Whole Body Diffusion-weighted MR Imaging of Children with Cancer: a solution to the challenge of Long-Term Side Effects from CT Scans

It has been shown that the use of 18F FDG PET/CT is superior to conventional imaging modalities such as contrast-enhanced CT and MRI for the staging of most malignant lymphomas. Especially with pediatric patients, however, there is growing concern about the increased risk of secondary tumors developing later in life as a result of the radiation associated with PET/CT. Whole body, diffusion-weighted MRI can image tumors but conventional WB-DW MRI has several disadvantages in pediatric patients, as well as the problem that the enhancement gained with standard MR contrast agents does not last for the duration of a whole body scan. This article summarises our experience using iron supplement ferumoxytol as a contrast agent for improved tumor detection on DW MR scans and describes the potential of the approach in providing necessary pediatric staging with no CT-associated radiation risks.

Imaging tests are essential for cancer staging in pediatric patients. However, to date, children with a newly diagnosed solid tumor have to undergo a series of diagnostic imaging procedures, which are stressful, time consuming, in part redundant, expensive and may require repetitive anesthesias. The overarching goal of our research efforts is to develop one single "one stop shop" imaging test, which could provide a comprehensive evaluation of the primary tumor and metastases in one session.

Towards this goal, the use of CT and PET/CT staging exams in pediatric oncology patients has grown rapidly during the last several years [1-4]. 18F-FDG PET/CT has been established for staging of most types of malignant lymphoma [5-7]. Many authors have shown, that 18F-FDG PET or PET/CT is superior to conventional imaging modalities for lymphoma staging, including contrast-enhanced CT, MRI, bone scintigraphy, ultrasoundography and Ga-67 scintigraphy [6-12]. The tumor extent, diagnosed on 18F-FDG PET/CT, significantly influences treatment decisions and radiation field definition in high risk patients [13]. However, in pediatric patients, using CT images for anatomical co-registration of 18F-FDG PET data has some caveats. CT imaging has been associated with a risk of secondary cancer development later in life [14-16]. This is particularly concerning for young patients, since they are more susceptible to radiation effects than older patients and they live long enough to develop secondary cancers [15-17,18] Pearce et al. reported that cumulative doses from diagnostic CT scans, applied for tumor staging in children, almost tripled the risk of secondary leukemia and brain cancer later in life [19]; and Mathews et al. found a 24% increase in cancer incidence in 11 million Australians who underwent CT scans for cancer staging during childhood and adolescence [20]. Thus, there is an urgent need for new staging tests with reduced or eliminated radiation exposure. In order to solve the conundrum of obligatory diagnostic cancer staging tests and concurrent risk of secondary cancer development later in life, we recently developed an alternative radiation-free staging test, based on whole body diffusion weighted magnetic resonance imaging (WB-DW MR)[21].

Previous approaches for WB-MRI and DW-MRI also imaged tumors [22-24]. But these technologies were not tailored to specific problems of pediatric patients. In children, the spleen and bone marrow show a similar signal compared with tumors on DW MR scans.
**CLINICAL PERFORMANCE OF RADIATION-FREE WB-DW MRI**

Our radiation-free WB-DW MRI imaging technique detected 158 of 174 malignant tumors and FDG-PET/CT detected 163 of 174 malignant tumors [21]. The resultant sensitivities, specificities, and diagnostic accuracies were all excellent, with values above 90%, and were not significantly different between the two imaging modalities [21]. Tumour staging results also showed very good agreement between both imaging modalities with a $\kappa$ of 0.93. At the same time, the associated radiation exposure could be reduced from about 12.5 mSv for the PET scans to zero for the WB-DW scans. Both exams required roughly the same time between tracer injection and end of scan and the estimated exam costs were comparable.

**SAFETY PROFILE OF IRON OXIDE NANOPIRATE MRI CONTRAST AGENTS**

Of note, our team has applied various iron oxide nanoparticle compounds as MR contrast agents in phase I-IV clinical trials [31-38]. These agents are generally well tolerated and show excellent safety profiles [35-37,39,40]. Considering a Ferumoxytol dose of 5 mg/kg and a concentration of 30 mg Fe/ml, a teenager with an average body weight of 50-80 kg would receive a dose of 250-400 mg Fe (note, these are coated iron particles, not free iron). This iron dose is lower than the FDA-approved ferumoxytol dose for anemia treatment and comparable to the iron dose administered with one blood transfusion. Ferumoxytol has been safely applied in more than 150,000 adult patients to date. Anaphylaxis or anaphylactoid reactions to ferumoxytol were reported in 0.1-0.2% of exposed adult patients, which is comparable to other MR contrast agents [40-42]. We and others did not observe any adverse effects in our pediatric patients so far 43. Ferumoxytol is not excreted via the kidneys and thus, not associated with any risk of nephrogenic sclerosis (a potential adverse event with Gd-chelates) [40-42].

In our study, we investigated the use of ferumoxytol-enhanced WB-DW MRI for initial staging only and additional studies need to show the utility of this technique for treatment monitoring. A reduced radiotracer uptake on a PET/CT scan after two cycles of chemotherapy compared to the initial scan has shown to predict overall response and outcome in patients with malignant lymphomas and is currently used to stratify patients to more or less aggressive therapies. We have to prove that we can generate that same information with our technique and this is a major focus of a recently initiated multi-center initiative.
CONCLUSION AND FUTURE PROSPECTS

In the era of personalized medicine, we are trying to create the most accurate, most efficient, savest and most cost-effective imaging test for each individual patient. We assume that the radiation-free WB-DW MRI test will be particularly attractive for young children, for patients with benign diseases, for patients with an increased susceptibility to radiation effects and for patients with a genetic predisposition for cancer development, who have to undergo many imaging procedures throughout their lives for cancer screening. For other patients, we may still need the information from metabolite PET scans and this refers specifically to treatment monitoring. We are in the process of performing additional studies that evaluate the value of WB-DW scans with and without addition of PET data for treatment monitoring. The combination of PET and MR data would still eliminate radiation exposure from CT scans and substantially reduce radiation exposure by up to 80%. Future studies will have to show, which patients will benefit most from a completely radiation-free WB-DW MR imaging test, as described in our article, versus new integrated PET/MR imaging tests. This is a major focus of our future multi-institutional research efforts.

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REFERENCES