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How PET/MR Can Add Value For Children With Cancer

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Abstract

Purpose—To review how PET/MR technology could add value for pediatric cancer patients.

Recent Findings—Since many primary tumors in children are evaluated with MRI and metastases are detected with PET/CT, integrated PET/MR can be a time-efficient and convenient solution for pediatric cancer staging. ^{18}F-FDG PET/MR can assess primary tumors and the whole body in one imaging session, avoid repetitive anesthesia and reduce radiation exposure compared to ^{18}F-FDG PET/CT. This article lists 10 action points, which might improve the clinical value of PET/MR for children with cancer. However, even if PET/MR proves valuable, it cannot enter mainstream applications if it is not accessible to the majority of pediatric cancer patients. Therefore, innovations are needed to make PET/MR scanners affordable and increase patient throughput.

Summary—PET/MR offers opportunities for more efficient, accurate and safe diagnoses of pediatric cancer patients. The impact on patient management and outcomes has to be substantiated by large-scale prospective clinical trials.

Keywords

Pediatric Cancer; Pediatric Lymphoma; Pediatric Sarcoma; Magnetic Resonance; Positron Emission Tomography; PET/MR

Introduction

For children with cancer, accurate staging of the primary tumor and whole body is pivotal for appropriate patient management and optimized outcomes [1–4]. Currently, children with a newly diagnosed solid tumor have to undergo a series of imaging tests, including x-rays, ultrasound, magnetic resonance imaging (MRI), computed tomography (CT), positron emission tomography (PET), methylene diphosphonate (MDP) scintigraphy and meta-

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Conflict of Interest

Heike Daldrup-Link declares no potential conflicts of interest.

Human and Animal Rights and Informed Consent

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iodobenzylguanidine (MIBG) scintigraphy, among others. Decades of experience have demonstrated excellent sensitivities and specificities of these imaging modalities. However, for children with cancer, undergoing a series of imaging tests is stressful, time consuming, can be redundant, expensive and may require repetitive anesthesia. Recent efforts are directed towards the development of comprehensive, patient-tailored "one stop" imaging tests, which can provide a comprehensive evaluation of the primary tumor and metastases in one session. Towards this goal, ^{18}F-FDG PET/CT technologies have been increasingly used for pediatric cancer staging, specifically for staging of malignant lymphomas and sarcomas [1–5]. Several studies have shown excellent agreement between ^{18}F-FDG PET/CT and whole body MR scans for detection of these tumors in children [6–10]. Recently, ^{18}F-FDG PET/MR has been added to the repertoire of clinically available staging techniques, which allow for simultaneous acquisition of ^{18}F-FDG PET and MRI data [11–15] – an advantage for children requiring both tests. Systematic comparisons between these new technologies are critically needed in order to understand and utilize their respective advantages and limitations.

The Children's Oncology Group (COG) has united pediatric oncologists from hospitals across North America to assess treatment outcomes of specific tumor types. In order to add clinical value, pediatric radiologists need to similarly unite and systematically investigate the impact of new imaging technologies on clinical management and outcomes. Single center investigations of ^{18}F-FDG PET/MR scans for pediatric cancer staging obtained so far cover a limited number of patients with a wide range of different pediatric tumors [11, 12]. These investigations provide limited, often case-based information on clinical impact. To investigate the clinical value of PET/MR in larger and more homogenous pediatric patient populations, the American College of Radiology (ACR) Pediatric Imaging Research Committee (ACR-PIR) has recently formed a consortium of PET/MR investigators at major academic institutions [16]. As these early adopters explore *if* PET/MR is valuable, a transition to use this technology at a majority of pediatric oncology centers can only occur, if and when this new technology can be provided in a time- and cost-efficient manner to the majority of pediatric cancer patients. Even if PET/MR proves clinically valuable, it cannot enter mainstream applications if it is not accessible to the majority of providers and patients. Robertson et al reported that the capital investment required for initial purchase and infrastructure upgrade, coupled with the lower volume of PET imaging performed in pediatric centers, puts procurement of a new PET/MRI scanner outside the financial capacity of many pediatric centers [17]. Potential solutions to this problem could entail integrating PET technology into 1.5 T MR scanners or the design of MRI coils with integrated PET-detectors, which could be used in existing MRI systems [18]. In addition, technical innovations are needed to accelerate the speed of PET/MR image data acquisition, in order to improve patient acceptance and throughput in oncology centers. The goal would be to provide widely available "one stop" medical imaging solutions with equal or faster acquisition times and improved diagnostic information compared to PET/CT.

1. Focus on Pediatric Patients with Lymphomas and Sarcomas

To date, children and adolescents with cancer are referred to specific staging tests based on the organ of origin and histology of the primary tumor. An overview of current clinical

