Diagnostic Value of Diffusion-Weighted MRI for Tumor Characterization, Differentiation and Monitoring in Pediatric Patients with Neuroblastic Tumors

Diagnostischer Stellenwert der diffusionsgewichteten MRT zur Tumorcharakterisierung, Tumordifferenzierung und zur Verlaufskontrolle bei pädiatrischen Patienten mit neuroblastischen Tumoren

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Key words
neuroblastoma, ganglioneuroblastoma, ganglioneuroma, therapy response, MR imaging, MR diffusion/perfusion

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ZUSAMMENFASSUNG
Ziel Untersucht wurde die diagnostische Aussagekraft der diffusionsgewichteten MRT (DWI) für die Tumorcharakterisierung, Tumordifferenzierung und Verlaufskontrolle bei Kindern mit extrakraniellen neuroblastischen Tumoren.

Material und Methoden Alle 29 Patienten (14 Mädchen, medianes Alter 3 Jahre) mit Neuroblastom (NB, n = 19), Ganglioneuroblastom (GNB, n = 4) und Ganglioneurom (GN, n = 6)

und mindestens einer DWI-Studie in domo seit 2005 wurden retrospektiv analysiert. Zwei unabhängige geblindete Untersucher bestimmten die ADC-Werte (Einheit: 10−3 m²/s) und Signalintensitätsquotienten (SIR) für Primärtumor und, falls zutreffend, für Tumor nach Chemotherapie, Metastasen und Tumorrezidiv.

Ergebnisse Initial betrugen der ADC-Wert 0,90 ± 0,23 für NB/GNB und 1,70 ± 0,36 für GN ohne Überlappung beider Entitäten bei beiden Untersuchern, 0,67 ± 0,14 für Metastasen und 0,72 ± 0,18 für Rezidive. Unter Chemotherapie stieg der ADC auf 1,54 ± 0,33 bei NB/GNB und 1,23 ± 0,27 bei Metastasen (p < 0,05). Die medianen SIR der Tumorläsionen vs. Leber, vs. Muskel und vs. benachbartes Gewebe waren signifikant höher in der DWI (min...max 2,4...9,9) als in ce-T1w (1,0...1,8, alle p < 0,05). Der Variationskoefizient (CV) lag ≤ 8,0 % für ADC und ≤ 16,4 % für SIR.

Schlussfolgerung DWI unterscheidet anhand des ADC zuverlässig zwischen NB/GNB und GN und liefert plausible quantitative Daten zum Therapieansprechen. Die Sichtbarkeit von Tumorherden, gemessen als SIR, ist in der DWI deutlich besser als in der ce-T1w. DWI als nicht-invasive und weithin verfügbare Bildgebungstechnik ohne Strahlenexposition sollte integraler Bestandteil jeder MR-Bildgebung bei neuroblastischen Tumoren sein und sollte in multizentrischen Studien prospektiv evaluiert werden.

Kernaussagen
• DWI differenziert anhand des ADC-Werts zuverlässig zwischen Neuroblastom/Ganglioneuroblastom und Ganglioneurom.
• Die DWI liefert plausible quantitative Daten zum Therapieansprechen.
• Die Erkennbarkeit von Tumorherden ist höher mit DWI als mit ce-T1w.
• DWI sollte als Standardtechnik für die MR-Bildgebung neuroblastischer Tumoren betrachtet werden.
Purpose We explored the diagnostic value of diffusion-weighted MRI (DWI) for tumor characterization, differentiation and therapy monitoring in pediatric patients with extracranial neuroblastic tumors.

Materials and Methods All 29 patients (14 girls, median age: 3 years) with neuroblastoma (NB, n = 19), ganglioneuroblastoma (GNB, n = 4) and ganglioneuroma (GN, n = 6) had had at least one in-house DWI examination since 2005 were identified and retrospectively analyzed. Two independent blinded readers measured ADC values (unit: 10−3 mm2/s) and signal intensity ratios (SIRs) of the primary tumor and, if applicable, of the tumor after chemotherapy, metastases and tumor relapse.

