Future Challenges of Multimodality Imaging

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Abstract

During the last decade, 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. The recent introduction of systems that combine PET and MRI opens new horizons for multimodality molecular imaging. These systems offer simultaneous morphologic, functional, and molecular information of a living system. Moreover, other combinations of anatomic and functional imaging modalities (for example CT and MRI or PET and optical imaging) are emerging, holding promise in basic medical research or in clinical medicine. These developments are paralleled by advances in the field of biomolecules and particles, to provide new agents useful for more than one imaging modality and to facilitate the study of the same target by different imaging devices. In the near future PET/MRI may emerge as a new powerful multimodality technique in clinical oncology, offering considerable potential for imaging applications beyond correlation of functional and anatomic images. Future developments should include the simultaneous acquisition of multifunctional data such as PET tracer uptake, MR spectroscopy, or fMRI along with high-resolution anatomic MRI.

Contents

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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.

During the last 10 years, 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, with simultaneous development of quantitative methods to measure absolute concentration of radiotracers related to the severity and/or progression of cancer.

The recent introduction of systems that combine PET and MRI is opening new horizons for multimodality molecular imaging to acquire simultaneously morphologic, functional, and molecular information of a living system. Moreover, other combinations of anatomic and functional imaging modalities (for example CT and MRI or PET and optical imaging) are emerging, holding promise in basic medical research or in clinical medicine. These developments are paralleled by advances in the field of biomolecules and particles, to provide new agents useful for more than one imaging modality and to facilitate the study of the same target by different imaging devices.

2 Technology and Probe Design

During the last 10 years, the introduction of multimodality systems combining CT with SPECT and PET has 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 as the current paradigm, present research efforts are focused on the integration of MRI with PET and SPECT (Patton et al. 2009).

2.1 SPECT/CT

New technologies have improved the performance of SPECT and SPECT/CT beyond the technology invented by Hal Anger in 1957 (Anger 1957). The initial primary goal of simultaneous SPECT and CT studies was to facilitate lesion localization and attenuation correction. Recently, with the implementation of diagnostic CT, clinical information from SPECT/CT has been significantly improved. In consequence, guidelines of clinical practice need to be adapted and clinical protocols for staging and restaging of cancer should incorporate SPECT/CT when necessary to facilitate precise diagnosis and to reduce patient radiation burden.

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. Considerable research efforts are addressed to develop 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. Future developments should provide automated correction with minimal radiation dose. On the other hand, the role of attenuation correction in SPECT/CT for oncologic applications is not fully established, with a relatively small number of studies comparing the diagnostic accuracy of attenuated and non-attenuated SPECT images.

In future, silicon photodiode or solid-state materials incorporated to detectors may replace photomultiplier tube technology, improving spatial and energy resolutions, and increasing stability with a more compact size (Despres et al. 2007). Development of these new technologies, will improve overall performance and cost-effectiveness of future SPECT/CT equipment.

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 (Beyer et al. 2000). Compared with two separated systems, 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. PET/CT is now a critical component of diagnosis and treatment management of oncologic disease.

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 by incorporating time-of-flight (TOF) information. Motion-free gated imaging is offered for specific applications, such to plan appropriate fields of radiotherapy.

The introduction of lutetium oxyorthosilicate, as faster scintillator than bismuth germinates, improves the count rate capability of PET scanners. The increased light output allows improved spatial resolution and energy resolution with reduction of scatter fraction. The dead-time of system is also decreased allowing reduction of the coincidence window and implementation of TOF. The increased aFOV offers an increase of sensitivity that improves spatial resolution. Moreover, increased aFOV procures fewer acquisition positions taking more advantage of the radiation emitted from the patient. The development of new PET image reconstruction algorithms broadens the point spread function or High-Definition PET or HD-PET and results in improved intrinsic resolution and uniformity throughout the FOV (Panin et al. 2006).

