Quantitative Apparent Diffusion Coefficient as a Response Biomarker in Pediatric Neuroblastoma Imaging

A single-centre retrospective feasibility study

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Rationale: Response assessment in neuroblastoma

Clinical Background

- Neuroblastoma is the most common extracranial solid malignancy in children[1].
- Clinical behaviour is highly variable, ranging from spontaneous regression to aggressive progression[1].
- Accurate assessment of treatment response is essential for clinical management.

Limitations of Size-Based Assessment

- Conventional CT and MRI primarily assess changes in tumor size and morphology.
- Tumor shrinkage does not necessarily indicate complete treatment response or absence of viable tumor.
- In a retrospective cohort, 5 of 7 chemotherapy-treated patients relapsed despite a 48–88% reduction in tumor volume[2].

Rationale for Quantitative Imaging

- Diffusion-weighted imaging (DWI) provides information on tumor microstructure (cellularity) through the apparent diffusion coefficient (ADC)[3].
- ADC may complement conventional MRI by identifying treatment-related changes not captured by tumor size alone i.e necrosis[3].



Figure 1. Coronal T1-weighted fat-suppressed post-gadolinium MRI demonstrating a right adrenal neuroblastoma extending to the right renal hilum in a 17-month-old girl with neuroblastoma

Rationale: ADC as a Marker of Treatment Response

Effective treatment may reduce tumor cellularity, leading to increased water diffusion and higher ADC values

Pre-Treatment

↓

High tumor cellularity

↓

Restricted water diffusion

↓

Lower ADC

Post-Treatment

↓

Reduced tumor cellularity

↓

Increased water diffusion

↓

Higher ADC

Rationale: Prior Studies of ADC in Neuroblastoma

Previous studies suggest that ADC changes with chemotherapy and may reflect treatment response, but findings remain heterogeneous.

Study	Cohort	Main Findings*
Demir et al., 2015[4]	11 children (of 15)	Median ADC increased from 0.74 to 1.05 following chemotherapy (p = 0.003).
Neubauer et al., 2017[5]	29 children	Mean ADC increased from 0.90 ± 0.23 to 1.54 ± 0.33 following chemotherapy.
Peschmann et al., 2019[2]	19 children	Baseline ADC < 0.80 was observed in all neuroblastomas that subsequently relapsed; ADC tended to decrease in relapsing tumors.

*ADC values expressed in $\times 10^{-3}$ mm^2/s.

Knowledge Gap and Hypothesis

Knowledge gap

- Existing studies evaluating ADC as a treatment response biomarker in neuroblastoma are limited by small sample sizes.
- Differences in MRI acquisition protocols and region of interest (ROI) methodology limit comparability across studies.
- The prognostic value of baseline ADC and proposed thresholds remain uncertain, and its association with image-defined risk factors (IDRFs) is unknown.
- The feasibility and reproducibility of ROI-based ADC measurements on routine clinical MRI remain insufficiently established.

Hypothesis

1. ROI-based ADC measurement is feasible and reproducible on routine clinical MRI.
2. ADC increases within patients after chemotherapy, reflecting reduced tumor cellularity.
3. Lower baseline ADC values are associated with adverse clinical outcomes (relapse or death).

Objectives

Objective 1

1. Assess the feasibility and within-examination variability of ROI-based ADC measurements on routine clinical MRI.

Objective 2

2.1 Quantify within-patient ADC changes following treatment (ΔADC = post-treatment ADC − baseline ADC).

2.2 Characterize baseline and post-treatment ADC values.

2.3 Explore associations between baseline ADC and clinical outcomes.

Study Design

Study Design

- Retrospective, single-centre study at the Montreal Children's Hospital (REB approved)
- Baseline (pre-treatment) and post-treatment examinations analyzed when available
- Clinical outcomes taken from medical records

Eligibility Criteria

1. Inclusion Criteria

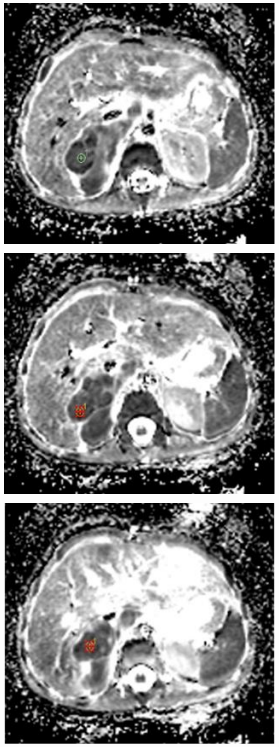
- Pediatric patients (≤18 years) with proven neuroblastoma
- Availability of baseline pre-treatment and/or post-treatment MRI with ADC maps
- Sufficient clinical data for outcome assessment

