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Current Status of Hybrid PET/MRI in Oncologic Imaging

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Abstract

OBJECTIVE—This review article explores recent advancements in PET/MRI for clinical oncologic imaging.

CONCLUSION—Radiologists should understand the technical considerations that have made PET/MRI feasible within clinical workflows, the role of PET tracers for imaging various molecular targets in oncology, and advantages of hybrid PET/MRI compared with PET/CT. To facilitate this understanding, we discuss clinical examples (including gliomas, breast cancer, bone metastases, prostate cancer, bladder cancer, gynecologic malignancy, and lymphoma) as well as future directions, challenges, and areas for continued technical optimization for PET/MRI.

Keywords

cancer; hybrid PET/MRI; MRI; PET

Biomedical imaging plays an increasingly important role in all phases of cancer management, including screening, diagnosis, biopsy guidance, staging, prognostic assessment, selection of a treatment plan, prediction and monitoring of treatment response, and assessment for recurrent disease [1–6]. Through the end of the last century, advancements in CT, MRI, SPECT, and PET drove innovation in tumor imaging. In the early 2000s, combined PET/CT and SPECT/CT became a reality, fusing the molecular sensitivity of nuclear imaging with the anatomic specificity of CT, further increasing diagnostic accuracy in cancer imaging. Hybrid imaging was born and would enjoy rapid growth over the following 15 years [7].

In recent years, a third major hybrid imaging modality has come into existence in the form of combined PET and MRI (PET/MRI). Hybrid PET/MRI scanners are now readily available for clinical use at any site with the resources and desire to acquire and maintain them. PET/MRI combines the unique tissue characterization of MRI—achieved through an array of conventional and emerging pulse sequences—with the quantifiable functional and molecular information provided by PET, thereby providing distinct potential clinical

advantages over other imaging modalities. This review article explores recent advancements in PET/MRI for clinical oncologic imaging.

Technical Considerations

PET/MRI technology became clinically viable with the advent of solid-state PET detectors that are compatible with MRI's strong magnetic fields, replacing the photomultiplier tubes used in traditional PET and PET/CT. Three major types of PET/MRI scanners are available for clinical use. The first is a trimodality system that uses separate PET/CT and MRI systems with a shared bed that immobilizes the patient and allows software-based registration of separately acquired PET/CT and MR images. An advantage of this system is the availability to use industry-standard CT-based attenuation correction of PET data. Disadvantages include increased scanner space requirements, potential increases in misregistration due to patient transport requirements and mechanical misalignment, and involuntary patient motion between temporally and spatially separate acquisitions.

A second major system design is the sequential system that is based on separate PET and MRI gantries in the same room, with a table that moves on a single track between the two systems. This approach potentially offers improved registration compared with totally separate scanning rooms connected only by a rolling table, but it is not able to make use of CT-based attenuation correction.

The third major system design is an integrated system in which the PET detector rings are placed inside the MRI gantry. Solid-state PET detectors, such as semiconducting avalanche photodiodes, are not only compatible with external magnetic fields but also considerably smaller than traditional PET detectors, thereby facilitating the integrated design. Although this configuration is not yet widely used in clinical PET/MRI systems, an alternative approach based on silicon photomultiplier tubes has been described. Compared with solid-state detectors, silicon photomultipliers minimize or even eliminate bidirectional interference between PET and MRI circuitry, speed the detector response time, and improve scanner performance [8–10]. The integrated design allows truly simultaneous PET and MRI, with practical advantages including reduced scanning time and improved coregistration as well as potential advantages for simultaneous imaging of dynamic processes visualized on both PET and MRI. CT-based attenuation correction is not possible in either the sequential or the integrated system, thus presenting a challenge for engineers to optimize MRI-based attenuation correction [11]. However, hybrid PET/MRI has a potential future advantage of performing MRI-based motion correction of individual PET coincidence events.

The installation of a PET/MRI system shares many design challenges with a successful PET/CT system, given that an appropriate space for handling radiopharmaceuticals must be configured and appropriate shielding must be in place throughout the department. However, technologists must take extra steps to ensure magnetic field safety in the PET/MRI scanning area. Accordingly, MRI-safe radio-pharmaceutical transport containers (often referred to as “pigs”) and syringe shields have been developed for use in PET/MRI systems and are strongly encouraged. In addition, either technologists with training in PET and MRI must

work in teams, or technologists may become trained in both PET and MRI, which may require dual licensing depending on individual state requirements.

