

MR Total Tumor Load – First Clinical Experience in Pediatric Oncology Patients

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Abstract

The *syngo.via* Frontier MR Total Tumor Load application¹ comes with benefits in pediatric oncology evaluation not only in cases of metastatic bone disease but also in solid tumors, and could further help to establish DWI as a prognostic factor in the assessment of tumor therapy.

Introduction

In recent years, advancements in MR techniques have shortened examination times. This has led to whole-body (WB) MRI becoming essential in staging and managing pediatric oncology patients, where a curative approach is much more common [1]. As a result, an S1 guideline entitled “Whole-body MRI in children” was recently published in Germany [2]. Besides the benefits of radiation-free examinations and excellent tissue characterization, MRI offers the possibility of combining anatomical and functional imaging using techniques such as diffusion-weighted imaging (DWI) for local staging and precise assessments of metastatic spread and total tumor burden at diagnosis as an important factor in planning treatment and predicting outcomes. Several recent studies have compared the diagnostic accuracy of whole-body DWI (WB-DWI) in pediatric lymphomas with conventional methods such as computed tomography (CT), scintigraphic methods, and positron emission tomography (PET). The results are promising [3, 4]. In neuroblastic tumors, DWI has also proved valuable for differentiating malignant and benign tumors based on differences in the apparent diffusion coefficient (ADC), finding higher ADC values in benign tumors like ganglioneuroma than in malignant neuroblastoma [5–7]. Two recent papers further evaluated the role of, respectively, DWI and ADC values as a complementary prognostic marker in neuroblastoma. The findings showed that, under therapy, increasing ADC values were an indicator of good response and prognosis [8, 9]. A limitation

of quantitative ADC measurement is the lack of tools to perform efficient evaluation for multifocal disease. The recently introduced *syngo.via* Frontier MR Total Tumor Load prototype application¹ provides a solution that uses threshold-based segmentation on diffusion-weighted images to identify regions of disease and to analyze the overall tumor volume and histogram metrics of the corresponding ADC maps [10]. A pilot study demonstrated excellent inter- and intra-observer agreement using this application in metastatic bone disease [11].

In this report, we will show the diagnostic options for the *syngo.via* Frontier MR Total Tumor Load application in pediatric oncology based on three case studies on Hodgkin lymphoma and stage 4 neuroblastoma respectively.