practice for pediatric cancer staging and restaging is provided in Table 1, along with a summary of important clinical questions that need to be addressed for PET/MR in order to impact clinical decisions and and outcomes. Based on the accumulated evidence with ^{18}F-FDG PET/MR imaging studies thus far [11–15], added value is particularly expected for pediatric patients with lymphomas and sarcomas. These patients also represent the main pediatric patient population referred to ^{18}F-FDG PET/CT to date [19–21, 5]. In patients with lymphomas, a main motivation to consider ^{18}F-FDG PET/MR as a potential alternative to PET/CT is a reduction in radiation exposure by 50–70% [11–15]. ^{18}F-FDG PET/MR provides excellent soft tissue contrast (Fig. 1) and has shown equivalent or superior sensitivity compared to traditional ^{18}F-FDG PET/CT for the detection of malignant lymph nodes.[22] Tumor SUV values obtained in the same patients with ^{18}F-FDG PET/MR and ^{18}F-FDG PET/CT showed a high correlation, although SUV values obtained with 18F-FDG PET/MR were systematically lower.[23] In pediatric patients with bone and soft tissue sarcomas, MRI is already the clinical standard for local staging and ^{18}F-FDG PET/CT is often added for whole body staging [24–26, 11, 27]. Initial experiences testify excellent sensitivity of ^{18}F-FDG PET/MR for whole body staging of patients with sarcomas [11, 12]. In these patients, integrating MRI and ^{18}F-FDG PET can create value by providing local and whole body staging in one session. The label “patient convenience” in this context might be underrated. Systematic studies are needed to measure and optimize the time-efficiency of diagnostic tests and the whole process of rendering a cancer diagnosis, counting not only the time a patient spends in a scanner, but the overall time a patient spends in the Imaging Department and Hospital. Results could be used to uncover previously missed opportunities to accelerate and integrate medical tests for comprehensive cancer diagnoses.

2. Reduce Radiation Exposure

Radiation exposure is of higher concern for pediatric patients than adults because children are more susceptible to radiation effects and they live long enough to encounter secondary cancers [28–31]. Cumulative ionizing radiation exposure above 50–100 mSv can increase the risk of secondary cancers later in life [28], such as leukemia or brain cancer [32, 33]. Improved detector technology and longer acquisition times of PET/MR compared to PET/CT, along with replacement of CT by MR for anatomical co-registration, enable reduced radiotracer doses. In accordance with others [11–15], we prescribe an ^{18}F-FDG dose of 3 MBq/kg for four-minute PET data acquisitions per bed position, with excellent tumor-to-background contrast at about 1 hour after ^{18}F-FDG injection (Fig. 1–3). Others calculated that the ^{18}F-FDG dose could be further reduced to 1.5 MBq/kg for four-minute PET data acquisitions [34]. Current data are based on tumor staging results at baseline, when most pediatric tumors show high metabolic activity. Further studies need to clarify, if major reductions in ^{18}F-FDG dose would impact the diagnosis of partial versus complete metabolic response after therapy. If we administer lower radiotracer doses, would we diagnose fewer partial responses and how would this impact patient management and outcomes?

3. Optimize the diagnostic accuracy of MRI scans used for co-registration of PET data

Pediatric staging protocols for lymphoma require a iodinated contrast-enhanced diagnostic CT scan as part of or in addition to a ^{18}F-FDG PET/CT scan [35]. This is different to ^{18}F-FDG PET/CT protocols for adults where unenhanced scans are often sufficient. It has not been established yet, if the same principle applies to PET/MRI, i.e. if pediatric protocols need to include contrast-enhanced scans. A wide variety of T1- and T2-weighted pulse sequences have been proposed for anatomical co-registration of ^{18}F-FDG PET data in children [11–15]. We found in accordance with others that pediatric tumors can be equally well delineated on Gd-enhanced T1-weighted scans and unenhanced T2-weighted scans [36]. However, if the faster T1-weighted scans were applied, intravenous contrast improved vessel and tumor delineation compared to unenhanced T1-weighted scans (Fig. 2). This was particularly useful for accurate tumor measurements and surgical planning.

Similar to the concept of adding “diagnostic” CT scans to low dose CT scans for attenuation correction (AC) for a PET/CT, whole body PET/MR scans can utilize AC pulse sequences for co-registration of ^{18}F-FDG PET data or use dedicated sequences with increased anatomical resolution [37]. We found significant value in using higher resolution scans (Fig. 3). This currently requires the acquisition of two sequences: a low resolution, dual-echo gradient echo sequence for AC correction (with image matrix matched to the matrix of the PET scan) plus a higher resolution scan for anatomical co-registration of PET data. In principle, it should be possible to acquire one single, high resolution dual-echo gradient echo sequence, from which a lower resolution scan could be reconstructed. However, such technology has not yet been established. The saved acquisition time might be considered negligible for adult patients, but would be valuable for children.

4. Integrate Information about tumor cell density and glucose metabolism

Whole body staging of pediatric cancers can be obtained with classical ^{18}F-FDG PET/CT [4, 38], whole body diffusion weighted MRI [39, 10] or integrated ^{18}F-FDG PET/MR [12, 11]. Whole body MR has been used for screening patients with cancer predisposition syndromes, cancer staging of patients with hereditary increased radiosensitivity, staging of benign disease such as Langerhans Cell Histiocytosis, staging of non ^{18}F-FDG-avid tumors and patients without access to an ^{18}F-FDG PET/CT scan [40, 39, 41]. Since most tumors have a higher cell density than normal organs, the diffusional motion of water protons is more restricted in tumors and displayed by an increased signal intensity on diffusion weighted MR images [8, 42, 43]. Diffusion-weighted MR images can be color-encoded and superimposed on anatomical MR images such that they provide a visual tumor depiction similar to a ^{18}F-FDG PET/MR or ^{18}F-FDG PET/CT scan [10]. Several authors reported comparable sensitivities and specificities of ^{18}F-FDG PET/CT and diffusion weighted MR scans for staging patients with lymphoma and other solid tumors [44–46, 10]. Large scale prospective clinical trials are needed to compare the clinical accuracy and clinical impact of these three imaging technologies for specific pediatric tumor types: Who should get which imaging test at which time and how often?