Results The pre-treatment ADC was 0.90 ± 0.23 in NB/GNB and 1.70 ± 0.36 in tumor relapse. With chemotherapy, mean ADC increased to 1.54 ± 0.33 in NB/GNB and to 1.23 ± 0.27 in metastases (p < 0.05). The median SIRs of various tumor lesions vs. liver, vs. muscle tissue and vs. adjacent tissue were significantly higher on DWI (range: 2.4 – 9.9) than on ce-T1w (range: 1.0 – 1.8, all p < 0.05). The coefficient of variation (CV) was ≤ 8.0 % for ADC and ≤ 16.4 % for signal intensity data.

Conclusion Based on mean ADC, DWI distinguishes between NB/GNB and GN with high certainty and provides plausible quantitative data on tumor response to therapy. Lesion conspicuity, as measured by SIR, is superior on DWI, compared to ce-T1w. DWI as a noninvasive, radiation-free and widely available imaging technique should be an integral part of MR imaging for neuroblastic tumors and should undergo prospective evaluation in multicenter studies.

Key Points
- DWI reliably distinguishes neuroblastoma/ganglioneuroblastoma from ganglioneuroma, based on the mean ADC.
- DWI provides plausible quantitative data on tumor response to chemotherapy.
- DWI offers highly superior lesion conspicuity compared to contrast-enhanced T1w imaging.
- DWI should be considered a standard for imaging neuroblastic tumors.

Citation Format

Introduction
Neuroblastic tumors comprise a broad spectrum of neoplasia with highly diverse biological behavior, ranging from undifferentiated, highly malignant neuroblastoma (NB) to mature, usually benign ganglioneuroma (GN) [1]. NB is the most common extracranial malignant solid tumor in pediatric patients, accounting for about 8 % of all childhood malignancies [2, 3]. Based on standard imaging techniques, including radiography, ultrasound, CT and conventional MRI scans, differentiation between NB, ganglioneuroblastoma (GNB) and GN is not possible with diagnostic confidence [4, 5]. Therefore, the role of diagnostic imaging in the clinical workup of patients with neuroblastic tumors is presently limited to detecting, or excluding, metastatic disease and local complications, such as infiltration of organs and vascular structures [6, 7], while over-all risk stratification relies on clinical, histopathological and genetic criteria [8]. Diffusion-weighted MRI (DWI) has, with some success, been introduced as an adjunct to pediatric oncological MR imaging protocols [9]. Preliminary results suggest that, based on apparent diffusion coefficient (ADC) values, DWI can indeed distinguish between NB, GNB and GN with some confidence [10, 11]. Recent reports confirm these findings [12] and propose diagnostic value for detecting metastases [13] and for monitoring therapy response [14].

We undertook this study to test our assumptions of a substantial diagnostic value of DWI in comparison to standard contrast-enhanced MRI for tumor differentiation, therapy response and imaging of metastases in a comparably large cohort of children with extracranial neuroblastic tumors from a single center.

Materials and Methods
Patients
Based on PACS queries, tumor board documents and medical history reports, we retrospectively identified all patients with extracranial neuroblastic tumors who underwent imaging and treatment at our institution between January 1, 2005, and September 5, 2016 (Fig. 1). Screening all MRI examinations of these patients for DWI scans, we eventually enrolled all 29 patients (14 girls, median age at primary diagnosis: 3 years, range: 2 months to 19 years) who had at least one MRI study with DWI at our institution. All eligible sets of imaging data containing both standard and diffusion-weighted MRI were identified and assigned to the following categories: (1) initial imaging/before therapy n = 18 patients with primary tumor location cervical n = 3, adrenal n = 11, paravertebral-retroperitoneal n = 2 and intrapelvic n = 2; (2) evaluating therapy response n = 15 patients; (3) synchronous metastasis before therapy n = 4 patients with 8 lesions; (4) synchronous metastases under treatment n = 6 patients with 10 lesions; (5) patients with relapse/recurrence n = 5 patients with 9 lesions. If more than one examination per patient was available in one category, only the first eligible MRI scan was used for analysis.