2. Exclusion Criteria

- Absence of both baseline and post-treatment MRI
- Missing ADC maps or inadequate image quality
- Inaccessible medical records

ADC Measurement

1. ADC maps reviewed alongside T1- and T2-weighted images to identify viable tumor and exclude cystic/necrotic areas.
2. Elliptical ROIs (~0.3 cm²) placed in homogeneous solid tumor regions across multiple axial slices.
3. Mean ADC (×10^{-3} mm²/s) calculated; separate lesions analyzed independently.
4. Reproducibility of the measurements assessed.



ROI 1: 0.88 × 10^{-3} mm²/s

ROI 2: 0.73 × 10^{-3} mm²/s

ROI 3: 0.92 × 10^{-3} mm²/s

Figure 2. Three ROIs (0.30 cm^2 each) on three axial ADC slices of a right-sided retroperitoneal mass in a 5-year-old boy (baseline MRI) Mean examination ADC: 0.84 × 10^{-3} mm^2/s.

Statistical Analysis

Analysis	Method
Descriptive statistics	Mean ± Standard Deviation (SD), median, range, and 95% confidence interval (CI).
Feasibility	Proportion (%) of included patients with measurable ADC
ADC reproducibility	Intraclass correlation coefficient (ICC)
Treatment-related changes	Absolute and percentage ADC changes in paired examinations.
Clinical outcomes	Exploratory comparison of baseline ADC with relapse or death.

Given the small sample size, analyses were descriptive and exploratory

Statistical analyses were performed using RStudio

Results: Study Cohort

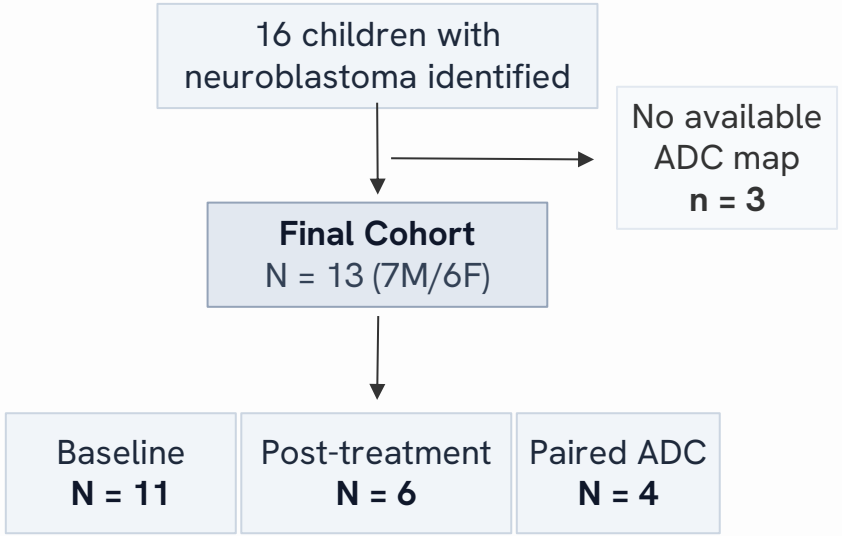


Figure 3. Cohort flow diagram

Cohort characteristics

Characteristic	Value
Included, n	13
Age, mean ± SD	5.2 ± 3.3 years
Sex, n(%)	7M (54%) / 6F (46%)

Results: Objective 1

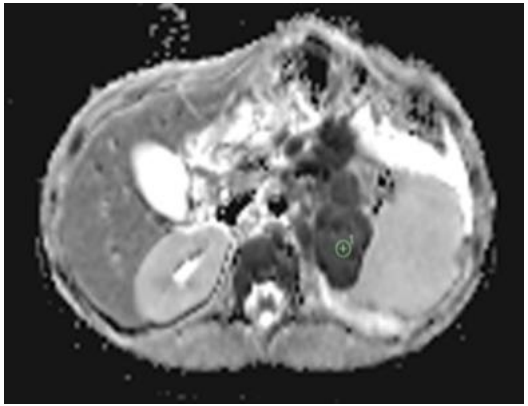
Feasibility and Reproducibility

ROI-based ADC measurement was feasible in 13 of 13 patients (100%) on routine clinical MRI