In addition, we need to evaluate, if and when adding metabolic information to diffusion-weighted MRI or adding diffusion weighted scans to an ^{18}F-FDG PET/MR scan will add clinical value. Either scenario will add time and costs to an already advanced imaging test and therefore, needs to be considered carefully. ^{18}F-FDG PET can add value to diffusion weighted scans by detecting tumor deposits in the spleen and bone marrow. In children, the high cellularity of these organs can mask tumor deposits [44, 47, 48], which can confound tumor detection and carry a risk for under-staging and under-treatment [49, 50]. In pediatric patients who undergo ^{18}F-FDG PET/MR scans, adding diffusion-weighted sequences can be particularly useful for differentiating mediastinal lymphoma and normal thymus [35], as well as benign and malignant abdominal tumors [51]. In brain gliomas, Cuccarini et. al. found that normalized ADC values were directly associated with tumor grade and anaplastic progression [52], which could help to prescribe personalized follow up imaging or interventions. In sarcomas, the degree of restricted diffusion [53, 54] and metabolic activity of the primary tumor at the time of initial diagnosis has been linked to overall survival [55–57]. Patients with soft tissue sarcomas and tumor SUVmax/SUVliver values above 4.6 had significantly decreased survival rates compared to patients with ratios below 4.6 [55]. Since both SUV and ADC are related to tumor grade, but represent different biological tumor characteristics (glucose metabolism and cell density), some investigators proposed the ratio of SUVmax and ADCmin as a combined biomarker for clinical outcomes [58]. Other investigators found that the extent rather than degree of tumor FDG hypermetabolism and diffusion restriction in soft tissue sarcomas is a more robust predictive and prognostic biomarker [59]. This is consistent with the notion that the volume of aggressive tumors is linked to clinical outcomes [60, 61]. Future studies have to show if the volume of high SUVmax/ADCmin tumor parts in heterogenous tumors such as sarcomas is a better predictive biomarker than the overall tumor volume.

5. Increase specificity with nanoparticles

Currently, a wide range of sequences is applied for integrated ^{18}F-FDG PET/MR: T2-weighted sequences require relatively long acquisition times and Gd-enhanced T1-weighted sequences do not provide sufficiently long-lasting vessel enhancement for whole body scans. This problem can be solved with iron oxide nanoparticles, such as the FDA-approved iron supplement ferumoxytol, which can be used “off-label” as a contrast agent. [62] Ferumoxytol is composed of ultrasmall superparamagentic iron oxide nanoparticles, which cause a long lasting positive (bright) signal on T1-weighted MR images and negative (dark) signal on T2-weighted images [63]. Ferumoxytol is currently evaluated for potential FDA-approval as an imaging agent, which would facilitate clinical imaging applications. It should be noted that in rare cases, ferumoxytol can cause severe adverse events or anaphylactic reactions [62]. Therefore, specific FDA guidelines for its administration have to be followed [64]. We found ferumoxytol particularly useful for PET/MRI because this blood pool agent causes long-lasting vascular T1-enhancement for the entire duration of a whole body scan [10]. In addition, ferumoxytol improved the detection of tumors in organs of the reticuloendothelial system, i.e. liver, spleen, bone marrow and lymph nodes, in accordance with previous experiences with first generation nanoparticles [65, 66]. Ferumoxytol can help detect tumors in highly cellular normal marrow in young children and patients after

chemotherapy. Reconverted bone marrow is diffusely hypermetabolic on ^{18}F-FDG PET scans and shows restricted diffusion on diffusion weighted MR scans. This can mask tumor deposits. Ferumoxytol nanoparticles lead to differential T2-enhancement of normal, reconverted marrow and tumor (Fig. 4): Macrophages in normal bone marrow phagocytose and retain ferumoxytol nanoparticles, while tumors contain much fewer macrophages and show less ferumoxytol retention. This leads to hypointense (dark) enhancement of normal marrow and relatively hyperintense (bright) signal of tumors on T2-weighted MRI scans [44, 47]. Prospective clinical trials are needed to evaluate if ^{18}F-FDG PET/MR can replace bone marrow biopsies and if the addition of nanoparticles adds clinical value. Do Fe-enhanced ^{18}F-FDG PET/MR scans upstage cancer patients and do these results impact patient management?