Treatment plans were determined by interdisciplinary tumor conferences in cooperation with the national study coordination office. NB/CNB patients had initial tumor biopsy and were then referred for further treatment. Chemotherapeutic treatment at our institution is based on the NB-2004 trial protocol and its later
single-shot echo-planar imaging (SS-EPI-DWI), TR = 4600 – 7544 ms, TE = 88 – 100 ms, b-value = 50 and 800 s/mm², 5 – 10 averages, voxel size: 1.2 × 1.2 mm² to 2.8 × 2.8 mm², slice thickness: 4 – 6 mm, acquisition time: 4 – 6 min). Two scans for cranial osseous metastases were performed at b-values of 0 and 1000 s/mm². The parameters FOV and number of slices were adapted as needed for optimal fit in each patient. ADC maps for the mean ADC (unit: x10−3 mm²/s) were automatically calculated on the MRI console. After intravenous injection of one weight-adapted standard dose gadolinium-based contrast agent, fat-saturated sequences, e.g., T1w TSE for cervical and pelvic scans, T1w 2D-FLASH (Magnetom Symphony) or CAIPIRINHA-accelerated 3D-FLASH (Magnetom Aera) for thoracic-abdominal scans, were acquired as clinically appropriate with volume coverage and slice thickness corresponding to DWI. Patients aged ≤ 6 years underwent MRI in sedation administered by a pediatric anesthesiologist.

Image processing and analysis
All image analysis was performed on a dedicated radiological workstation (Merlin Version 5.1, Phoenix PACS GmbH, Freiburg, Germany). A board-certified pediatric radiologist with 8 years of pediatric extracranial DWI experience (1st reader) performed complete readings of all examinations with full access to the routine radiological reports, histopathological reports and tumor board documents as reference. At this stage, tumor location, tumor size, presence/absence of metastases and tumor relapse and ADC values of reference tissues (muscle tissue, liver, spleen renal cortex, pons cerebri, bulbus oculi, as included in the scan volume) were recorded. Two weeks later, the 1st reader repeated the measurements of ADC values in reference tissues for the assessment of intra-observer variation and then measured ADC values of primary tumor manifestation, metastases and sites of tumor relapse using large polygonal regions of interest (large ROI) comprising the whole of the tumor on the level of its largest transverse cross-section, and small ROI with an area of 1 to 2 cm², targeting tumor portions with the highest signal on DWI b = 800 and corresponding low ADC, presumably representing those with the highest cellularity. Portions of the tumor showing a high DWI signal along with a high ADC were avoided, so as not to include T2 shine-through in our ADC data. Signal intensity of the tumor, muscle and liver tissue was measured with a small ROI on DWI b = 800 and on post-contrast T1w scans. The signal intensity of the surrounding tissue was measured in a similar fashion in a 1 cm perimeter of the tumor. All quantitative data were recorded as the mean value of three measurements. Signal intensity (SI) data was used to calculate signal intensity ratios (SIRs) dividing SI tumor by SI reference tissue as a measure of lesion conspicuity on DWI and on contrast-enhanced imaging.

For the analysis of inter-observer variability, a board-certified radiation oncologist with six years of experience in diagnostic MR imaging, MRI research and MRI-based radiation therapy eventually repeated the tumor-related quantitative measurements for all predefined lesions as a second reader, though not necessarily in the same slice position, while being blinded to data from the first reading. Prior to measuring study data, the two observers completed a non-blinded training session reading and analyzing ten data-
sets of pediatric tumor patients not included in this study so as to arrive at a common strategy for measuring quantitative data.

Statistical analysis

Normally distributed data is presented as mean ± standard deviation, and data deviating from normal distribution as median [interquartile range]. The Mann-Whitney test was used to compare means of unrelated samples, e.g. ADC of NB and GNB vs. ADC of GN. The Wilcoxon paired-sample test was employed to compare means of two related datasets, e.g. signal on DWI vs. signal on T1w imaging and ADC before and after therapy. P-values < 0.05 were considered as indicating statistically significant differences. The coefficient of variation was computed to quantify intra-observer variation and inter-observer variation in quantitative data. All data analyses were performed with IBM SPSS Version 21 for Windows.

Results

Neuroblastic tumors on initial imaging

All tumor manifestations were identifiable and were visualized on both DWI and contrast-enhanced T1w imaging. The median tumor size was 46 mm, ranging from 27 to 113 mm, without a significant difference in size between DWI and ce-T1w imaging (paired sample t-test, p > 0.05). The mean ADC was 1.17 ± 0.53 [range: 0.61 – 2.33] with a large ROI and 0.96 ± 0.43 [range 0.50 – 2.03] with a small ROI for all tumors. NB/GNB had lower mean ADC values, compared to GN (▶Table 1). A statistically significant difference was observed for NB vs. GN (p < 0.001), for NB+GNB (p < 0.001) vs. GN and for GNB vs. GN (p = 0.023). While mean ADC was ≥ 1.18 in all GN patients (▶Fig. 2A-C), NB and GNB showed a consistently high signal on DWI b = 800 with a corresponding low mean ADC ≤ 0.98 (▶Fig. 2E, F, 3A-C). A cut-off value of ~1.3 with large ROIs and ~1.0 for small ROIs grouped NB/GNB vs. GN without overlap. The signal intensity ratios (SIR) of tumor vs. muscle and tumor vs. liver were significantly higher on DWI compared to ce-T1w (▶Table 1).