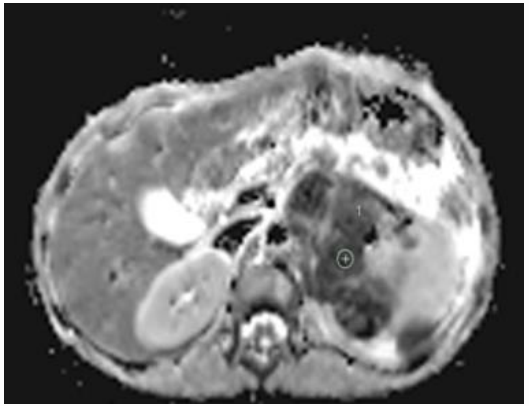
Intraclass Correlation Coefficient (ICC): 0.93 (95% CI: 0.86–0.97)

- High ICC across three ROI measurements per tumor, suggesting strong relative consistency in ADC measurements within the same examination

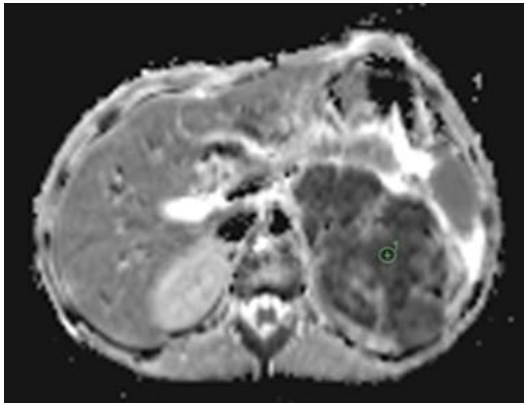
Figure 4. Three ROIs within the same tumor of a 10-year-old boy (baseline MRI)



ROI 1: Mean ± SD = 0.66 ± 0.08*



ROI 2: Mean ± SD = 0.68 ± 0.08*



ROI 3: Mean ± SD = 0.70 ± 0.09*

*Values expressed as mean ± SD ($\times 10^{-3}$ mm^2/s)