PET Tracers for Imaging Various Molecular Targets in Oncology

Oncologic PET uses positron-emitting radioisotopes created in a cyclotron (e.g., ^{18}F , ^{11}C , ^{64}Cu , ^{124}I , ^{89}Zr , ^{86}Y , ^{15}O , and ^{13}N) or in a generator (e.g., ^{68}Ga). The role of nuclear medicine in oncology changed dramatically after ^{18}F -FDG became commercially available and recognized as a biomarker for malignancy. FDG and ^{18}F -NaF (for bone imaging) were the only tracers approved by the U.S. Food and Drug Administration for oncologic imaging until 2012, when ^{11}C -choline was approved for detecting recurrent prostate cancer [12].

Despite the success of FDG in cancer imaging, it is of limited value for several cancers, including prostate cancer, hepatocellular carcinoma, and gastric cancer [13–15], so other tumor-specific PET markers are needed to meet clinical demands. Several promising PET tracers are currently being developed and evaluated in preclinical and clinical oncologic trials. Many of these tracers target biologic activities such as hypoxia, proliferation, apoptosis, angiogenesis, and vascular function. Their application to clinical use, aimed at the same or closely related processes, is anticipated to benefit treatment planning and therapeutic strategies [16–18]. For example, in radiation oncology, there is a compelling need to identify hypoxic tissue because of its decreased sensitivity to chemotherapy and chemoradiotherapy [19]. Furthermore, FDG PET is not useful for monitoring therapy response in many cancers. Assessment of target expression before therapy and possible change after therapy are required for an individualized approach to cancer treatment. For example, information on expression of *ErbB-2*, also known as *HER2/neu*, or growth receptor expression may be useful in monitoring drug response and therapy outcome in breast cancer. As a result, various targeted agents for cancer markers (e.g., cell proliferation, gene expression, protein synthesis, signal transduction, integrin, vascular $\alpha_v\beta_3$ endothelial growth factor, epidermal growth factor receptors, carcinoembryonic antigen, prostate stimulating membrane antigen, somatostatin receptors, and folate receptors) have been developed for basic, preclinical, and translational research.

Advantages of Hybrid PET/MRI Versus PET/CT

PET/MRI has many potential advantages over PET/CT (Table 1). The improved lesion detection within the brain, breast, liver, kidneys, and bone of MRI compared with that of CT is expected to achieve an overall diagnostic advantage for PET/MRI over PET/CT. In addition, lesion margins may be better defined by MRI than by CT in certain locations, such as the pelvis and breast. Preliminary data also suggest that lesion registration is improved through hybrid PET/MRI, an advantage that will potentially improve tissue segmentation, attenuation correction, and ultimately PET quantification [20]. Although CT is superior to MRI for detection of small lung nodules, emerging rapid high-resolution MRI sequences will likely mitigate this difference [21].

In addition, PET/MRI offers practical advantages for patients requiring both PET and MRI examinations for oncologic assessment by providing both modalities within a single appointment and imaging session. Radiation exposure is also reduced because CT is not used in the imaging protocol.

Finally, PET/MRI allows accurate, temporally and spatially aligned multiparametric imaging that combines high-contrast anatomic MR images with the quantitative power of molecular imaging of both PET and MRI, including DWI, perfusion MRI, and MR spectroscopy. This potential creates numerous opportunities for characterizing tumor biology across all of the dimensions of imaging offered by PET and MRI.

Challenges

Despite many potential advantages, a number of challenges to clinical adoption of PET/MRI remain. First, attenuation correction must be optimized through more advanced MRI-based estimates of tissue density. Current Dixon-based attenuation-correction methods suffer from breath-hold induced mis-registration and substantial errors due to signal dropout from metallic artifact. Variable segmentation of sinuses and other air cavities also introduce small but potentially significant quantitative errors [22]. The presence of MRI contrast agents or of MRI coils within the PET FOV, as well as both B_0 and B_1 field inhomogeneity, may impact standardized uptake value (SUV) measurements [23]. MRI-compatible PET phantoms require further development, and efforts are needed to standardize quantification across scanners and manufacturers to the extent possible. Given such concerns, agreement in SUV values between PET/CT and PET/MRI remains uncertain. One study of 32 patients suggested excellent correlation in maximum SUV (SUV_{max}) of pulmonary nodules between PET/CT and PET/MRI, although the reported findings may have been impacted by the specific generation of PET/MRI scanner used [24].