6. Improve the delineation of primary tumors and diagnosis of tissue infiltration

MR imaging is the modality of choice for local staging of bone and soft tissue sarcomas. The extent of bone sarcomas (compartments involved, presence or absence of skip lesions) determines the required surgical procedure. On conventional MR images, the delineation of tumor and peri-lesional edema can be difficult [67]. Various approaches have been tested to solve this problem, such as differential morphological criteria on T2-weighted scans (e.g. “feathery” edema versus mass-like tumor core), differential contrast dynamics (earlier enhancement of the tumor core compared to delayed and often stronger enhancing edema) or differential signal of tumor and edema on diffusion weighted scans (restricted diffusion of the tumor core and prolonged diffusion of the tumor center) [68–72]. All of these criteria yielded limited specificity. Overestimating tumor size can lead to unnecessary surgical resections of too much normal tissue, affect the approach for limb-sparing surgery and lead to unsatisfactory long-term outcomes [70, 73]. Conversely, incomplete tumor resection can impact prognosis and post-surgical care [74–76]: In Ewing sarcomas, a wide surgical margin (R0) with normal tissue around the lesion does not require additional local control while a marginal excision (R1), which includes tumor cells at the cut surface, must be treated by radiotherapy and/or intensified chemotherapy [77]. Recent evidence shows that ^{18}F-FDG-PET can help differentiating tumor tissue and peri-lesional edema: The primary tumor shows marked ^{18}F-FDG uptake while peri-lesional edema shows little or no ^{18}F-FDG uptake [78] (Fig. 5). Prospective clinical trials are needed to evaluate if this information can increase the number of limb-sparing surgeries and thereby, improve long-term outcomes.

For soft tissue sarcomas, standard imaging technologies have a low specificity for the assessment of tumor infiltration of adjacent organs. Incidental evidence suggests that FDG-avid tumor areas may indicate locally infiltrating tumor parts (Fig. 3). In addition, soft tissue sarcomas frequently present with local lymph nodes, which are associated with poor prognosis. The metabolic information from ^{18}F-FDG PET studies is more sensitive (94%–100%) than lymph node size on anatomical images (75%–94%)[5]. Prospective controlled clinical trials are needed to evaluate, if the additional metabolic information up- or downstages patients and if this affects patient management and outcomes.

7. Solve the pulmonary nodule detection dilemma

Recent technological advances have substantially improved the sensitivity of MRI for the detection of pulmonary nodules [79, 80]. However, to date, MRI scans, with or without integrated FDG-PET information, do not yet reach the sensitivity of a CT scan. This is clinically important, because pulmonary disease significantly affects the prognosis and management of pediatric cancer patients: In patients with lymphoma, a pulmonary nodule is considered extra-lymphatic disease, upstages the patient and requires intensified therapy. In patients with sarcomas, pulmonary nodules are usually surgically excised and successful excision significantly affects prognosis. Thus, a missed pulmonary nodule could have severe consequences for patient survival. Of note, current clinical treatment protocols for most pediatric sarcomas suggest surgical management only for one pulmonary nodule above 5 mm or more than three nodules with diameters of more than 3 mm (e.g. COG trial AEWS1221). Most MR imaging sequences have sufficient anatomical resolution to detect such nodules [81]. Recent investigations revealed that the reason for missed pulmonary nodules on MRI is the inability to differentiate pulmonary vessels from small pulmonary nodules (on MRI, vessels can usually not be continuously followed as on a CT scan) [81]. Technical innovations to address this challenge are needed, including breath-hold, data averaging and retrospective respiratory gating schemes. In addition, advanced techniques are needed for improved co-registration of ^{18}F-FDG PET-data and MRI [80]. Clearly, major technical advances are needed until a chest CT scan can be safely replaced by an MRI for the evaluation of pulmonary nodules. In principle, the multi-parametric information of a ^{18}F-FDG PET/MR scan should lend itself to much needed improved specificity: Current CT technologies cannot differentiate pulmonary metastases, which are surgically excised in sarcoma patients, from inflammatory granulomas and intra-pulmonary lymph nodes, which are not excised. Technical innovations that can reliably differentiate benign and malignant nodes would have major impact on patient management.

8. Improve the Accuracy for the Diagnosis of Treatment Response

If ^{18}F-FDG PET/MR should replace ^{18}F-FDG PET/CT as a new “one stop” staging approach with reduced radiation exposure, then this new imaging test would not only have to provide sensitive tumor detection at baseline, but also accurate therapy response assessment.

Systematic tumor-type specific comparative analyses have to analyze if technical and procedural differences between ^{18}F-FDG PET/CT and PET/MR scans can cause differences in tumor therapy response assessments and classifications of responders and non-responders. In pediatric patients with lymphoma, SUVs measured from ^{18}F-FDG PET/MRI indicated good intra-patient reliability [23] and ^{18}F-FDG PET SUVs were strongly correlated between PET/CT and PET/MRI ($\rho > 0.72$), although PET/MRI showed systematically lower SUV measurements [22]. Technical variables, which may lead to differences in SUV values between PET/CT and PET/MR studies, include differences in AC correction, different radiotracer doses, longer PET acquisition times and more sensitive PET-detectors in some PET/MR scanners [23].

In patients with malignant lymphomas, a decline in tumor glucose metabolism, measured on ^{18}F-FDG PET scans, provided additional information to tumor size measurements for therapy response assessment, which changed patient management in up to 32% [82–84, 21]. Current therapy response assessments of pediatric lymphomas by the St. Jude's consortium evaluate both changes in tumor size and tumor metabolism, while current protocols of the Children's Oncology Group solely rely on semi-quantitative measures of tumor metabolism, according to the 5-point Deauville or Lugano criteria [85, 86]. The most frequent management change based on imaging findings is avoiding radiotherapy of residual soft tissue masses at the end of therapy.

In pediatric patients with sarcomas, therapy response is determined by changes in tumor size on imaging studies according to RECIST criteria [85]. The metabolic information from ^{18}F-FDG-PET scans may improve therapy response assessment, especially for tumors with small extraosseous soft tissue components [87, 88]. Due to its high soft tissue contrast, ^{18}F-FDG PET/MR can accurately diagnose hypermetabolic brown fat and hypermetabolic reconverted hematopoietic marrow after chemotherapy [89–91].