As it happens in SPECT/CT, motion between or during PET/CT studies may pose a technical problem, with remaining uncertainties in the registration process. The correction of respiratory motion effects, that 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 (Bundschuh et al. 2008; Cheng et al. 2009; Chang et al. 2010). However, at present, the optimal approach that provides automated correction with minimal radiation dose has yet to be demonstrated.

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 ^{18}F-FDG uptake optimizing biopsy and improving the planning of surgical procedures (Goerres et al. 2005). 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 (Faria et al. 2008; Guido et al. 2009).

2.3 SPECT/MRI and PET/MRI

Since few years, numerous working prototypes of PET/MRI systems have been described and introduced (Catana et al. 2008; Judenhofer et al. 2008; Schlemmer et al. 2008). 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 particular 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 (Hofmann et al. 2008; Zaidi 2007).

To integrate SPECT and PET with MRI is a technical challenge because these systems can interfere each other. At present, several prototypes have been designed and are at various stages of development (Raylman et al. 2006; Woody et al. 2007). 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 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 is being developed (Townsend 2008). These detectors, based on avalanche photodiodes, have the advantage that to be 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 loss less light. At present, 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 (Cherry et al. 2008). Certainly, new fully integrated PET/MR systems, eventually coupled to SPECT will be developed and become available in the near future.

3 Tracers

Tumors are hypermetabolic and may be distinguished from nonmalignant tissue by their elevated glucose metabolism. ^{18}F-FDG is a nonspecific tracer for detecting malignant tumors employed for PET imaging and quantification of glucose metabolism in vivo. The standardized uptake value (SUV) is a simple semi-quantitative method widely used to standardize the ^{18}F-FDG uptake. The presence or absence of ^{18}F-FDG accumulation is used to characterize CT findings in multimodality imaging of cancer patients using PET/CT (Bar-Shalom et al. 2003; Gerth et al. 2007; Czernin et al. 2007; la Fougère et al. 2006; Raanani et al. 2006).

In parallel to the technological advances in PET/CT, positron emitter labeled radiopharmaceuticals beyond ^{18}F-FDG are in continuing development, from isotopes such as ^{124}I to highly specific compounds such as ^{68}Ga-DOTATOC. ^{124}I has favorable conditions as much for dosimetry as for quality of images. Its half-life of 4.2 days allows imaging over some biological half-lives of iodine accumulation in thyroid cancer metastases. In consequence, iodine accumulation in lesions even in the submillimeter range, may be detected because of lower background activity (Freudenbersg et al. 2008), with assessment of tumor volumes and adequate dosimetric calculations (Jentzen et al. 2008a, b). As example of highly specific tracer, ^{68}Ga-DOTATOC binds to somatotropin receptors, which are frequently overexpressed in neuroendocrine tumors that may be clinically active even when having very little dimensions. Therefore, their early detection represents an important clinical challenge (Buchmann et al. 2007). Other tracers available for PET/CT, such as as choline labeled with ^{11}C or ^{18}F for prostate cancer, may be less specific. These radiopharmaceuticals are inhomogeneously distributed in the background and may shows some nonspecific binding in the intestine, being the tumor specific binding only moderate (Bouchelouche and Oehr 2008).

New PET compounds for multimodality imaging include those capable to target specific key biologic processes in oncogenesis, such as proliferation (^{18}F-3-fluoro-3-deoxy-L-thymidine [^{18}F-FLT]), hypoxia (^{18}F-fluoromisonidazole [^{18}F-FMISO] and ^{18}F-fluoroazomycin arabinoside [^{18}F-FAZA]), angiogenesis (^{18}F-galacto-arginine-glycine-aspartic acid [^{18}F-galacto-RGD]), and apoptosis (^{124}I- or ^{64}Cu-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.

^{18}F-FMISO is a highly stable radiopharmaceutical directly derived from misonidazole and is the most extensively studied PET agent for hypoxia mapping. ^{18}F-FMISO shows high accumulation in hypoxic tissue which is proportional to the hypoxic fraction of the tumor. PET/CT using ^{18}F-FMISO offers the possibility of in vivo mapping of regional tumor hypoxia, identifying patients who may benefit from changes in their therapeutic regimen because hypoxia has been identified as a major adverse prognostic factor for tumor progression and for resistance to anticancer treatment. In addition, such mapping of hypoxia can be used to guide intensity-modulated radiotherapy (Rajendran et al. 2003; Hicks et al. 2005). At present, assessment of therapy response with hypoxia tracers is still experimental.