Aside from optimization of attenuation correction and SUV measurements, rapid multiparametric MRI sequences are needed to reduce scanning times and increase patient comfort while maintaining image quality. As noted, improved lung nodule detection is also a priority [24]. Furthermore, motion correction requires further optimization so that breath-hold MRI sequences can be optimally fused with free-breathing PET [25]. Dynamic gated combined PET and MRI with motion correction may offer significant gains in this area and is an area of active research. Finally, not all PET/MRI systems offer resolution recovery (point-spread-function) and time-of-flight capabilities, which are now standard features available on top-of-the-line PET/CT systems. Preliminary work indicates that these capabilities will improve quantitative accuracy in PET/MRI [26].

Further advancements in hardware and software instrumentation may help solve or minimize most of these challenges. Thus, long-term challenges faced by PET/MRI may largely entail achieving adequate reimbursement and evidence-based validation of improved patient outcomes compared with PET/CT or MRI alone. Additional practical considerations will also need to be addressed to establish successful institutional PET/MRI programs and optimized workflows. For instance, both radiologists and nuclear medicine physicians will need training in interpreting hybrid examinations. Potential issues of territorial conflict

between these two groups will need to be addressed. Consistent protocols that provide maximal morphologic, functional, and metabolic data while fitting within examination time slots must be developed. Viewing software for robust and efficient display of fused complex multiparametric PET/MRI datasets is needed. Reporting templates to effectively capture whole-body multiparametric data from the two modalities must be developed. Quality assurance programs for both modalities are needed, and buy-in regarding the added value of PET/MRI must be sought from all stakeholders within the institution. Clinical PET/MRI currently serves as an approach for patients who have an indication for both PET and MRI or for patients warranting PET/CT to reduce radiation dose, when both the oncologist and radiologist are willing to use basic MRI sequences in conjunction with PET.

Clinical Examples

Brain Tumors

Contrast-enhanced MRI is the primary imaging modality used to guide biopsy procedures, treatment planning, and surgical de-bulking of brain tumors. However, available treatment regimens have not improved patient survival, especially for high-grade gliomas, so more reliable characterization of brain tumor biology at the molecular level is urgently needed. PET can provide this detailed metabolic information, which when combined with the high spatial and contrast resolution of MRI could help tailor treatment regimens at an early stage. Although MRI is routine in this setting, compelling data support the added value of PET information. For example, Mertens et al. [27] found that FDG uptake, evaluated at the site of stereotactic biopsy, could be used to differentiate between low- and high-grade gliomas. In addition, Pirotte et al. [28] observed that PET findings had a significant impact on surgical decisions in pediatric patients with brain tumors, including improved target selection and diagnostic yield of stereotactic biopsies. These authors also observed improved lesion delineation with PET of lesions that were poorly delineated using MRI, as well as improved postoperative detection of residual tumor [28]. In addition, Takenaka et al. [29] found that ^{11}C -methionine PET could play a role in distinguishing glioma recurrence from posttreatment radiation necrosis, which is challenging with conventional MRI. A particular potential advantage of hybrid PET/MRI systems for glioma evaluation is the associated ease of coregistration of critical functional data, such as tumor blood volume derived from perfusion MRI with FDG uptake. Key applications of PET/MRI are anticipated to include improved localization of focal targets for surgical biopsy planning, especially in spatially heterogeneous gliomas, improved gross tumor volume and tumor margin delineation for radiotherapy planning, and improved detection of post-treatment recurrences.

We use hybrid PET/MRI to help guide biopsies of gliomas, combining high-resolution MR images with parametric maps from perfusion MRI and FDG PET to confidently identify biopsy targets (Fig. 1). We are also applying combined PET/MRI data to help differentiate recurrent tumor from radiation necrosis (Fig. 2). Such evaluation is particularly challenging given the heterogeneous imaging appearance of mixed necrosis and tumor in the posttreatment setting. For these cases, a neuroradiologist and nuclear medicine physician interpret the fused cerebral blood volume and FDG maps together and issue a combined report.

