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 MRI, which can be used to measure spatially dependent differences in cell density, tissue organization, perfusion, and metabolism. In parallel, 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 preclinical or clinical studies. 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 and colleagues, the authors have combined multiparametric MRI and PET imaging to address the important issue of intratumoral heterogeneity in breast cancer using both preclinical and clinical data. With combined PET and MRI and sophisticated machine-learning tools, they have been able to identify multiple coexisting 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.

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Noninvasive imaging is an important tool for state-of-the-art patient management. Although seen by many as a source of increasing health care 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 MRI or to reliably quantify metabolism by 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 noninvasively for cancerous lesions and to provide whole-lesion information in the context of a high spatiotemporal resolution and anatomic sensitivity (MRI) as well as a high metabolic sensitivity (PET).

Driven by the clinical success of combined PET and CT (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). Although 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 anatomic colocalization of molecular image information obtainable from MRI versus CT. From a purely anatomic 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 the extent of disease (14, 15). Although numerous studies have compared CT versus 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 is 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 bloods flow. mpMRI in breast and prostate cancer has shown excellent prognostic and diagnostic potential and has
yielded significantly new information regarding these disease pathophysologies (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 [68Ga]-PSMA that binds specifically to prostate-specific membrane antigen, PSMA (22) and [18F]-choline (FCH) to assess local lymph node involvement (23). Voxel-wise fusion of these images and analyses with machine learning and classifier modeling yields a probability map, which can then be compared and validated with 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 and colleagues (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 preclinical work in mouse models and translates this application to human studies. Using the polyoma middle-T transgenic 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 coregistered between the PET or MR images. These were manually (hence, approximately) registered to hematoxylin and eosin 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 preclinical 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, that is, 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 with pathologic exams. The fitting models identified five habitats by FDG-PET and two habitats by DW-MRI; combining these following baseline subtraction yielded three distinct
h Habitats, that would be correlated to Ki67 staining the manually coregistered histology. As with most important studies, there are often more questions generated than answers. Clearly, reliance on manual coregistration 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 (Fig. 1) requires robust and reproducible data, which can be provided by standardized imaging protocols or improved postacquisition image processing tools. Although 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 multicenter initiative 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 "anatom-biochemical 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 (24), 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, such 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 methodologic 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 and colleagues (24) is an important step along this path.

Disclosure of Potential Conflicts of Interest

T. Beyer is the managing director at cmi-experts Ltd. and reports receiving a commercial research grant from Siemens Healthcare. No potential conflicts of interest were disclosed by the other authors.

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Conception and design: R.J. Gillies, T. Beyer
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Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): T. Beyer
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