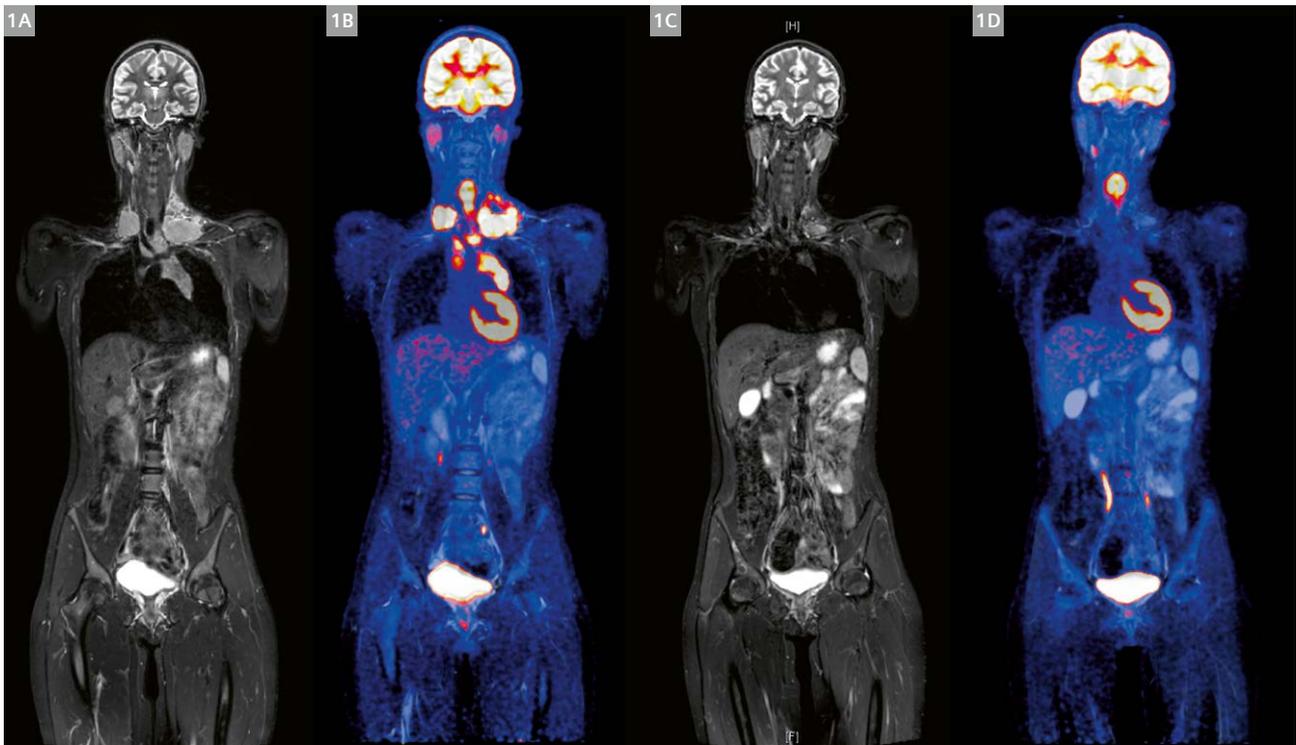
Case study 1

A 14-year-old girl presented with a supraclavicular swelling first noticed a week previously. Sonography revealed pathological lymph node enlargement suspicious for lymphoma. Biopsy of the lymph node established the diagnosis of classical Hodgkin lymphoma. A WB-PET-MRI using a standardized protocol including WB-DWI on a 3T PET/MR imaging system (Biograph mMR; Siemens Healthcare, Erlangen, Germany) [12] was performed for initial staging and early response after two months.

In the initial staging, cervical, mediastinal, and left axillary lymph node involvement without extranodal manifestations was demonstrated, resulting in a stage 2 classification. The early response study after two cycles of chemotherapy shows a complete metabolic response with only a small residual morphological tumor on the left supraclavicular region (Fig. 1).

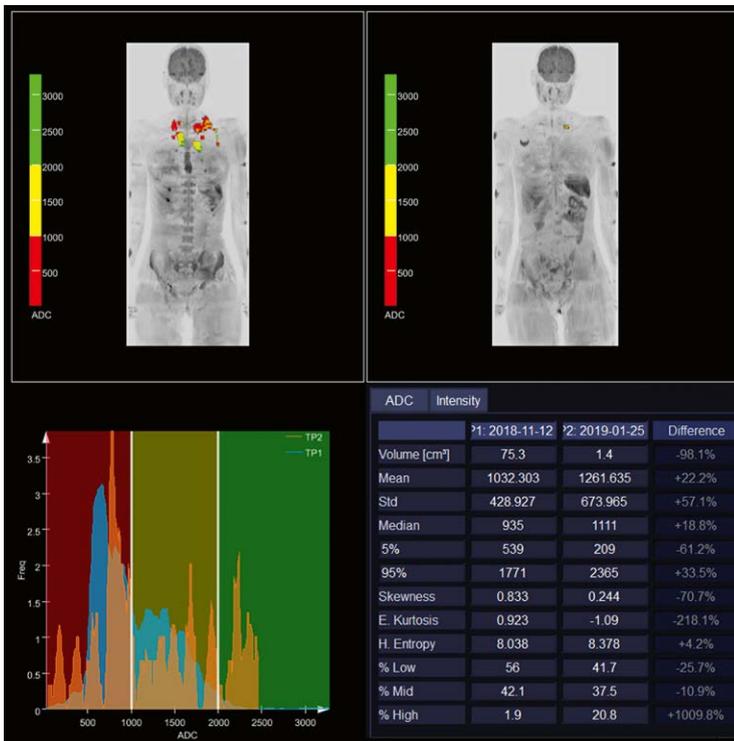
The diffusion-weighted images of both examinations were analyzed using a *syngo.via* Frontier MR Total Tumor Load threshold-based segmentation. The pretreatment ADC histogram shows a unimodal distribution of ADC values with high excess kurtosis (Fig. 2). The follow-up study after two months shows significant reduction in volume and a greater spread in the lower ADC range, which is related to partial response.

¹*syngo.via* Frontier is for research only, not a medical device. *syngo.via* Frontier MR Total Tumor Load is a released research prototype.



1 Morphological and functional images of baseline and follow-up PET/MRI

Baseline examination (1A, 1B) shows cervical and mediastinal lymph node involvement in a coronal short tau inversion recovery whole-body sequence (1A) and fused ¹⁸F FDG-PET and short tau inversion recovery sequence. In the follow-up examination (1C, 1D), only morphological residuals in the left supraclavicular regions remain.



2 ADC histogram changes over time

WB tumor load segmentations were undertaken using the *syngo.via* Frontier MR Total Tumor Load software¹. Besides the reduction in tumor volume, a shift in ADC value distribution between baseline and follow-up examination indicate a partial response.