Breast Cancer

FDG PET/MRI may offer improvements in both breast imaging and whole-body staging for patients with breast cancer. PET/CT and breast MRI are typically performed separately during initial staging. However, combined initial whole-body and breast FDG PET/MRI would offer a more seamless patient experience while providing similar or even more information at a decreased radiation dose.

In whole-body imaging for metastatic breast cancer, accurate localization of lesions is important for treatment planning. Detection and treatment of isolated hepatic and brain metastases is critical for achieving prolonged survival and improved quality of life, respectively [30–32]. In an initial comparison of whole-body FDG PET/MRI and FDG PET/CT in 36 patients with breast cancer, Pace et al. [33] observed equivalent detection of the primary lesion as well as of nodal, bone, and pulmonary metastases. Subsequent data in 50 patients with breast cancer corroborated these lung, bone, and node findings and found that FDG PET/MRI outperformed FDG PET/CT for detection of brain and liver metastases (Melsaether A, et al., presented at the International Society for Magnetic Resonance in Medicine 2014 annual meeting). In addition, Taneja et al. [34] explored the clinical value and feasibility of a single-visit breast and whole-body FDG PET/MRI in patients with newly diagnosed breast cancer. They performed whole-body unenhanced PET/MRI for 36 patients, followed by contrast-enhanced breast PET/MRI and a whole-body contrast-enhanced MRI sequence. The total examination time was just over an hour. Although metastatic disease detection at the patient level was similar for PET and MRI alone, significantly more metastatic lesions were seen on MRI than on PET alone. Although primary tumor detection was equivalent between PET and MRI, MRI showed an additional 14 satellite lesions at the cost of four false-positive lesions. PET/MRI changed management compared with the initial clinical staging in one third of patients. This potential for similar or improved detection of metastatic disease at a decreased radiation dose suggests a role for wider clinical implementation of hybrid PET/MRI, especially in young patients with breast cancer.

Although dynamic contrast-enhanced MRI is the current reference standard in morphologic breast cancer imaging, localized PET/MRI of the breast has been shown to be feasible with four-channel and now 16-channel MRI coils [35, 36]. Breast cancer treatment strategies are becoming increasingly individualized to reflect a patient's tumor type as well as dynamic to reflect early therapeutic response over time. Thus, quantitative metrics derived from PET, DWI, and perfusion MRI are of increasing interest for complementing traditional contrast-enhanced breast MRI (Fig. 3). For example, increasing SUV_{max} has been associated with breast cancers that are not of the luminal A subtype, a higher proliferation index, and estrogen- and progesterone-receptor negativity [37]. In addition, changes in SUV_{max} and apparent diffusion coefficient (ADC) have been independently associated with early treatment response before changes in tumor volume [37], and a combination of SUV_{max} and ADC has shown increased accuracy over either measurement alone [38]. Finally, lesser reductions in SUV_{max} and MRI slope and a lesser increase in ADC after the first cycle of chemotherapy have negative prognostic implications and are associated with reduced disease-free survival [39]. Multiparametric hybrid PET/MRI of the breast may provide the best examination for evaluating these imaging biomarkers, potentially establishing imaging-

based phenotypes and serving as a virtual biopsy for identifying heterogeneous metabolic, vascular, and cellular tumor properties.

Soft-Tissue and Musculoskeletal Malignancies

Little research has been done to evaluate the role of PET/MRI for musculoskeletal malignancies. Nonetheless, PET/MRI is expected to allow more accurate interpretation of bone tumors through the combination of multiple quantitative metrics. For instance, perfusion MRI is able to detect changes in blood flow in the setting of marrow infiltration by tumor cells [40], whereas ADC can be used to predict and monitor treatment response of bone metastases from prostate cancer [41, 42]. PET/MRI may also be useful for screening and surveillance in marrow infiltrative disorders such as multiple myeloma [43] and leukemia or lymphoma [44] given the utility of MRI's high contrast for detection of marrow and soft-tissue infiltration by tumor cells.

