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PET and MRI: Is the whole greater than the sum of its parts?

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Abstract

Over the past decades, imaging in oncology has been undergoing a “quiet” revolution to treat images as data, not as pictures. This revolution has been sparked by technological advances that enable capture of images that reflect not only anatomy, but also of tissue metabolism and physiology *in situ*. Important advances along this path have been the increasing power of magnetic resonance imaging (MRI), which can be used to measure spatially dependent differences in cell density, tissue organization, perfusion, and metabolism. In parallel, positron emission tomography (PET) imaging allows quantitative assessment of the spatial localization of positron emitting compounds, and it has also been constantly improving in the number of imageable tracers to measure metabolism and expression of macromolecules. Recent years have witnessed another technological advance, wherein these two powerful modalities have been physically merged into combined PET/MRI systems; appropriate for both pre-clinical or clinical imaging. As with all new enabling technologies driven by engineering physics, the full extent of potential applications is rarely known at the outset. In the work of Schmitz et al. in this volume, the authors have combined multiparametric MRI and PET imaging to address the important issue of intratumoral heterogeneity in breast cancer using both pre-clinical and clinical data. With combined PET and MRI and sophisticated machine learning tools, they have been able identify multiple co-existing regions (“habitats”) within living tumors and, in some cases, have been able to assign these habitats to known histologies. This work addresses an issue of fundamental importance to both cancer biology and cancer care. As with most new paradigm shifting applications, it is not the last word on the subject, and introduces a number of new avenues of investigation to pursue.

Keywords

PET/MR; multi-parametric imaging; disease characterization; translational medicine

Non-invasive imaging is an important tool for state-of-the-art patient management. Whilst seen by many as a source of increasing healthcare costs, imaging by itself contributes to only a small fraction of the overall costs (1) If used efficiently and appropriately, radiographic and/or nuclear medicine imaging can provide key information for the diagnosis and appropriate choice of therapy for a wide range of clinical indications. Over the last decades, there has been a revolution in oncologic imaging with the advent of volumetric techniques to

assess physiology by magnetic resonance imaging (MRI) or to reliably quantify metabolism by positron emission tomography (PET). This information can be generated in a single diagnostic exam to plan the course of therapy, or over the course of time to monitor therapy response. Individually, these two technologies have significantly changed the workup of cancer patients, and have led to critical discoveries regarding biologies that contribute to tumor aggressiveness (2). Both PET and MRI provide means to screen patients non-invasively for cancerous lesions and to provide whole-lesion information in the context of a high spatiotemporal resolution and anatomical sensitivity (MRI) as well as a high metabolic sensitivity (PET).

Driven by the clinical success of combined PET and Computed Tomography (PET/CT) imaging (3–5), PET and MRI have recently been combined through a sustained engineering effort by both academics and industry (6), resulting in the commercial availability of combined PET/MRI systems for both small animals and human patients (7). While dual-modality imaging systems will undoubtedly be enabling to new investigations and new capabilities, there is uncertainty regarding exactly what types of studies will be most appropriate for integrated PET/MRI systems (8–11). Indeed there is some controversy regarding this, as recent studies have highlighted the lack of clinical evidence for the added value of integrated PET and MR imaging over existing clinical imaging pathways, such as the more common PET/CT systems (12, 13). Notably, such comparisons have invariably addressed only the anatomical co-localization of molecular image information obtainable from MRI vs. CT. From a purely anatomical perspective, CT and MRI are often interchangeable; MRI is only favored over CT in defined oncological applications such as brain cancers, thyroid, cervical cancer, and colorectal cancers, where MRI is superior to CT in delineating extent of disease (14, 15). Although numerous studies have compared CT vs. MRI for anatomic localization of the PET signals, very few have exploited the full diagnostic potential of MRI and its unique capabilities to measure tumor physiology. In breast and prostate cancers, for example, multiparametric MRI (mpMRI) has been used wherein information from different MR pulse sequences are combined into a single exam. Typically, such exams include diffusion-weighted MRI (DW-MRI), which is sensitive to cell density, and dynamic contrast enhanced MRI (DCE-MRI) which can report regional variations in blood flow. mpMRI in breast and prostate cancer has shown excellent prognostic and diagnostic potential, and has yielded significantly new information regarding these disease pathophysiologies (16–19). Importantly, recent studies have pointed to diagnostic synergies of integrating mpMRI and dynamic, quantitative PET information in these clinical indications (20, 21). FIGURE 1 illustrates the concept of integrating mpMRI and PET for improved cancer diagnosis and, moreover, a more accurate description of the tumor. In this example, an estimate of cellular density and regional blood flow of the prostate gland was obtained from DW-MRI and DCE-MRI, respectively. For the simultaneously acquired PET examination, patients were injected with [^{68}Ga]-PSMA that binds specifically to prostate specific membrane antigen, PSMA (22) and [^{18}F]-choline (FCH) to assess local lymph node involvement (23). Voxelwise fusion of these images and analyses with machine learning and classifier modeling yields a probability map, which can then be compared and validated to histology, thus, helping to build automated and image-

based classifiers that provide the user with a characterization of the lesion with regards to hosting cancerous lesions (e.g., through a tumor probability map).