Some investigators found concordant changes in glucose metabolism and tumor cell density after chemotherapy in solid tumors of adult patients [85, 53, 54], while other investigators found complementary information of diffusion weighted scans and PET scans [92, 93]. Thus, combining ADC and SUV data might increase diagnostic accuracy in some tumors. [59] It is not clear if chemotherapy-induced normalization of ADC and SUV values occurs at the same time in pediatric cancers.

9. Make ^{18}F-FDG PET/MR useful for radiation planning

To date, CT is the clinical standard method for planning radiation therapy of pediatric cancer patients. CT provides important information about the location of the primary tumor, presence and location of metastases, and linear attenuation coefficients of target tissues for radiotherapy. Linear attenuation coefficients correlate directly with the electron density needed for radiotherapy and therefore, can be used for dose calculations. Due to its higher soft tissue contrast, MRI can add information about the exact delineation and internal composition of target tumors, which can be used for individualized radiotherapy schemes [94]. ^{18}F-FDG PET information has been useful in detecting metastases and determining morphological tumor characteristics, such as internal necrosis and hypoxic areas. A major challenge for the use of PET/MR for radiation planning is that it does not contain direct information about photon attenuation of target tissues. Several investigators are working on solutions to this problem [95, 96]. For example, MR data have been "translated" to pseudo-CT values using deformable image registration algorithms in combination with pattern recognition [96]. In order to make PET/MR data useful for radiation planning, the patient needs to be placed on a flat tabletop in a reproducible manner, e.g. by using specific markers and/or MRI-compatible patient positioning aids. In addition, local radiofrequency coils have to be positioned without deforming the surface of the patient. This can be achieved by using specific RF coil holders [95]. If PET/MR images should be used for radiation planning, a close collaboration between radiologists/nuclear medicine physicians and radiation oncologists is important to ensure clinical value of the acquired scans.

10. Detect chemotherapy-induced tissue injuries

Continuous improvements in cancer therapies lead to a growing number of cancer survivors, with currently more than 14.5 million cancer survivors in the United States.[97] Up to 95% of these patients will develop morbidities due to cancer therapy-induced tissue injuries.[98, 99] While pediatric patients and young adults comprise a minority among cancer survivors, cancer therapy can have more severe effects on their growing and developing tissues.[97, 98] For example, close to 50% of patients with ALL who are treated with intravenous and intrathecal methotrexate (MTX) develop neurological problems, such as chronic headaches, seizures, motor problems and cognitive impairment, which severely limit a child's social re-integration and academic development. [100–102] In contrast to transient acute toxicities of cytotoxic drugs, these late effects develop slowly over time due to an impaired growth and regeneration of the affected organ.[98] At the end of cancer therapy, patients typically have no or minor clinical symptoms. However, months to years later, they experience debilitating functional impairments.[97, 98, 100, 103–106],[107] There is a window of time between exposure to cancer therapy and future morbidity, which could be used for corrective actions. Unfortunately, once cancer survivors present with clinical symptoms, it is often too late for health-preserving interventions. To prevent morbidities, it is important to develop diagnostic tools, which can detect early stages of tissue damage that are still reversible. Finding on conventional MRI studies showed a poor correlation between white matter abnormalities and neurologic deficits in children with ALL.[108] T2 prolongation in the deep cerebral white matter, noted in 15–75% of patients, were not consistently associated with neurologic deficits.[109, 110] Cheung et al speculated that there is a threshold effect, such that differences in neurobehavioral problems do not become apparent until white matter damage to the brain is extensive enough to result in clinically detected leukoencephalopathy [111]. This might explain the high number of asymptomatic MRI findings in our cohort. Accordingly, Bhojwani et al. found asymptomatic leukoencephalopathy in 73 out of 355 (20.6%) ALL patients [112]. FDG PET can provide additional information about cognitive reserve and its modulation.[113–115] Chiaravalloti et al. [116, 117] reported FDG PET brain results in a cohort of 74 adult patients with lymphoma before, during and after ABVD chemo-therapy. In a groupwise analysis, FDG activity was reduced on the mid-treatment PET in Brodmann areas 10, 11, and 32 bilaterally. In addition, Ponto et al. reported long-term frontal FDG hypometabolism in asymptomatic breast cancer patients undergoing cyclophosphamide, MTX, and 5-FU/doxorubicin therapy.[118] Our team found a significant reduction in cerebral blood flow in specific brain areas and significantly lower mean SUV values in the hippocampus of pediatric cancer survivors compared to normal controls [119]. These initial studies suggest potential value of ^{18}F-FDG PET/MR as a biomarker for chemotherapy induced brain injury. Larger prospective clinical trials are needed to evaluate, if early detection and rescue interventions can improve the long-term health of cancer survivors.