Case study 2

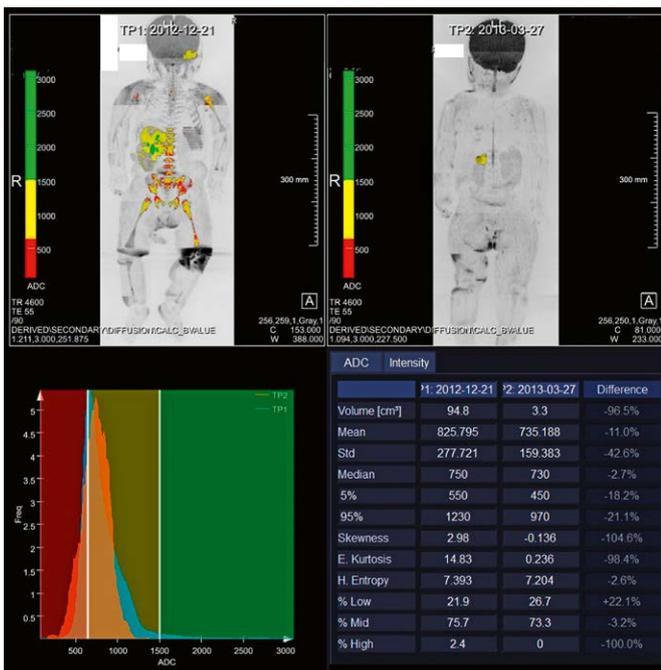
A 10-month-old² boy presented with ptosis that had been noted for four weeks. In addition, a palpable abdominal mass was detected. WB-MRI was performed using our institution's standard protocol as previously published [13] on a 1.5T MR imaging system (MAGNETOM Avanto; Siemens Healthcare, Erlangen, Germany). The examination demonstrated a suprarenal mass on the right side with suspicious mesenteric nodes and hepatic metastases as well as osseous lesions in the left orbit, both proximal

humerus and femora, the lumbar vertebra, and the pelvis. Chemotherapy was initiated. In the follow-up study after three months, the osseous lesions show almost complete regression and the suprarenal mass also shows a significant reduction (Fig. 3). Evaluation with *syngo.via* Frontier MR Total Tumor Load shows an unimodal distribution of ADC values with high excess kurtosis (Fig. 4) in both examinations without significant change in the mean ADC value. After surgical resection, the histopathological evaluation of the suprarenal mass revealed that it still contained 90% vital tumor cells.



3 Morphological images of baseline and follow-up WB-MRI

The baseline examination (3A–C) shows a suprarenal mass in a coronal short tau inversion recovery whole-body sequence (3A) and a transversal T2-weighted fat-suppressed sequence (3C, orange arrow) with signs of tumor bleeding and necrosis. Osseous metastases are also visible in the right femur (3A, white arrow) and left orbit (3B, white arrow). The follow-up examination (3D–F) shows only residual suprarenal tumor on the right side (3F, right-hand arrow).



4 ADC histogram changes over time

WB tumor load segmentations indicate a clear reduction in tumor volume is visible, but the distribution of ADC values of tumor mass has not changed significantly between baseline and follow-up examination. This is interpreted as a sign of tumor vitality.

²MR scanning has not been established as safe for imaging fetuses and infants less than two years of age. The responsible physician must evaluate the benefits of the MR examination compared to those of other imaging procedures. Note: This disclaimer does not represent the opinion of the authors.

Case study 3

A 10-year-old girl presented with a histopathologically proven ganglioneuroma after surgical biopsy at a different hospital. The MRI shows a heterogenous suprarenal tumor on the left side with heterogenous ADC values suspicious for a mixed tumor in the form of a ganglioneuroblastoma (Fig. 5A). Evaluation with *syngo.via* Frontier MR Total Tumor Load shows the heterogeneity of the tumor with a three-modal distribution of ADC values that were measured in the complete tumor (Fig. 5B).

Discussion

The *syngo.via* Frontier MR Total Tumor Load application has been developed for ADC histogram analysis. The main advantage is the possibility to analyze the ADC histogram of the complete tumor volume, rather than just a region of interest (ROI) or volume of interest (VOI). Several case reports show the opportunities for using the application in cases of metastatic bone disease in particular [14–16]. Further, a pilot study demonstrated that the application achieved excellent inter- and intra-observer agreement in metastatic bone disease [11].

