body PET/MRI versus PET/CT. Eur J Radiol 85:1941–1947
50. Salamon N, Kung J, Shaw S et al (2008) FDG-PET/MRI coregistration improves detection of cortical dysplasia in patients with epilepsy. Neurology 71:1594–1601
51. Santhanam P, Taieb D, Solnes L et al (2017) Utility of I-124 PET/CT in identifying radioiodine avid lesions in differentiated thyroid cancer: a systematic review and meta-analysis. Clin Endocrinol (Oxf) 86(5):645–651
52. Sawicki LM, Grueneisen J, Buchbender C et al (2016) Evaluation of the outcome of lung nodules missed on 18F-FDG PET/MRI compared with 18F-FDG PET/CT in patients with known malignancies. J Nucl Med 57:15–20
53. Sawicki LM, Grueneisen J, Buchbender C et al (2016) Comparative performance of 18F-FDG PET/MRI and 18F-FDG PET/CT in detection and characterization of pulmonary lesions in 121 oncologic patients. J Nucl Med 57:582–586
54. Schelhaas S, Heinzmann K, Bollineni VR (2017) Preclinical applications of 3′-deoxy-3′-[18F] fluoro-thymidine in oncology-A systematic review. Theranostics 7(1):40–50
55. Schillaci O, Urbano N (2019) Digital PET/CT: a new intriguing chance for clinical nuclear medicine and personalized molecular imaging. Eur J Nucl Med Mol Imaging 46(6):1222–1225
56. Schlemmer HPW, Pichler BJ, Schmand M et al (2008) Simultaneous MR/PET imaging of the human brain: feasibility study. Radiology 248:1028–1035
57. Schmidt H, Brendle C, Schraml C et al (2013) Correlation of simultaneously acquired diffusion-weighted imaging and 2-deoxy-[18F] fluoro-2-D-glucose positron emission tomography of pulmonary lesions in a dedicated whole-body magnetic resonance/positron emission tomography system. Invest Radiol 48:247–255
58. Schulz S, Rocken C, Mawrin C et al (2004) Immunocytochemical identification of VPAC1, VPAC2 and PAC1 receptors in normal and neoplastic human tissues with subtype specific antibodies. Clin Cancer Res 10:8234–8242
59. Sekine T, Delso G, Zeimpekis KG et al (2018) Reduction of (18)F-FDG dose in clinical PET/MR imaging by using silicon photomultiplier detectors. Radiology 286:249–259
60. Shah C, Miller TW, Wyatt SK, McKinley ET, Olivares MG, Sanchez V, Nolting DD, Buck JR, Zhao P, Ansari MS, Baldwin RM, Gore JC, Schiff R, Arteaga CL, Manning HC (2009) Imaging biomarkers predict response to anti-HER2 (ErbB2) therapy in preclinical models of breast cancer. Clin Cancer Res 15:4712–4721
61. Sikkandhar M, Krishna KG, Sachin M et al (2017) PET/MRI: a frontier in era of complementary hybrid imaging. Eur J Hybrid Imaging 2018; 2(1):12

62. Slomka PJ, Pan T, Germano G (2016) Recent advances and future progress in PET instrumentation. Semin Nucl Med 46(1):5–19
63. Smith CP, Laucis A, Harmon S et al (2019) Novel imaging in detection of metastatic prostate cancer. Curr Oncol Rep 21(4):31
64. Specht L, Berthelsen AK (2018) PET/CT in radiation therapy planning. Semin Nucl Med 48 (1):67–75
65. Stieb S, Eleftheriou A, Warnock G et al (2018) Longitudinal PET imaging for tumor hypoxia during the courseof radiotherapy. Eur J Nucl Med Mol Imaging 45(12):2201–2217
66. Tan PH, Bay BH, Yip G et al (2005) Immunohistochemical detection of Ki67 in breast cancer correlates with transcriptional regulation of genes related to apoptosis and cell death. Mod Pathol 18:374–381
67. Tang C, Nie D, Tang G et al (2017) Radiosyntesis and biological evaluation of N-(2-[18F] fluoropropionyl)-3,4-dihydroxy-l-phenylalanine as a PET tracer for oncologic imaging. Nucl Med Biol 50:39–46
68. Tian X, Aruva MR, Qin W et al (2004) External imaging of CCND1 cancer gene activity in experimental human breast cancer xenografts with 99mTc-peptide–peptide nucleic acid-peptide chimeras. J Nucl Med 45:2070–2082
69. Tian X, Aruva MR, Wolfe HR et al (2005) Tumor-targeting peptide-PNA peptide chimeras for imaging overexpressed oncogene mRNAs. Nucleosides Nucleotides Nucleic Acids 24:1085–1091
70. Tian X, Aruva MR, Zhang K et al (2007) PET imaging of CCND1 mRNA in human MCF7 estrogen receptor positive breast cancer xenografts with oncogene-specific [64Cu] chelator-peptide nucleic acid-IGF1 analog radiohybridization probes. J Nucl Med 48:1699–1707
71. Townsend DW (2008) Multimodality imaging of structure and function. Phys Med Biol 53: R1–R39
72. Velikyan I (2014) Prospective of 68 Ga-radiopharmaceutical development. Theranostics 4 (1):47–80
73. Voigt W (2017) Advanced PET imaging in oncology: status and developments with current and future relevance to lung cancer care. Curr Opin Oncol 30(2):77–83
74. Woody C, Schlyer D, Vaska P et al (2007) Preliminary studies of a simultaneous PET/MRI scanner based on the RatCAP small animal tomograph. Nucl Instrum Methods A 571:102–105
75. Wright C, Binzel K, Zhang J et al (2017) Advanced functional tumor imaging and precision nuclear medicine enabled by digital PET technologies. Contrast Media Mol I. https://doi.org/10.1155/2017/5260305
76. Zaidi H (2007) Is MR-guided attenuation correction a viable option for dual modality PET/MR imaging? Radiology 244:639–642