Comparing NB patients with (n = 4) and without (n = 4) MYCN gene amplification, MYCN-positive tumors showed a higher median tumor size (10.2 cm vs. 3.6 cm), lower median ADC with a large ROI (0.71 vs. 0.81), lower median ADC with a small ROI (0.54 vs. 0.67) and lower median SIR tumor/surrounding tissue (5.3 vs. 6.6) compared to MYCN-negative lesions (all p > 0.05).

Therapy response in NB/GNB

Imaging for therapy response was performed as scheduled by the referring pediatric oncologists, that is after 2 blocks of standard chemotherapy in 10 patients, after 3 blocks in 2 patients, after 1 block in 1 patient and after 6 blocks in 1 patient referred from a foreign institution. One patient showed extensive intralesional hemorrhage, as seen by partial intralesional signal loss on T2w and T1w and by hyperintensity on native T1w, with artificially high signal at b = 800 and consecutively false-low ADC (▶Fig. 4) [16]. Eight of 15 patients had in-house pre-therapy scans. Comparing tumor size on initial and on follow-up imaging in these patients, the median tumor size decreased from 53 mm to 23 mm post-therapy, while the mean ADC increased from 0.82 ± 0.21 to 1.72 ± 0.33 (large ROI) and from 0.63 ± 0.14 to 1.38 ± 0.42 (small ROI) (all p < 0.05). The ADC of all post-therapy NB/GNB scans, excluding the one patient with intralesional hemorrhage, was 1.54 ± 0.33 with a large ROI and 1.21 ± 0.41 with a small ROI (▶Table 1). The median diameter decreased by 56.6 % (range: 15 – 75 %). A significantly higher SIR of tumor lesions was seen on DWI, compared to ce-T1w (all p < 0.01), while the SIR on both DWI and on ce-T1w decreased with therapy (p < 0.05) (▶Table 1). Δ diameter showed a statistically non-significant correlation of r = 0.38 (p = 0.164) with mean ADC after therapy. The therapy-induced change in diameter was less than 25 % in 2 of 15 patients with an ADC > 1.3 (large ROI) of the remaining tumor. One of these two patients died from tumor progression two months later in spite of continued therapy, while the other patient underwent further therapy with resection of liver metastases, 113I-MIBI therapy, HD chemotherapy and autologous stem cell transplantation and is now in complete remission three years after primary diagnosis. One 18-month-old patient with cervical stage 3 NB showed spontaneous significant decrease in tumor size on physical examination and ultrasonography while preparing for chemotheraphy and was put on ‘wait-and-watch’. Follow-up MRI after 4 months showed a decrease in tumor diameter from 34 to 11 mm and an increase in ADC from 0.63 to 1.39, and the tumor eventually resolved completely on further imaging follow-up.

Therapy in GN patients

Four of six GN patients underwent complete surgical resection. Subtotal resection was achieved in one patient with an adrenal GN and partial resection was performed in one patient with a large pelvic GN extending into the sacral foramina. The residual tumor remained stable on subsequent follow-up MRI imaging.