MRI plays an important role in pediatric radiology, and this is not only due to its ability to perform radiation-free examinations. A variety of pediatric oncologic diseases have a better prognosis than oncologic diseases in adults, but precise staging and follow-up are crucial for the out-

come. In addition to providing morphological information, MRI offers the opportunity to combine functional imaging using DWI. So far, DWI has been analyzed visually or by measuring the ADC values in an ROI. The possibility of evaluating ADC histograms of the total tumor volume opens up new approaches for assessing treatment response or even generating a complementary prognostic factor.

In the first case study, we demonstrated that, as well as a reduction in tumor volume, a shift in the distribution of ADC values is observed with a good therapy response in Hodgkin lymphoma.

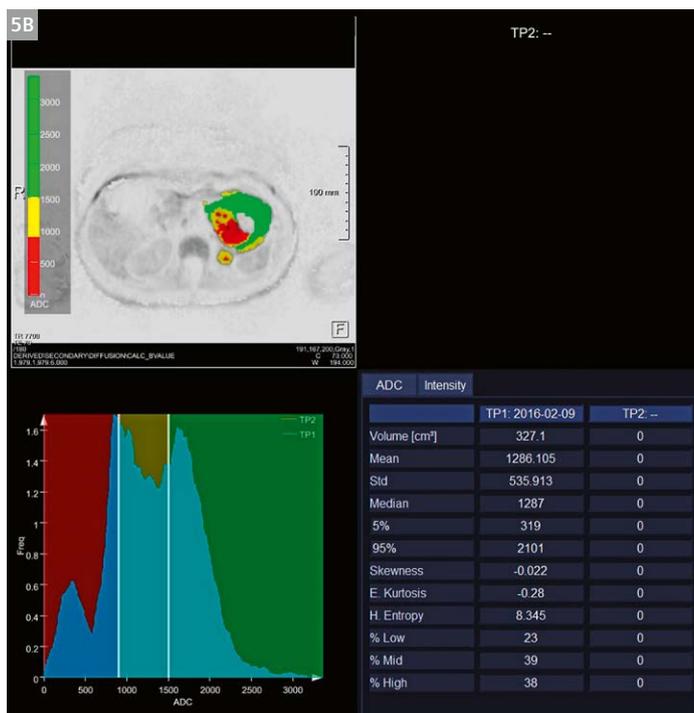
The second case study shows that, in neuroblastoma, a lack of change in ADC value distribution under therapy is a sign of persistent tumor vitality despite a significant reduction in tumor volume.

In the third case study, we saw that *syngo.via* Frontier MR Total Tumor Load can visualize tumor heterogeneity in neuroblastic tumors using ADC color projections, histograms, and descriptive histogram statistics.

We have demonstrated that the *syngo.via* Frontier MR Total Tumor Load application has benefits for evaluating pediatric oncology in both metastatic bone disease and solid tumors, and could further help to establish DWI as a prognostic factor in assessments of tumor therapy. However, proving this hypothesis will require large-scale, multicenter studies.



5 Morphological images and ADC histogram
 In the transversal T2-weighted fat-suppressed sequence (5A) the heterogeneous suprarenal tumor of the left side is well demonstrated. Correlating the ADC histogram (5B) in the MR Total Tumor Load software¹ shows the heterogeneity in the color projection and also in the three-modal distribution of the ADC values. The lowest ADC peak corresponds to active tumor core and is visualized in red, the second peak at an ADC of approximately 900–1300 $\mu\text{m}^2/\text{s}$ represents surrounding tissue with increased cellularity and is overlaid in yellow. ADC values of 1500 $\mu\text{m}^2/\text{s}$ and above are considered fluid components and are back-mapped in green.



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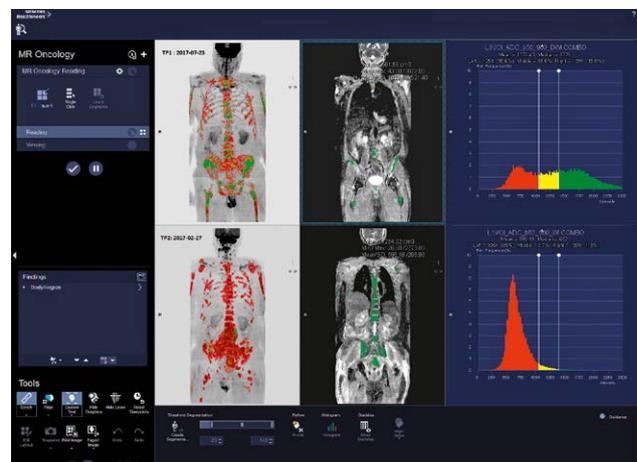
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