In summary, ^{18}F-FDG PET/MR can provide safer, more specific and more efficient cancer staging for pediatric patients than currently available. A number of open questions specific to the pediatric oncology population have to be elucidated through tumor-type tailored prospective clinical trials. Study quality, cost, length of total anesthesia time for young

children, and time to complete the entire staging evaluation have to be compared with the current clinical standard. This might show that PET/MR is superior in terms of quality, cost, anesthesia time, and/or time efficiency. However, even if PET/MR proves valuable, it cannot enter mainstream applications if it is not accessible to the majority of pediatric cancer patients. Therefore, innovations are needed to make PET/MR scanners affordable and increase patient throughput. The availability of novel radiotracers will likely be limited to few teritary centers, such as ^{18}F-FDG-DOPA PET/CT for evaluation of persistent hyperinsulinaemic hypoglycemic of infancy and detection of insulinomas, ^{18}F-fluoride PET for staging of osteosarcoma, ^{124}I PET for iodine-positive thyroid cancer, ^{18}F-FDOPA for medullary thyroid carcinoma, ^{68}Ga-DOTATOC for neuroendocrine tumors and ^{124}I MIBG for neuroblastoma, among others. PET/MR imaging protocols need to be homogenized across centers to facilitate centralized data analyses by the Children's Oncology Group and other stakeholders. Efforts are under way to generate a consensus regarding pediatric ^{18}F-FDG PET/MR procedures at major academic institutions in North America and Europe.

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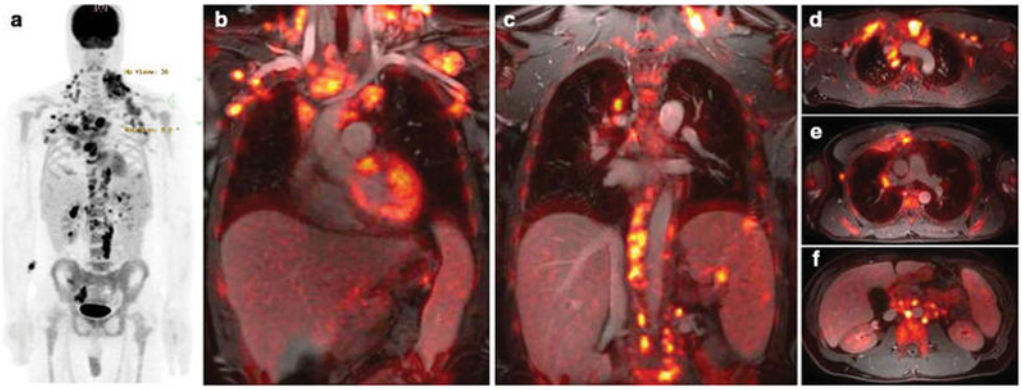

Figure 1. Whole Body ^{18}F-FDG PET/MR of a patient with Hodgkin Lymphoma

(a) ^{18}F-FDG PET maximum intensity projection shows FDG-avid disease of the neck, chest, axillaries, abdomen and pelvis. (b) Coronal ^{18}F-FDG PET images superimposed on ferumoxytol-enhanced T1-weighted LAVA images clearly show the relation between vessels and multiple hypermetabolic lymph nodes. Three lesions in the spleen are also noted. (c) Axial integrated ^{18}F-FDG PET/LAVA images provide diagnostic information similar to a PET/CT scan, but with improved soft tissue contrast.

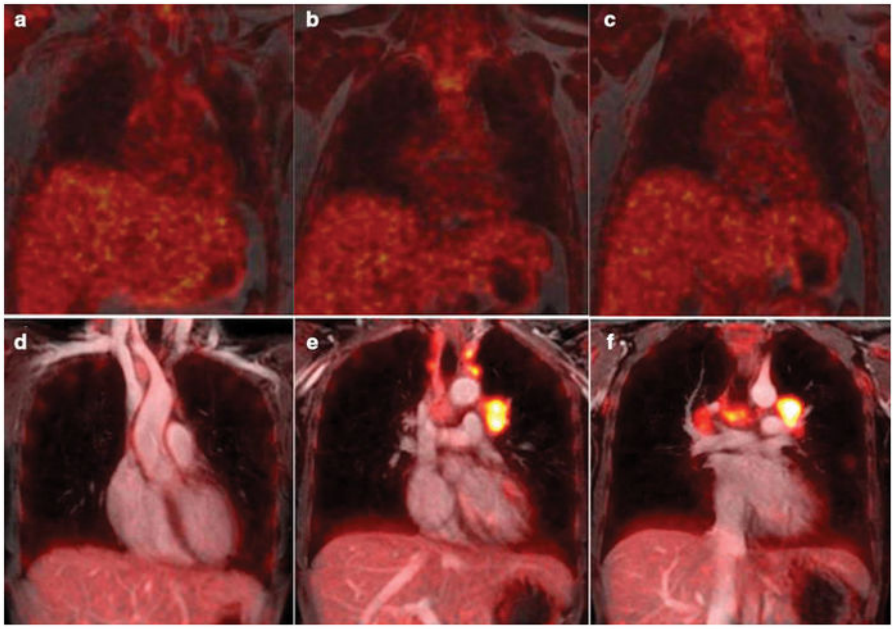

Figure 2. Intravenous MR contrast agent administration improves soft tissue contrast of integrated PET/MR images

(a–c) Coronally reconstructed ^{18}F-FDG PET images, superimposed on unenhanced T1-weighted LAVA images show limited soft tissue resolution. (d–f) Coronal ^{18}F-FDG PET images, superimposed on ferumoxytol-enhanced T1-weighted LAVA images of a patient with Hodgkin lymphoma show improved soft tissue contrast: The ferumoxytol-enhanced ^{18}F-FDG PET/MR images facilitate the delineation of mediastinal vessels and hypermetabolic lymph nodes. This is important, because current clinical protocols require accurate assessment of the tumor size and metabolic activity before, during and after therapy.