Initial imaging and therapy response of synchronous metastases

Sites of metastatic disease included cranial bone metastasis (patient 1), retroperitoneal lymph node and paravertebral intramuscular metastases (patient 2), retroperitoneal lymph node, multiple subcutaneous and pleural metastases (patient 3), as well as external iliac lymph node and pleural metastases (patient 4). Two metastatic manifestations in patient 3 and one distant external iliac lymph node metastasis in patient 4 were nearly occult on T2w and ce-T1w imaging, while clearly delineated on DWI. In total, four patients with eight metastatic lesions were analyzed. The initial median lesion diameter was 14 mm and the mean ADC was 0.67 ± 0.14 and 0.62 ± 0.14 with a large ROI and a small ROI, respectively (▶Table 1). With therapy, four of eight lesions completely resolved without discernible residuals on DWI or ce-T1w. The remaining four lesions decreased in size by 29 % to 80 % and showed an increase in ADC to 1.31 ± 0.24 and 1.11 ± 0.15 with a large ROI and a small ROI, respectively. There were two more metastasized patients without DWI on initial imaging. With therapy, retroperitoneal lymph node metastasis (patient 5) showed a 23 % decrease in size in comparison to initial ce-T1w
Table 1  ADC values and signal intensity ratios (SIRs) of the various tumor entities on diffusion-weighted (DWI) and on contrast-enhanced (ce-T1w) imaging. ADC values (unit: \(10^{-3} \text{mm}^2/\text{s}\)) are presented as mean ± SD and range [minimum – maximum], the SIR values as median [inter-quartile range].

<table>
<thead>
<tr>
<th>reader</th>
<th>NB/GNB before therapy Patients n = 12</th>
<th>GN patients n = 6</th>
<th>NB/GNB with therapy patients n = 14</th>
<th>metastases before therapy patients n = 4, 8 lesions</th>
<th>metastases with therapy patients n = 6, 10 lesions</th>
<th>tumor relapse patients n = 5, 9 lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADC, large ROI</td>
<td>0.90 ± 0.23 [0.61 – 1.27]</td>
<td>1.70 ± 0.36 [1.44 – 2.33]</td>
<td>1.68 ± 0.33 [1.41 – 2.01]</td>
<td>0.67 ± 0.14 [0.51 – 0.94]</td>
<td>1.23 ± 0.27 [0.85 – 1.35]</td>
<td>0.72 ± 0.18 [0.59 – 1.17]</td>
</tr>
<tr>
<td>ADC, small ROI</td>
<td>0.76 ± 0.17 [0.50 – 0.98]</td>
<td>1.47 ± 0.31 [1.18 – 2.03]</td>
<td>1.43 ± 0.35 [1.12 – 1.87]</td>
<td>0.62 ± 0.14 [0.44 – 0.87]</td>
<td>0.72 ± 0.14 [0.50 – 0.88]</td>
<td>1.01 ± 0.22 [0.64 – 1.30]</td>
</tr>
<tr>
<td>SIR ce-T1w tumor/adjacent tissue</td>
<td>1.4 [1.0]</td>
<td>1.3 [1.2]</td>
<td>1.4 [1.3]</td>
<td>1.3 [0.7]</td>
<td>1.1 [0.6]</td>
<td>1.1 [0.9]</td>
</tr>
<tr>
<td>SIR DWI tumor/muscle</td>
<td>6.7 [4.4]</td>
<td>2.9 [1.5]</td>
<td>3.8 [3.0]</td>
<td>7.0 [2.0]</td>
<td>2.4 [2.0]</td>
<td>8.5 [8.4]</td>
</tr>
<tr>
<td>SIR ce-T1w tumor/muscle</td>
<td>1.4 [0.8]</td>
<td>1.8 [1.0]</td>
<td>1.4 [0.5]</td>
<td>1.3 [0.2]</td>
<td>1.0 [0.3]</td>
<td>1.1 [0.4]</td>
</tr>
<tr>
<td>SIR ce-T1w tumor/liver</td>
<td>1.0 [0.6]</td>
<td>1.1 [0.7]</td>
<td>1.0 [0.2]</td>
<td>1.4 [0.5]</td>
<td>1.0 [0.3]</td>
<td>1.2 [0.4]</td>
</tr>
</tbody>
</table>

1 of 15 NB/GNB patients with therapy was excluded from quantitative analysis due to gross intralesional hemorrhage.

Tab. 1  ADC und relative Signalintensitäten (SIR) der untersuchten Tumorentitäten mit Diffusions- (DWI) und kontrastverstärkter MRT (ce-T1w). Die ADC-Werte (Maßeinheit: \(10^{-3} \text{mm}^2/\text{s}\)) werden angegeben als Mittelwert ± Standardabweichung und den Datenbereich [Minimum – Maximum], die SIR-Werte als Median [Interquartil-Abstand].