Results: Objective 2.1

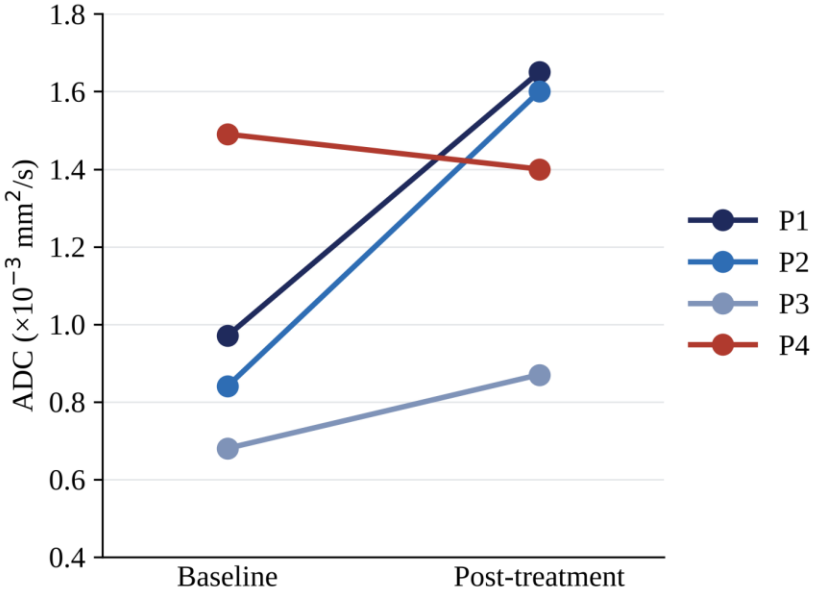
Patient Cohort & Clinical Outcomes

Patient	Age / sex	Baseline ADC	Post-treatment ADC	ΔADC*	ΔADC between chemotherapy cycles	Outcome / follow-up
P1	7 y / M	0.96	1.65	+0.69	—	Good partial response after 4 cycles
P2	5 y / M	0.84	1.59 (0.99 at end of therapy)	+0.75	—	Complete response; no relapse
P3	10 y / M	0.68	0.87	+0.19	—	Initial response; then relapse
P4	6 y / F	1.49	1.40	−0.09	—	Relapse
P5	2 y / F	—	0.97 (post-C4) → 1.04 (post-C5)	—	+0.07	Complete remission after chemotherapy and surgery
P6	10 mo / M	—	3.20 (post-C2) → 1.73 (repeat)	—	−1.47	Residual disease after cycle 2
P7	12 mo / F	0.78	—	—	—	Pending (no follow-up yet)
P8	8 y / M	0.76	—	—	—	Pending (no follow-up yet)
P9	8 y / F	0.81	—	—	—	Good response
P10	5 y / F	0.49	—	—	—	Deceased; MYCN-amplified
P11	2 y / F	0.70	—	—	—	No relapse after surgery
P12	3 y / M	0.81	—	—	—	Pending (no follow-up yet)
P13	10 y / M	1.10	—	—	—	Pending (no follow-up yet)

ADC values are expressed in $\times 10^{-3}$ mm²/s (mean of ROIs). Baseline refers to the first pre-treatment examination; *ΔADC = post-treatment ADC − baseline ADC. P = patient; y = years; mo = months; M = male; F = female; C = chemotherapy cycle

Results: Objective 2.1
Within-Patient ADC Change

Figure 5. ADC values at baseline and post-treatment in four patients with paired examinations.



Patient	Baseline	Post	ΔADC	%Δ	Outcome
P1	0.96	1.65	+0.69	+72%	Good partial response
P2	0.84	1.59	+0.75	+89%	Complete response; no relapse
P3	0.68	0.87	+0.19	+28%	Initial response; then relapse
P4	1.49	1.40	−0.09	−6%	Relapse

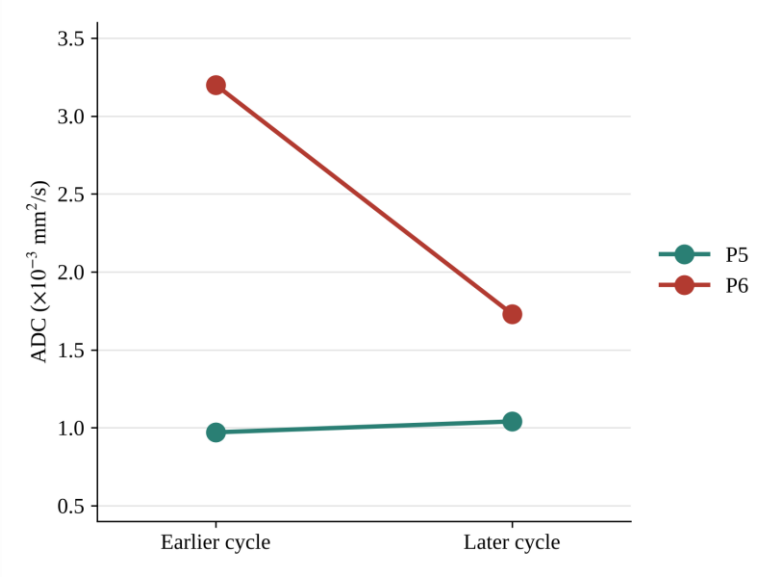
ADC values expressed in ×10⁻³ mm²/s. ΔADC = post-treatment ADC − baseline ADC.

- **ADC increased in 3 of 4 patients (75%), including two with favorable outcomes and one who subsequently relapsed.**
- **The only ADC decrease was observed in a patient with relapse.**

Results: Objective 2.1

Interval ADC Change Between Chemotherapy Cycles

Figure 6. Interval ADC change during chemotherapy



In two patients without baseline MRI, interval ADC changes showed different patterns:

- P5: ADC increased slightly (+0.07), with complete remission.
- P6: ADC decreased (−1.47), with residual disease.