Our initial experience with the use of ^{18}F -NaF PET/MRI in the diagnosis of bone metastases from prostate cancer is promising [45]. Although detection of bone metastases from prostate cancer is traditionally performed with bone scanning, that technique has a low specificity of 41% [46] because of overlap of bone metastases with benign conditions such as healing fractures, degenerative or inflammatory joint disease, Paget disease, benign neoplasms, or metabolic disorders [47, 48]. NaF PET/CT is a more recent examination with both higher sensitivity [49] and higher specificity [50] than bone scanning for bone metastases from prostate cancer. Furthermore, DWI has shown higher specificity, although lower sensitivity, than NaF PET/CT [51]. Hybrid PET/MRI may prove to be the most accurate imaging examination in this context by combining the superior sensitivity of NaF PET with the superior specificity of DWI (Fig. 4).

Prostate Cancer

MRI is widely used in clinical practice for the detection, localization, and assessment of aggressiveness of prostate cancer, facilitated by high spatial resolution, excellent depiction of the prostate anatomy, and comprehensive multiparametric assessment that provides metrics highly associated with prostate cancer grade [52]. Nonetheless, the heterogeneity of benign prostate tissue and of prostate cancer contribute to false-positive and false-negative interpretations [53], such that alternative imaging approaches may be able to address current limitations of MRI for prostate cancer evaluation. PET has been explored for this purpose given its unique assessment of tissue physiology [54]. FDG PET has shown poor performance in assessing prostate cancer, stemming from a combination of low FDG uptake in many prostate tumors, frequent uptake of FDG by benign prostate hyperplasia, and accumulation of excreted tracer in the urinary bladder [55–57]. By comparison, PET/CT using other agents, including ^{11}C -choline [58–60] and ^{11}C -acetate [61], has exhibited reasonable diagnostic performance for localized prostate cancer. Nonetheless, the accuracy of PET/CT using such agents is suboptimal, partly because of the combination of the small size of many prostate tumors, the limited spatial resolution of PET, and the lack of anatomic detail in the prostate on both PET and CT. Accordingly, PET/CT using such agents has not outperformed MRI [58, 59, 61], and PET/CT is not widely used for evaluation of localized prostate cancer outside of a limited number of academic centers [55].

PET/MRI combines detailed multiparametric tumor assessment and reliable lesion localization from multiparametric MRI with complementary physiologic information from PET (Fig. 5), thereby potentially providing additional diagnostic value not possible with MRI alone. Several studies support the role of PET/MRI for prostate cancer evaluation. For example, one study of 15 patients with prostate cancer who underwent ^{18}F -fluorocholine PET/MRI reported excellent correlation between areas of abnormal fluorocholine uptake and focal abnormalities on T2-weighted imaging, as well as PET positivity in three lesions lacking a correlate on DWI [62]. Another study of fluorocholine PET/MRI in 35 patients with prostate cancer reported significant differences in both ADC and SUV between benign and malignant prostate tissue but a lack of substantial correlation between these two metrics, suggesting that the metabolic data provided by PET is complementary [63]. An additional study of fluorocholine PET/MRI in patients awaiting radical prostatectomy observed excellent correlation between abnormalities on T2-weighted images and areas of increased uptake and higher accuracy for tumor using PET/MRI compared with MRI alone [64]. We have shown the ability to evaluate prostate cancer using graphic analysis with an image-derived arterial input function based on dynamically acquired PET data obtained immediately after nearly simultaneous injection of both PET and MRI contrast agents as part of a hybrid PET/MRI examination [65]. Our data suggested added potential of the dynamic PET metrics compared with traditional static PET metrics, such as SUV obtained at a delayed equilibrium time point after radiotracer injection.

Bladder Cancer

FDG PET historically has not been used for the assessment of localized bladder cancer, given accumulation of excreted radiotracer in the bladder lumen obscuring focal mural lesions [62, 66]. However, more recent studies have attempted to perform FDG PET/CT for bladder cancer evaluation using a forced diuresis protocol [67–69]. With this approach, before initiation of PET, the patient receives oral hydration and an IV diuretic and then attempts to void completely. This protocol has been shown to effectively clear excreted FDG from the bladder lumen and allow robust visualization of focal increased FDG activity within mural lesions [67, 68].