NB/GNB before therapy
Patients n = 12

GN
patients n = 6

NB/GNB with therapy
patients n = 14

metastases before therapy
patients n = 4,
8 lesions

metastases with therapy
patients n = 6,
10 lesions

tumor relapse
patients n = 5,
9 lesions
imaging and an ADC with therapy of 1.29. Patient 6 with a large liver metastasis with a diameter of 60 mm on initial CT imaging was seen with a persisting liver metastasis of similar size (63 mm) and a low ADC of 0.85 and 0.64 measured with a large ROI and a small ROI, respectively, after three blocks of chemotherapy. Analysis showed significantly higher SIRs of metastatic lesions on DWI, as compared to ce-T1w (all p < 0.01). The SIR on both DWI and on ce-T1w decreased with therapy (Table 1).

Imaging of tumor relapse

Five patients in our study experienced one tumor relapse (n = 1) and repeated relapse/progression (n = 4). Tumor relapse involved the retroperitoneum in 3, the thoracic wall in 2 and bone metastases in 4 instances. The tumor ADC in patients with recurring lesions was low with 0.72 ± 0.18 (large ROI) and 0.61 ± 0.12 (small ROI). The SIR was very high on DWI (Table 1, Fig. 5), while the SIR on contrast-enhanced imaging was similar to, or somewhat lower than, the SIR of initial tumor manifestations. Two patients underwent intensified or HD chemotherapy, which induced tumor response with a decrease in diameter by about 50% and an ADC increase with a large ROI to 1.10 and 1.56, respectively. One of these patients is presently still under treatment, the other four patients died from tumor progression.
Mean ADC values of reference tissues were measured as follows:
erector spinae muscle 1.15 ± 0.10, liver 1.06 ± 0.20, spleen 0.84 ± 0.17, renal cortex 1.61 ± 0.17, pons cerebri 0.82 ± 0.06, bulbus oculi 2.74 ± 0.31. No significant difference was found for ADC values comparing examinations performed on Magnetom Symphony and Magnetom Aera (all p > 0.05).

The intra-observer coefficient of variation (CV_intra) was measured as follows: tumor ADC with a large ROI: 5.5 %, tumor ADC with a small ROI: 7.8 %, tumor signal at DWI b = 800: 8.9 %, muscle signal at DWI b = 800: 13.8 %, liver signal at DWI b = 800: 16.4 %, tumor signal at ce-T1w: 6.2 %, muscle signal at ce-T1w: 8.7 %, and liver signal at ce-T1w: 7.5 %.

A large ROI: 5.5 %, tumor ADC with a small ROI: 7.8 %, tumor signal at DWI b = 800: 8.9 %, muscle signal at DWI b = 800: 13.8 %, liver signal at DWI b = 800: 16.4 %, tumor signal at ce-T1w: 6.2 %, muscle signal at ce-T1w: 8.7 %, and liver signal at ce-T1w: 7.5 %.

**Discussion**

Based on retrospective data from a large single-center patient cohort, our study results confirm the previously reported excellent diagnostic value of diffusion-weighted MRI for the initial diagnostic workup of pediatric patients with neuroblastic tumors. Ganglioneuroma, characterized by almost exclusively benign biological behavior, presented with distinctly higher mean ADC values than neuroblastoma and ganglioneuroblastoma. In NB/GNB patients undergoing chemotherapy, DWI showed generally increasing ADC values with some correlation between the degree of therapy response and the magnitude of ADC increase. Our study expands upon previously published work insofar that we demonstrate excellent lesion conspicuity for DWI of metastases.
and tumor relapse. In addition, we provide quantitative data on lesion conspicuity comparing diffusion-weighted and contrast-enhanced MRI. While metastases and relapsing tumor showed signal characteristics similar to primary NB before and after treatment, if only in a small sample of patients, lesion conspicuity with DWI was highly superior, as compared to standard MRI techniques.