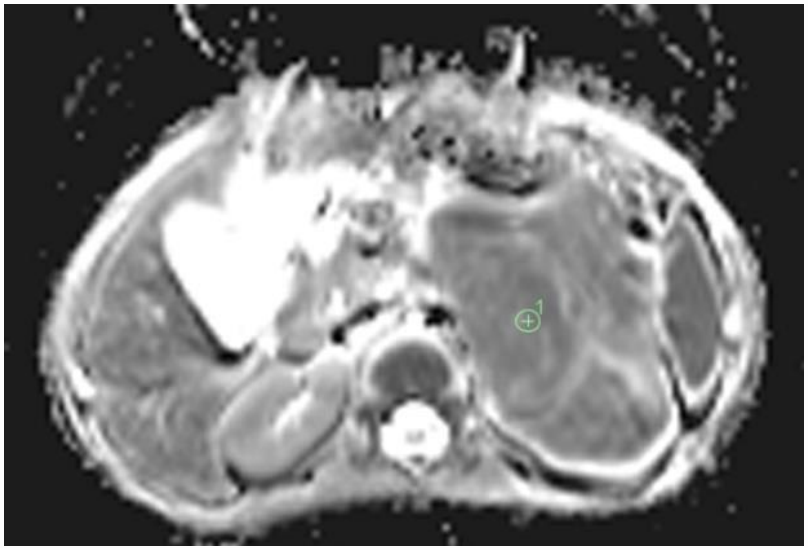
Patient	Earlier ADC	Later ADC	ΔADC	Outcome
P5	0.97 (post-C4)	1.04 (post-C5)	+0.07	Complete remission
P6	3.20 (post-C2)	1.73 (repeat)	−1.47	Residual disease

ADC values expressed in ×10⁻³ mm²/s.
C = chemotherapy cycle. *ΔADC = later cycle ADC − earlier cycle ADC.*

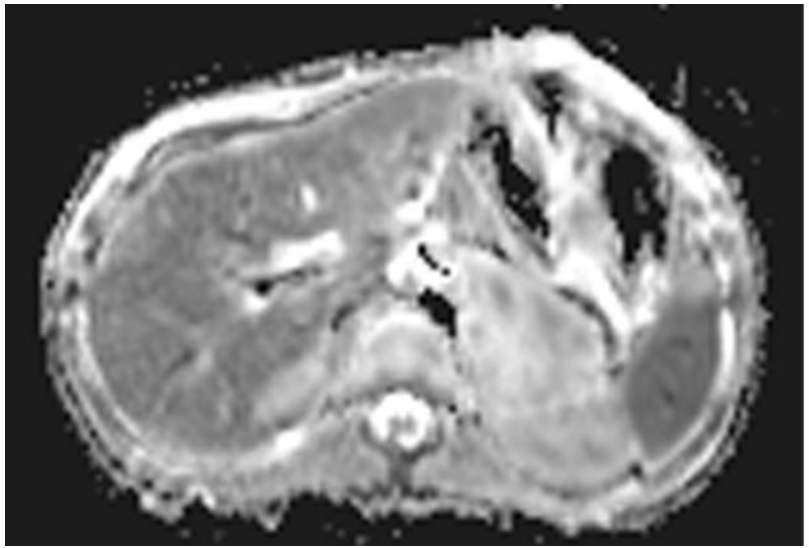
The direction of ADC change was consistent with clinical outcomes, with an increase observed in the patient achieving complete remission and a decrease in the patient with residual disease.

Results: Case Example

Figure 7. Baseline and post-treatment ADC maps in a 7-year-old boy with neuroblastoma showing a good partial response to chemotherapy.



Baseline: mean 0.96 (ROIs 0.97, 1.01, 0.90)