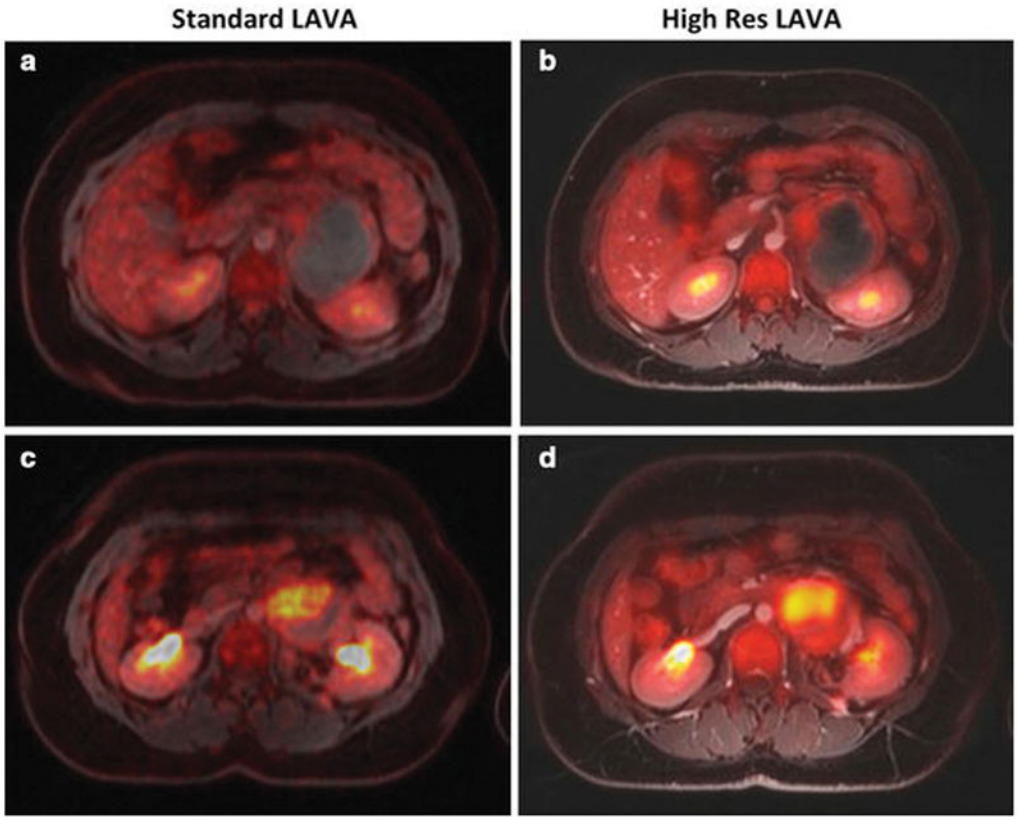

Figure 3. Spatial resolution on ^{18}F-FDG PET/MR is important to render accurate diagnostic information in a young adult with retroperitoneal soft tissue sarcoma

(a,c) Axial ^{18}F-FDG PET images, superimposed on ferumoxytol-enhanced T1-weighted LAVA images (TR/TE/alpha = 4.1ms/1.7ms/15), obtained for attenuation correction of ^{18}F-FDG PET data. These images with a field of view (FOV) or 50 cm, a matrix of 256 x 128 pixels and a slice thickness of 5.2 mm provide limited anatomical resolution. For example, the superior mesenteric artery is not seen on these scans. (b,d) Axial ^{18}F-FDG PET images, superimposed on ferumoxytol-enhanced T1-weighted LAVA images (TR/TE/alpha = 4.2ms/1.7ms/15), acquired for diagnostic purposes. These images with a field of view (FOV) or 48 cm, a matrix of 320 x 224 pixels and a slice thickness 3.4 mm provide improved tumor delineation from adjacent vessels and bowel. We conclude that current pulse sequences for AC correction do not have sufficient anatomical resolution to be used for diagnostic purposes.

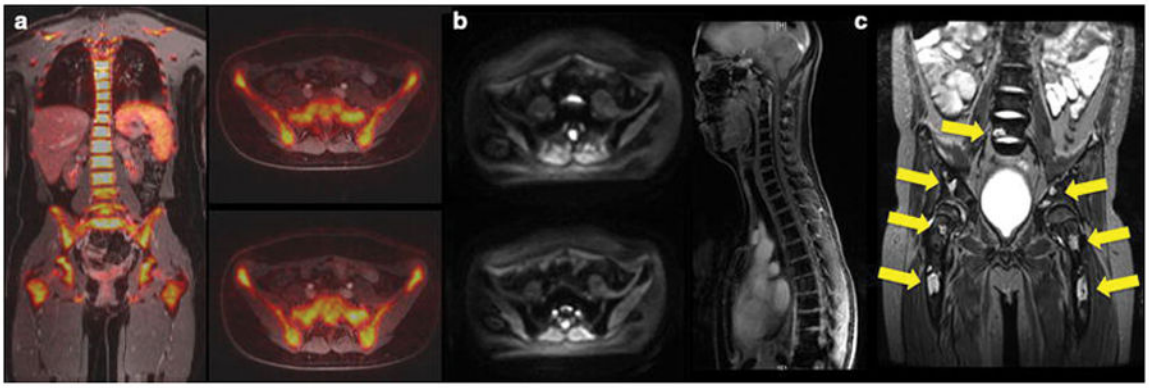

Figure 4. Ferumoxytol shows differential enhancement of hypercellular hematopoietic marrow and tumor