The various entities of neuroblastic tumors in children cannot be distinguished reliably with standard MR imaging techniques [4, 5]. The earliest report on restricted diffusivity in seven NB patients with a mean ADC of 1.1 and a range of 0.9 to 1.2 dates back to 2002 [10]. In a study on children with a variety of malignant and benign tumors of the abdomen, three cases of neuroblastoma imaged on a 1.5 T Magnetom Symphony scanner exhibited low mean ADC values of 0.70, 0.77 and 0.78, while an ADC cut-off value of 1.11 distinguished malignant and benign lesions with 100% sensitivity and 79% specificity [9]. Gahr et al. recorded a mean ADC value of 0.81, ranging from 0.39 to 1.47, in 10 NB patients, while 4 GN and 2 GNB showed a mean ADC of 1.60, ranging from 1.13 to 1.99 [11]. A recent report on 24 children with 15 NB, 5 GNB and 4 GN observed a mean ADC of 0.869 in NB, 0.97 in GNB and 1.147 in GN with significant overlap and a proposed cut-off ADC value of 0.93 [12]. Our data on ADC of NB/GNB and GN compare well to previously reported results. Depending on the ROI definition, all NB showed mean ADC values
The ADC values we measured for GNB and GN were markedly higher than those reported by Serin et al. [12], resulting in a better discrimination between the tumor entities in our study. The underlying causes of this inconsistency remain unclear. Serin et al. also used Siemens hardware and free-breathing DWI. In their manuscript, however, they do not elaborate on scan parameters, such as TE and TR, single-shot vs. multi-shot acquisition, or indeed whether they used an SE sequence with EPI readout at all. Serin et al. scanned at b-values of 0 and 800. The acquisition time given is rather short with 1 min 24 s. As the manuscript does not provide any internal reference ADC, there is no objective approach to hypothesize whether the observable differences arise from a variation in technical parameters or rather from any of the numerous other potential intervening factors, such as different ethnicity, random variation in ADC with only four patients in the GN group, etc. We want to stress at this point, though, that we do not postulate a 100% discrimination of GNB from GN, or of malignant from non-malignant lesions, based on ADC values, in a larger patient cohort, or in the prospective setting of the clinical imaging routine. We do hold that measuring the mean ADC in neuroblastic tumors allows the best guess regarding biological malignancy that is presently possible based on data from noninvasive and radiation-free diagnostic procedures. Future research should address the potential correlation of tumor ADC with the presence or absence of MYCN gene amplification as a marker of high risk and poor outcome. Our data from very small subgroups showed a tendency towards a lower median ADC in MYCN-positive cases, a finding that warrants systematic investigation in a larger patient cohort.

In the present study, as well as in earlier reports, we observed a satisfyingly low degree of intra-observer and inter-observer variability for measured ADC values with coefficients of variation usually less than 10%, even across different DWI scanning techniques and on different scanners of the same manufacturer [17]. However, ADC variability arising from different acquisition techniques and from different scanner hardware needs to be taken into account. To illuminate this point, one patient with abdominal GN recently referred to our institution underwent initial MR imaging including DWI on a 1.5 T Intera scanner (Philips) at another imaging center. Exemplary quantitative analysis of this external dataset according to our study protocol showed the following results (reference data from our study in brackets): ADC of tumor with a large ROI: 1.13 (1.70), ADC of tumor with a small ROI: 0.70 (1.47), placing the lesion well within the range of neuroblastoma, as defined by our in-house reference. However, this patient also showed a lower-than-usual ADC for reference tissues (reference data from our study in brackets): muscle 0.82 (1.15), liver 0.83 (1.06), spleen 0.55 (0.84), renal cortex 1.09 (1.61). In order...
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be exposed to high radiation doses without need. While PET/MRI may be one approach to reduce radiation exposure from whole-body scans in the future, whole-body DWI as a radiation-free, cost-effective and readily available alternative should be evaluated prospectively head-to-head with PET/CT, PET/MRI and diagnostic MIBI scans [13]. Finally, concerns have recently been raised about the long-term safety of gadolinium-based contrast agents, based on the observation of intracranial gadolinium deposition in patients after contrast-enhanced MRI scans [26]. Based on our preliminary experience, DWI may serve as a useful diagnostic tool to perform native MRI scans with high intrinsic tissue contrast and to substitute at least some Gd-enhanced MRI scans. However, more data and higher evidence seems necessary in this respect in order to support more definite conclusions.

**CLINICAL RELEVANCE OF THE STUDY**

- Our study results provide evidence that diffusion-weighted MRI as a noninvasive, radiation-free, cost-effective, fast and high-contrast imaging tool provides reproducible quantitative parameters for comprehensive oncological imaging in pediatric patients with neuroblastic tumors.
- DWI is available on all modern MRI scanners and is to be recommended as part of standard MRI scanning protocols for childhood cancer.
- Whole-body DWI should undergo prospective evaluation in a head-to-head comparison with contrast-enhanced MRI, PET/CT and MIBI scans.

**Conflict of Interest**

The authors declare that they have no conflict of interest.

**References**