SPECT/MRI: dreams or reality?

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Multimodal diagnostic imaging has gained many supporters over the years, due to its distinct advantages over single imaging modalities. In many cases, a single imaging modality is insufficient to obtain all the necessary information for a particular subject. For many years, hybrid SPECT/CT and PET/CT systems have provided clinicians with high-resolution morphological images in combination with images depicting functional or molecular processes, providing specific characterization of disease status or treatment effect. MRI has distinct advantages over CT, such as better soft tissue contrast and lack of ionizing radiation. This has led to the recent introduction of combined PET/MRI systems that permit simultaneous acquisition of both modalities. The combination of SPECT and MRI now raises great expectations for further advantage of multimodal imaging. The radionuclide-based SPECT imaging techniques have relatively poor resolution but, like PET, are sensitive to picomolar tracer concentrations, while MRI gives high-resolution anatomical information but suffers from much lower sensitivity to concentration of contrast agent. The combination of both imaging techniques can offer synergistic advantages over either modality alone. With a SPECT/MRI system, simultaneous dynamic imaging of both structure and function would be feasible, even using multiple tracers simultaneously, thus reducing total scan time of the patient and providing valuable and accurate information with regard to disease staging and therapeutic outcome.

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The development of hybrid SPECT/MRI systems is still in its infancy; however, current interest in such systems has triggered an unprecedented quest for novel dual-modality imaging agents for application to such systems. Most of the multimodal agents to date have been combinations of either PET or MRI agents with optical agents. It is interesting to note that few SPECT/MRI agents have been reported but, now, with the development of suitable equipment, there is huge scope for the development of hybrid SPECT/MRI probes.

Although a lot of work is currently being executed to develop hybrid SPECT/MRI agents, all are in their preclinical stage of development. Recently, there has been great interest in developing nanoparticles (NPs) with dual-modality SPECT/MRI properties. NPs represent very attractive candidates for hybrid imaging due to their unique size and physical properties, allowing visualization of biological events at subcellular levels.

The opportunities provided by NPs are many. Functionalization of NPs with more than one targeting moieties increases the affinity of the NP to its biological target through a phenomenon known as multivalency, allowing for targeted imaging of the disease. Furthermore, their large surface area permits multiple "tagging" of imaging agents. This means that the NP can be linked to a large number of reporter molecules (e.g., radionuclides for SPECT imaging and contrast agents such as gadolinium ions for MRI) either via the attached targeting moiety or via an adequate chelating molecule conjugated onto the NP surface, thus increasing the signal-to-noise in imaging applications. Generally speaking, the ideal NP for application in disease diagnosis would be a multifunctional one, which would be

able to carry one or more targeting moieties for disease targeting, more than one imaging agent for bimodal/multimodal imaging, and a polymer coating for biocompatibility of the NP. In the case of hybrid SPECT/MRI NPs, these would simultaneously target the diseased site via the targeting molecules, and image the diseased site with great accuracy, due to their bimodal SPECT/MRI properties.

Superparamagnetic iron oxide NPs (SPIONs) are used as MRI agents in clinical practice (Endorem/Feridex). Radiolabeling of SPIONs with Technetium-99 m, the most commonly used radionuclide in SPECT, has given some promising preclinical examples of dual-modality SPECT/MRI agents. Madru et al. have reported on the development and evaluation of biocompatible SPIONs labeled with ^{99m}Tc for multimodality imaging with SPECT/MRI of the sentinel lymph node (SLN) [1]. The accumulation of ^{99m}Tc-SPIONs [expressed as percent injected dose/g (%ID/g)] in the SLN was 100 % ID/g, whereas in the liver and spleen it was less than 2 %ID/g.

In yet another example, Torres and his group conjugated a radiolabeled bisphosphonate (^{99m}Tc-dipicolylamine(DPA)-alendronate) directly to the surface of Endorem [2]. The bimodal imaging capacity of these NPs was confirmed by MRI and nanoSPECT/CT and showed localization in the liver and spleen in vivo, as expected for NPs of their size. The group has proceeded further by recently developing new stealth NP systems with dual-modality SPECT/MRI properties.

While there has been large interest in combining MRI with PET, with first commercial clinical systems now available, SPECT/MRI systems are not yet available as commercial clinical systems and, to our knowledge, only a relatively small number of SPECT/MRI systems are under development.

SPECT is attractive as an alternative to PET in preclinical studies, having potentially better spatial resolution due to the potential benefits from pinhole magnification. SPECT also provides the possibility for simultaneous use of multiple radionuclides targeting different biomarkers and typically longer lived and more readily accessible radionuclides. Operation costs are also lower for SPECT. The combination of SPECT and MRI has further appeal not only in providing high-contrast anatomical images to be combined with SPECT acquisitions, but with potential for use of several pulse sequences to provide further, complementary functional measures, including MR-spectroscopy. Moreover, the availability of high-resolution anatomy from MRI (with superior soft tissue contrast compared to CT) can aid in SPECT quantification with correction for partial volume effects.

There are many potential advantages offered by simultaneous acquisition of MRI and SPECT images, rather than simply sequential acquisition via adjacent gantries: the reduction of the overall scan time, the reduction of co-registration errors, the opportunity of combined dynamic imaging and the possibility to use MRI images or navigators to compensate for motion artifacts in SPECT images.

We mention here two developments of simultaneous SPECT/MRI systems. In one study [3], a prototype MRI-compatible SPECT system for preclinical imaging was constructed and simultaneous operation of SPECT and MRI was demonstrated. Also in a different project [4], a similar approach was adopted to develop a prototype preclinical SPECT/MRI system and experiments were conducted in simultaneous imaging to evaluate the interaction between the two systems.

A major limitation in the development of integrated SPECT/MRI systems is the compatibility of components (e.g., detectors, electronics) with MRI operation. In the mentioned SPECT/MRI developments, arrays of pixelated CdTe and CdZnTe (CZT) gamma detectors are employed. These detectors offer the advantage of a high-energy resolution which is suitable for SPECT, as it facilitates the simultaneous use of multiple radionuclides which emit gamma rays at different energies. These detectors are composed of a large number of pixels which requires a large number of electronic readout channels, implemented by the use of ASICs (application-specific integrated circuits). Moreover, such detectors have shown that a shift of the signal charge inside the detector caused by Lorentz forces produced inside the MRI affects performance and requires corrections.

A more recent approach for the development of MRI-compatible SPECT systems is based on scintillators, read out by SiPM (silicon photomultiplier) photo-detectors, although results from complete prototypes have not yet been demonstrated. These approaches offer the advantage of using SiPM technology, which is intrinsically robust for compatibility with MRI. Moreover, the adoption of an Anger camera architecture for the detection modules, based on a single scintillator readout by arrays of SiPM, compared to the use of pixellated detectors, provides a high intrinsic spatial resolution, achieved with a simple detector configuration and a limited number of channels. This advantage should be particularly important in the translation of this technology from preclinical to clinical systems in terms of complexity and cost. On the other hand, the energy resolution offered by scintillation detectors is poorer than that achievable using solid-state CdTe and CZT detectors, which makes multiple radionuclide acquisition more challenging. There are specific challenges in designing compact systems that support collimation in the confined space of an MRI system. The outstanding intrinsic resolution facilitates the use of pinhole collimation or novel alternative designs, based on minification rather than magnification, to achieve superior performance during simultaneous SPECT and MRI acquisition.

Conflict of interest Penelope Bouziotis and Carlo Fiorini declare no conflicts of interest.

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