We are exploring the use of FDG PET/MRI for bladder cancer evaluation using a forced diuresis protocol. This examination aims to combine the high spatial and contrast resolution of MRI, including MRI's ability to depict invasion of the muscularis propria of the bladder wall by urothelial tumors [70], with the metabolic information of PET. As previously achieved in PET/CT, the forced diuresis protocol achieves clearance of excreted FDG, facilitating reliable depiction of increased FDG activity within bladder tumors (Fig. 6). Preliminary data indicate that simultaneous PET and MRI acquisitions from hybrid PET/MRI achieve substantially improved coregistration of the bladder wall and slightly improved coregistration of bladder masses and pelvic lymph nodes compared with sequential acquisitions [65]. This PET/MRI protocol is being investigated for purposes such as identification of recurrent bladder tumor after transurethral tumor resection as well as prediction and monitoring of response to neoadjuvant chemotherapy.

Gynecologic Malignancy

PET/MRI may have value for detecting nodes and implants in patients with gynecologic malignancy who are undergoing disease staging. For example, in a study of 34 women undergoing whole-body staging for suspected recurrence of cervical or ovarian cancer, FDG PET/MRI accurately identified 98.9% of malignant lesions, compared with 88.8% by MRI alone, and had significantly higher lesion contrast and diagnostic confidence in the detection of malignant lesions compared with MRI alone [71]. In an additional study of 122 suspected lesions in 48 women undergoing staging for gynecologic malignancy, whole-body FDG PET/MRI achieved over 90% accuracy for identification of malignant lesions [72].

Lymphoma

One study reported a head-to-head comparison of PET/MRI and PET/CT in 28 consecutive patients with lymphoma [73]. PET/MRI identified the same 51 FDG-avid nodal groups as PET/CT with 100% sensitivity and concordant staging in all cases, aside from one patient who was accurately upstaged on MRI due to bone marrow involvement identified on DWI and subsequently confirmed by biopsy that was not seen on PET/CT. Although requiring validation in larger studies, these findings suggest that PET/MRI may be able to substitute for PET/CT in lymphoma staging.

From the Perspective of an Oncologist

Although multimodality imaging using PET/CT is routinely used to evaluate many cancers, hybrid PET/MRI systems are now commercially available and offer additional possibilities. This exciting new modality has the potential advantage of combining the success of clinical PET/CT with the unique features of MRI, including excellent soft-tissue contrast, quantitative multiparametric assessment including DWI and perfusion MRI, and no ionizing radiation. This approach affords patient convenience and is hoped to significantly improve clinical decision-making and outcomes.

The available data show strong concordance between PET/CT and PET/MRI for lesion localization [73] (Melsaether et al., 2014 ISMRM annual meeting) and suggest that PET/MRI achieves improved T categorization for primary bone, head and neck, and soft-tissue tumors and a higher accuracy for metastatic lesion detection in the brain, liver, and bone [73–75]. One of the most promising applications of hybrid PET/MRI is for radiation treatment planning and differentiation of posttreatment changes from viable tumor in patients with brain tumors [76]. PET/MRI may also become an important technology for assessing treatment response and prognosis in patients with head and neck, breast, prostate, and bladder cancer [39, 55, 77–79]. In prostate cancer, PET/MRI may also be used for guiding targeted biopsies and focal therapies. PET/MRI also seems preferable in pediatric patients, in whom cumulative radiation should be kept as low as reasonably possible (Fig. 7).

Are we ready to use hybrid PET/MRI as a standard of care for all cancer types or organs? The answer is no. We have yet to fully address many challenges, including clinical workflow, standardization of scanning protocols, and training and credentialing of interpreting radiologists [8, 80, 81]. The superiority of simultaneously acquired PET/MR

images to fused images obtained from different camera systems must be validated. However, the outlook remains bright because promising ongoing and future research across various disease types will elucidate the optimal clinical indications for hybrid PET/MRI. Such investigations will also help inform logistical and regulatory issues, including scanner availability, cost utility, comparative effectiveness, and reimbursement.

Future Directions

Clinical PET/MRI seems to be becoming a viable and potentially superior alternative to PET/CT in the initial or subsequent evaluation of patients with cancer. Staging of locally advanced rectal cancer, breast cancer, gynecologic malignancies, or other tumors that require accurate T and M categorization may comprise one general category of application. Another useful application is the ability to combine PET and MRI examinations that are warranted for distinct purposes, such as NaF PET whole-body staging of bone metastases and multiparametric MRI of primary prostate tumor, into a single session. Solidifying the role of PET/MRI in these scenarios is a key short-term goal for the PET/MRI user community.