The current work of Schmitz et al. in this volume (24) represents an important milestone in combined PET and MRI in using this technology to assess the fundamentally important property of heterogeneity in breast cancer. Importantly, this work proceeds from basic pre-clinical work in mouse models and translates this application to human studies. Using the polyoma middle-T transgenic (PyV-mT) breast cancer model, the investigators compared *regionally-specific* uptake of 18F-deoxyglucose (FDG) and D-MRI, in 26 tumors. Significant intratumoral heterogeneity precluded analysis of tumors with single values extracted from the entire volume. More specifically, histograms of both FDG-PET and DW-MRI data showed the existence of different populations. Statistical curve fitting (a Gaussian Mixture Model analyzed with Akaike or Bayesian information) was used to determine the most parsimonious models to identify distinct phenotypes that were spatially co-registered between the PET or MR images. These were manually (hence, approximately) registered to H&E histology, which resulted in correlated PET and MRI maps that identified three regions or “habitats” (25) as three distinct populations within single tumors; corresponding to solid acinar and solid nodular malignancies, as well as cystic hyperplasia. The solid nodular component, thought to have the highest prognostic value, was not identifiable from either PET or MRI modalities alone.

Importantly, the pre-clinical component of this work encompassed distinct training and test sets, which were then applied to human studies. This emphasizes one of the powers of molecular and functional imaging: i.e. the rapid translatability between animal and human studies. In 5 ER⁺/PR⁺ breast cancer patients with biopsy proven invasive carcinoma, fully-integrated PET/MRI studies were conducted a week before surgical resection; after which the imaging results were compared to pathological exams. The fitting models identified 5 habitats by FDG-PET and 2 habitats by DW-MRI; combining these following baseline subtraction yielded three distinct habitats, that would be correlated to Ki67 staining the manually co-registered histology.

As with most important studies, there are often more questions generated than answers. Clearly, reliance on manual co-registration of ex-vivo histology and in-vivo image data is suboptimal and, if combined with perfectly aligned digital histopathology, more habitats may be resolvable with more granularity. Although voxel-wise image data analysis is useful and forward-looking, its value depends on the accuracy of the alignment of the combined (histology and in vivo imaging) data that are acquired at different resolutions. In the future, studies that involve both imaging data and histology information may draw from existing expertise in registration frameworks previously set-up for correlating ex-vivo sample imaging and in-vivo whole-body assessment (26). In a clinical context, accurate spatial image volume alignment is currently possible only with the use of optimized imaging workflows and/or the adoption of motion detection and correction algorithms, which may become more routine in the future. Hence, further technological advances, including advances in image alignment tools and analytics will be needed to realize the full potential of this approach. Adopting texture analysis or machine-learning algorithms to extract and interpret specific, well-defined subtypes in heterogeneous lesions (FIGURE 1) requires

robust and reproducible data, which can be provided by standardized imaging protocols or improved post-acquisition image processing tools. While imaging standardization is a common goal among the quantitative imaging community, it is significantly more challenging in combined PET/MRI.

Finally, there is the question of relevance: Does the existence of these different habitats (or a single habitat) predict therapy response, recurrence or overall outcome? Here, long-term studies are required that may best be set up as prospective trials. Given the novelty of clinical PET/MRI, a multi-center initiatives based on standardized or harmonized imaging protocols may help gather informative data fast and engage a larger community. Nonetheless, this current study is representative of the paradigm shift occurring in modern clinical imaging to extract high content information from “anato-metabolic images” (27), and parsing these data with informatics approaches, or “radiomics” (28) to contribute meaningfully to improved decision support. Combined PET/MRI may be a leading tool in this endeavor.

To further support the use of PET/MRI along the ways laid out by Schmitz and colleagues, a number of defined steps can be identified that will benefit from a cross-specialty engagement of imaging experts in both academia and industry. First, there is a need to facilitate integration between clinical and research level investigations, much as PET and MR system technologies are now integrated into a common imaging platform. As illustrated in the work by Schmitz and colleagues, such efforts initiated in a research environment can translate quickly into a clinical application. Second, realizing the existing lack of a key clinical application, PET/MRI providers and adopters should partner to develop prioritized strategies to assess the full potential of this emerging technology. Third, the complexity of the hardware integration of PET and MRI needs to be matched with advances in software-based image analytics. Although PET/MRI provides a number of methodological advantages, such as intrinsic motion compensation, partial volume correction and model-based attenuation correction, it could also benefit from recent developments in advanced image reconstruction that, taken together, have the potential to markedly improve the diagnostic quality of PET/MRI. It is our considered opinion that PET/MRI will be a valuable tool to provide actionable information to individualize patient management. The study by Schmitz et al is an important step along this path.

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Figure 1.

Patient with prostate cancer undergoing a combined, dual-tracer protocol using a fully-integrated PET/MRI system and following subsequent ex-vivo histopathology of the prostate. The combined imaging protocol consists of T2-weighted MRI (anatomical referencing), DW-MRI with subsequent apparent diffusion coefficient (ADC) calculus as a measure of cellular density and sequential [68Ga]-PSMA ligand and [18F]-Fluorocholine imaging. Combined image data assessment allows the extraction of image features that are fed into a machine-learning (ML) process and subsequent computer-supported classifiers, which permit the delineation and classification of tumor heterogeneity. Courtesy of Laszlo Papp, MSc, Markus Hartenbach, MD, Martin Susani, MD (Medical University Vienna) and Sabrina Hartenbach, MD (HistoConsulting)