The thymidine analog ^{18}F-FLT, derived from the cytostatic drug azidovudine, has been suggested for noninvasive assessment of proliferation and more specific tumor imaging than ^{18}F-FDG. This tracer is stable in vitro and accumulates in proliferating tissues and malignant tumors (Shields et al. 1998; Wells et al. 2002). However, at present the uptake mechanism of ^{18}F-FLT is only partially understood, and the influence of membrane transporters and various nucleoside-metabolizing enzymes remains to be determined. Preliminary data have described a significant correlation between tumoral proliferation and ^{18}F-FLT uptake in various malignant tumors, suggesting that ^{18}F-FLT could be used for therapeutic monitoring in various clinical settings (Salskov et al. 2007; Bading and Shields 2008). Clinical trials are needed to further validate ^{18}F-FLT as a marker for therapy response.

Table 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 metabolism	Facilitate diffusion via glucose transporters Substrate for hexokinase in glucose metabolism
^{18}F-Fluoride	Bone metabolism	Incorporation in the hydroxyapatite crystals in bone
^{18}F-Fluorocholine	Membrane synthesis	Substrate for choline kinase in choline metabolism
^{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 ^{18}F-FMT ^{18}F-FCCA	AA transport and protein synthesis	Precursor for the synthesis of dopamine Transport into the cells involves amino acid carrier protein Intracellular trapping involves protein synthesis or transmethylation
^{18}F-FB-E[c(RGDyK)]2	Angiogenesis	Integrin receptors on endotelial cells of neovasculature
^{18}F-Oligonucleotide ^{18}F-FHBG	Gene expression	In vivo hybridization with mRNA Substrate to herpes virus thymidine kinase

At present, one of the primary goals in cancer research is to increase the knowledge on genetics of cancer and its proliferative nature. Along this line, non-somatostatin receptors 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, as breast, prostate, bladder, and colon, and VIP and PACAP can be labeled with ^{99m}Tc and also with ^{64}Cu, with opportunities to image these oncologic diseases early and specifically in the future (Germano et al. 2004; Schulz et al. 2004).

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 mRNAs copies with ^{99m}Tc and ^{64}Cu 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

Table 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
^{68}Ga-DOTATOC	Receptor binding	Specific binding to somatostatin receptor (SSTR-II)
^{68}Ga-DOTANOC		Specific binding to somatostatin receptor (SSTR-II, III, V)
^{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

and of proliferative tumoral status after treatment (Lendvai et al. 2009; Chakrabarti et al. 2005, 2007; Tian et al. 2004, 2005, 2007).

Molecular biology is rapidly progressing and offering new opportunities to molecular imaging. In the future, by use of new imaging probes it may be possible to determine cellular transcription in a cell or its rate of proliferation, predicting its susceptibility for cancer. At present, studies have examined the utility 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 (Shah et al. 2009; Tan et al. 2005). 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 (Lendvai et al. 2009; Hersey et al. 2009). However, at present there are still some challenges to be resolved, as in vivo stability, sequence length, and poor uptake in malignant cells. Moreover, the high costs of targeted therapy approaches and the considerable toxic side-effects are important obstacles for to overcome. Major challenges of new targeted therapy approaches comprise the identification of the correct concentration of

therapeutic agent and its dose schedule, the selection of patients suitable to benefit from treatment, and the assessment of the response of the tumor to therapy (Bennett and Swayze 2010). There are opportunities for targeted molecular multimodality imaging to help in all those challenges and to offer new means for non-invasive assessment of cancer biology.

Main existing PET tracers of ^{18}F 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 1 and 2.