PET/MRI is also a viable alternative for cancer that traditionally would be staged or restaged using PET/CT but that does not require high-resolution lung imaging. Potential applications in this category may include staging and restaging of lymphoma or myeloma or staging of neurofibromatosis in patients who present with concerning nerve sheath tumors. However, at present, imaging centers may only be reimbursed for the PET portion of such hybrid PET/MRI examinations.

A major future direction for hybrid PET/MRI is definition of applications in which the two modalities are truly synergistic in the context of simultaneous imaging. This conceptual advantage has been challenging to prove in a clinical setting. Conventional MRI and PET/CT already exceed 90% sensitivity for many cancers, such that proof of synergistic value will require carefully controlled, longitudinal studies with a large number of patients. To address this need, an international multiinstitutional PET/MRI registry is being developed to support large-scale efficacy trials (Intersocietal Working Group of PET-MR, presented at the Radiological Society of North America 2014 annual meeting). For now, simultaneous imaging in the clinical setting yields the benefits of patient convenience and improved image registration, which may offer some advantages in lesion delineation and quantitative assessment. Although motion correction of simultaneously acquired data will undoubtedly improve image quality, associated gains in patient management remain to be proven. Thus, discovery of ways to clinically apply temporally dynamic PET and MRI parameters remains an area of active research.

Studies of potential synergy to more firmly justify hybrid PET/MRI must more directly examine composite biomarkers, such as combining SUV and ADC. Such biomarker panels may help researchers better understand cancer biology and theoretically provide improved monitoring or prediction of treatment response. One preliminary study postulated that a higher SUV to ADC ratio indicates a more aggressive tumor [20]. Other advanced PET and MRI metrics, such as metrics extracted from dynamic PET acquisitions or from MR spectroscopy, as well as voxelwise correlations and texture analysis, also warrant

investigation in such biomarker panels. More extensive and carefully controlled research is required to better define the clinical value of quantitative biomarker panels derived from hybrid PET/MRI examinations.

Technical optimization is a pressing short-term goal for supporting the clinical use of hybrid PET/MRI. Improvement of the quantitative accuracy of PET/MRI will likely be necessary to fully realize the potential synergies of this combination of modalities. Improved motion correction [25] and attenuation correction are two of the most important aspects of such research. The mathematic foundations to improve the image acquisitions and reconstructions already exist, and manufacturers are expected to improve the ability of the systems to perform gated, motion-compensated MRI and PET reconstructions, resulting in significantly increased image quality. Of further interest is the possibility of using data from one modality to enhance data reconstruction by the other. MRI is currently used for PET attenuation correction; using PET data to enhance MRI reconstruction, while still highly preliminary, may help achieve faster MRI scanning times and generation of new, potentially useful, functional data. Finally, it is hoped that atlas-based estimates of bone location will serve as an intermediate step in the improvement of MRI attenuation correction [82] and that MRI detection of bone will achieve sufficient quality to allow MRI to directly compute bone density. If this aim is achieved, quantification of PET data from hybrid PET/MRI will be improved to a level matching, if not exceeding, that of PET/CT systems.

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Fig. 1. 45-year-old woman with multifocal nonenhancing glioma

A and B, Axial FLAIR (**A**) and contrast-enhanced T1-weighted (**B**) MR images show glioma involves right periventricular white matter (*arrow*).

C and D, FDG map (**C**) shows faint uptake, whereas regional cerebral blood volume (rCBV) parametric map (**D**) shows markedly increased rCBV in right periventricular white matter nonenhancing lesion (*arrow*), which was targeted with stereotactic biopsy and revealed grade III glioma.

Fig. 2. Recurrent enhancing lesions

A–C, 56-year-old man with previously treated lymphoma. Axial contrast-enhanced T1-weighted MR image (**A**), regional cerebral blood volume (rCBV) perfusion map (**B**), and corresponding FDG map (**C**) show increased rCBV as well as increased FDG uptake in small lesion (*arrow*) consistent with recurrent lymphoma.

D–F, 46-year-old woman with previously treated grade III glioma. Axial contrast-enhanced T1-weighted MR image (**D**), rCBV perfusion map (**E**), and corresponding FDG map (**F**) show markedly low rCBV and markedly low FDG uptake in recurrent enhancing lesions (*arrow*) suggestive of radiation necrosis that was proven with biopsy.