(a) Coronal and axial ^{18}F-FDG PET/MR in a young adult after chemotherapy shows diffusely hypermetabolic hematopoietic marrow, (b) axial diffusion-weighted MR images and coronal LAVA images in the same patient after intravenous injection of ferumoxytol show homogeneous iron oxide uptake in the bone marrow, as indicated by homogenous hypointense (dark) marrow signal. (c) Coronal ferumoxytol-enhanced T2-weighted fast spinecho scan of the lumbar spine and pelvis in an 11 year-old patient with biopsy-proven Hodgkin's leukemia shows multiple focal tumor lesions in the bone marrow (arrows). The normal marrow shows negative (dark) ferumoxytol enhancement while focal tumors show little or no ferumoxytol uptake and stand out as hyperintense (bright) lesions.

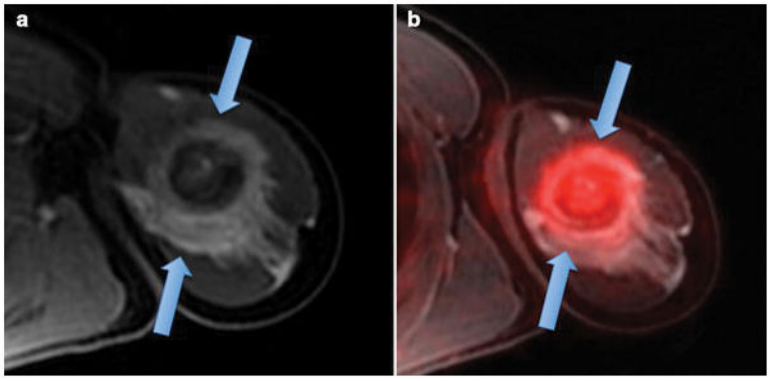

Figure 5. ^{18}F-FDG PET/MR shows differential enhancement of an osteosarcoma and peri-lesional edema

(a) Axial T1-weighted ferumoxytol-enhanced LAVA scan shows an ill defined, aggressive lesion in the proximal left humerus with extensive perilesional contrast-enhanced edema (arrows). (b) Integrated ferumoxytol-enhanced ^{18}F-FDG PET/LAVA scan shows improved delineation of the ^{18}F-FDG avid tumor (arrow) from enhancing peritumoral edema.

Table 1
Pathways for clinical translation of PET/MR studies for pediatric cancer staging

(Imaging protocol will require *whole body scan or ** whole body scan plus dedicated scan of primary tumor or #customized scan, which could be a local scan only or an extended scan, as deemed appropriate for a given patient)

Current Clinical Practice	Clinical Translation	Future Clinical Practice
Lymphoma: ^{18}F-FDG PET/CT before, during and after therapy	Validate equivalence of Deauville and Lugano Criteria for ^{18}F-FDG PET/CT and ^{18}F-FDG PET/MR for staging and therapy response assessment	^{18}F-FDG PET/MR before, during and after therapy*
Soft Tissue Sarcoma: ^{18}F-FDG PET/CT before, during and after therapy	Validate equivalence of ^{18}F-FDG PET/CT and PET/MR-derived SUV and Recist criteria for staging and therapy response assessment	^{18}F-FDG PET/MR before, during and after therapy**
Bone Sarcoma: Local MRI, Chest CT and Bone scan	Validate equivalence of conventional staging and ^{18}F-FDG PET/MR for staging and therapy response assessment	^{18}F-FDG PET/MR before, during and after therapy**
Melanoma and Carcinoma: ^{18}F-FDG PET/CT before, during and after therapy	Validate equivalence of ^{18}F-FDG PET/CT and PET/MR for staging and re-staging	^{18}F-FDG PET/MR before, during and after therapy**
Hepatoblastoma/HCC: MRI and bone scan before, during and after therapy	Evaluate if and for whom ^{18}F-FDG PET/MR may provide additional information. Define indications for a local, extended or whole body scan.	MRI and bone scan before, during and after therapy; ^{18}F- FDG PET/MR in selected patients with multifocal or extrahepatic disease#
Wilm's Tumor: MRI or CT scan	Evaluate if and for whom ^{18}F-FDG PET/MR may provide additional information. Define indications for a local, extended or whole body scan.	MRI before, during and after therapy; ^{18}F-FDG PET/MR in selected patients with extra-renal or recurrent disease#
Neuroblastoma: MRI or CT scan, MIBG scan, Bone scan	Compare diagnostic accuracy and efficiency of PET-radiotracers with classical ^{123}I-MIBG scan	^{124}I-MIBG PET/MR scan before, during and after therapy**
Germ Cell Tumors (GCT): MRI or CT scan, rarely ^{18}F-FDG PET/CT for malignant tumors	Validate equivalence of ^{18}F-FDG PET/CT and PET/MR for staging and therapy response assessment of malignant GCT	^{18}F-FDG PET/MR before, during and after therapy for selected cases of malignant GCT**