4 Optical Imaging

Optical techniques allow imaging of fluorescently tagged living cells in three dimensions with a high sensitivity down to the single-molecule level, with high submicrometric spatial resolution and with temporal resolution in the order of a millisecond. However, these techniques have limited penetration depth of light in living tissue, while the commonly used organic fluorophores and genetically encoded fluorescent proteins are often insufficiently bright and stable. Moreover, the toxic radicals and photoproducts generated prevent long-term in vivo imaging.

At present, advances in nanotechnology offer a vast array of artificial particulate systems capable of targeting different cells in vivo. The most desirable property of such nanoparticles is multifunctionality, containing both therapeutic components and multimodality imaging labels for efficient, specific in vivo delivery of drugs and for accurate quantitative assessment of the therapeutic efficacy noninvasively over time. Described nanoparticles are of several natures and include quantum dots, colloidal gold, superparamagnetic iron-oxide crystals, dendrimers, polymeric micelles and liposomes, nanotubes, nanowires, nanoshells, and others (Kirui et al. 2010; Hu et al. 2009; Bentolila et al. 2009). Molecules, such as peptides, proteins, and antibodies can be attached to these nanoparticles to perform PET, SPECT, MRI, ultrasound as well as optical imaging. Research on nanoparticles is focused on optimization of biocompatibility, in vivo kinetics, targeting efficacy, toxicity, and cost-effectiveness. These new nanoparticles and derived imaging probes will need to be translated into clinical applications.

Bioluminescence imaging is related to the light produced by the enzymatic reaction of a luciferase enzyme with its substrate. The most frequent luciferase enzyme used is the firefly (Photinus pyralis) luciferase. It is commonly used for preclinical cellular and molecular imaging in small animals. At present, bioluminescence imaging is a powerful tool to assess mechanisms of disease and to promote drug development in preclinical models. On the other hand, fluorescence imaging is obtained from a target fluorescent molecule that is excited by an external light of appropriate wavelength. This process is followed by release of longer-wavelength, lower-energy light as signal for imaging. Targets for fluorescence imaging may be endogenous molecules, as collagen or hemoglobin, fluorescent proteins or optical contrast agents that can be used for cellular and molecular imaging in small animal models. Both optical techniques have been used to assay pharmacodynamics of therapeutic agents in vivo, establishing dosing parameters to guide initial clinical trials, and eventual clinical applications

(Erickson et al. 2010). Future challenges include the improvement and development of new near-infrared spectroscopic methods useful for to identify cancer biomarkers and to retrospectively determine if benign and malignant lesions could be distinguished by using these methods (Kukreti et al. 2010).

Prototype instruments for optical/PET and optical/SPECT in small animals are under development in research laboratories (Peter and Semmler 2006; Vu et al. 2006). Hybridizing nuclear medicine and optical imaging systems can serve as a translational platform between the widely used bioluminescent or fluorescent techniques in small animal models, and the nuclear radiotracer medicine assays in human (Cherry 2004). The same rationale can be applied to optical imaging and MRI, localizing any significant and little optical signal on high-resolution 3D structural imaging. A promising line lies on the development of handheld-based optical imaging devices for the purpose of in vivo clinical studies, in particular in minimally invasive surgical environments. At present, there are new devices for in vivo clinical studies with demonstrated ability to perform fast 2D imaging and to detect a fluorescent target within a heterogeneous tissue-mimicking background as well as real human tissue (Erickson et al. 2010).

5 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 with ^{18}F-FDG for tumor imaging will ultimately replace SPECT/CT, advances in SPECT instrumentation, CT technology, and development of radiotracers have the potential to advance SPECT/CT beyond its current level of performance. The horizon for SPECT/CT imaging lies in the development of new tumor-specific agents that can improve oncologic clinical diagnostic and therapeutic applications.

In the near future PET/MRI may emerges as a new powerful multimodality technique in clinical oncology, offering considerable potential for imaging applications beyond simply correlation of functional and anatomic images. Future developments should include the simultaneous acquisition of multifunctional data, such as PET tracer uptake, MR spectroscopy, or fMRI along with high-resolution anatomic MRI.

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.

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