Fig. 3. 42-year-old woman with invasive lobular carcinoma (ILC) of right breast

A, ILC (*arrow*) fails to exhibit marked enhancement on early contrast-enhanced T1-weighted MR image.

B and **C**, ILC shows increased FDG activity (*arrow*) on FDG PET image fused with contrast-enhanced T1-weighted MR image (**B**) and FDG PET image (**C**).

D, Apparent diffusion coefficient (ADC) map of right breast shows ILC has decreased ADC (*arrow*), typical of malignancy.

Fig. 4. 85-year-old man with prostate cancer who underwent initial staging workup that showed metastases to bone

A, Standard bone scan shows one metastatic lesion in left acetabulum (*solid arrow*) and small subtle lesion in upper thoracic spine (*dashed arrow*) which was attributed to degenerative spine disease. ANT = anterior view, POS = posterior view.

B and **C**, NaF PET/MR image obtained 3 weeks later (**B**) reveals nine metastatic lesions (*circles*), showing higher sensitivity of PET/MRI. Lesion in T2 spinous process on PET/MRI (*dashed arrows*) corresponds to small subtle lesion on bone scan (*dashed arrow*, **A**). ANT = anterior view; LAT = lateral view.

D and **E**, Lesion in T2 spinous process shows low mean apparent diffusion coefficient (ADC) of $0.57 \times 10^{-3} \text{ mm}^2/\text{s}$ in ROI (*circle*) on ADC map (**D**) and high maximum standardized uptake value of 38.7 in ROI (*circle*) on fused PET/ADC image (**E**), consistent with metastatic lesion.

Fig. 5. 71-year-old man with prostate cancer imaged by hybrid ^{11}C -choline PET/MRI

A, Axial T2-weighted image shows T2-hypointense lesion involving both right anterior peripheral and transition zones (*arrow*).

B, Apparent diffusion coefficient (ADC) map shows decreased ADC within lesion (*arrow*).

C, Fusion image depicting PET image as color overlay on T2-weighted-image shows excellent registration of abnormality between two image sets (*arrow*). (Courtesy of Eiber M, TU Muenchen, Munich, Germany)

Fig. 6. 57-year-old man with bladder cancer imaged by hybrid FDG PET/MRI

A, Early contrast-enhanced T1-weighted image shows right anterolateral bladder thickening with early enhancement relative to remainder of bladder wall (*arrow*).

B, Fusion image depicting PET image as color overlay on T2-weighted-image shows marked increased activity (standardized uptake value = 19.8) within lesion (*arrow*), with excellent registration of abnormality between two image sets.

Fig. 7. 8-year-old boy with neurofibromatosis type 1 imaged by whole-body hybrid FDG PET/MRI

A–C, Coronal STIR MR image (**A**), coregistered PET/MR image (**B**), and coronal PET image (**C**) show large infiltrative plexiform neurofibroma in right retroperitoneum extending into right thigh. Foci of hypermetabolism (*arrows*, **B** and **C**) with maximum standardized uptake value (SUV_{max}) of 2.5 are seen within superior aspect of mass adjacent to inferior vena cava, but remainder of mass was not FDG avid. Findings were suggestive of benign plexiform neurofibroma given low-grade metabolic activity and stability since PET/CT done 1 year earlier (not shown). (Courtesy of Raad R, New York University School of Medicine, New York, NY)

TABLE 1**Advantages of PET/MRI Versus PET/CT**

Attribute	PET/MRI Advantages	PET/CT Advantages
Lesion detection	Improved lesion detection in the brain, breast, liver, kidneys, and bone	No advantage
Lesion margins	Better delineation of T category in nonpulmonary soft tissues and bone	Improved delineation of lesion margins within lung parenchyma
Lesion alignment	Better alignment of simultaneously acquired PET/MRI data compared with PET/CT	No advantage
Quantitative accuracy	Improved quantification by MRI-based motion correction without additional radiation	Industry standard (i.e., attenuation) is based on density seen on CT
Scanning time	No advantage	PET/CT body scanning protocols currently faster
Radiation exposure	Lack of CT reduces radiation exposure (up to 50% depending on CT protocol)	No advantage
Patient convenience	Single appointment for patients who require both PET and MRI; less scanner time overall	No advantage
Multiparametric quantitative imaging	Expanded capabilities such as DWI, perfusion MRI, and spectroscopy	No advantage
Availability	No advantage	More clinically available