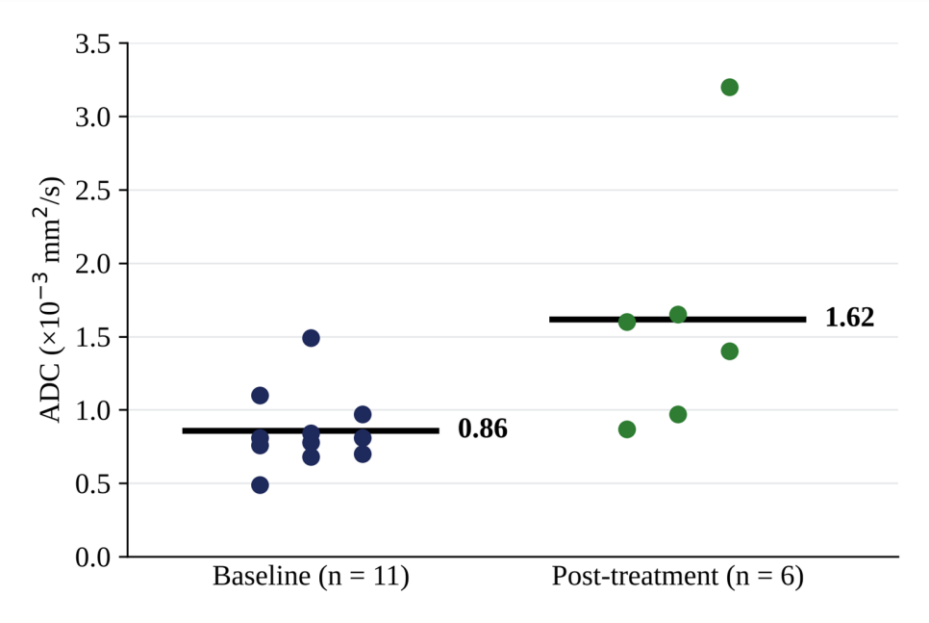
After 4 cycles: mean 1.65 (ROIs 1.86, 1.74, 1.35)

In this 7-year-old boy, mean ADC increased by 72% (0.96 to 1.65 × 10^{-3} mm^2/s), with a good partial response after 4 cycles of chemotherapy

Results: Objective 2.2

ADC values at baseline and after treatment

Figure 8. Distribution of ADC values at baseline and post-treatment



	Baseline	Post-treatment
n	11	6
Mean ± SD	0.86 ± 0.26	1.62 ± 0.84
Median	0.81	1.50
Range	0.49–1.49	0.87–3.20
95% CI	0.68–1.03	0.73–2.50

ADC values in $\times 10^{-3}$ mm^2/s. Confidence intervals calculated using the t-distribution.

Mean ADC was 0.86 ± 0.26 × 10^{-3} mm^2/s at baseline (n = 11), compared with 1.62 ± 0.84 × 10^{-3} mm^2/s after treatment (n = 6).

Results: Objective 2.3

Baseline ADC and Clinical Outcomes

Exploratory analysis using the previously proposed[2] ADC threshold of 0.80 × 10^{-3} mm^2/s

Baseline ADC (× 10^{-3} mm^2/s)	Relapse or Death	Favorable outcome	Unknown outcome
<0.80 (n=5)	n=2 (P3, P10)	n=1 (P11)	n=2 (P7, P8)
≥0.80 (n=6)	n=1 (P4)	n=3 (P1, P2, P9)	n=2 (P12, P13)

- Of 13 patients, 11 had baseline ADC measurements available for analysis (2 patients with post-treatment MRI only were excluded). Outcome known in 7 of 11 patients.
- Relapse or death: 2/5 patients (40%) in the low ADC group (<0.80), compared with 1/6 (17%) in the high ADC group (≥0.80)
- Favorable outcome: 1/5 patients (20%) in the low ADC group, compared with 3/6 (50%) in the high ADC group

Discussion: Objective 1

Feasibility and consistency of ROI-based ADC measurements on routine clinical MRI

- **Feasibility**: ADC was measurable in all 13 patients (100%) with available ADC maps. 3 of 16 identified patients (19%) without ADC maps were excluded a priori.
- **Measurement consistency**: High agreement among ROIs within the same tumor (ICC 0.93; 95% CI 0.86–0.97), supporting within-examination consistency.
- **Limitations**: Inter-reader and test–retest reproducibility were not assessed. They are planned for future analyses.

Discussion: Objective 2.1

Within-patient change in ADC following treatment (ΔADC).

- ADC **increased** in 3 of 4 patients (P1–P3) with paired examinations, consistent with previously reported increases following chemotherapy[4],[5].
- Similarly, P5 (without baseline MRI) showed an interval ADC **increase** between chemotherapy cycles and achieved complete remission.
- ADC **decreases** were observed only in patients with **unfavorable** outcomes: P4 (baseline to post-treatment), who relapsed, and P6 (between chemotherapy cycles), who had residual disease.
- Variability in ADC changes may reflect differences in treatment timing, tumor necrosis, intratumoral heterogeneity, and ROI placement. The small number of paired (n = 4) and interval (n = 2) examinations limits further interpretation.

Discussion: Objective 2.2

Baseline and Post-treatment ADC values

Present Study (N = 13)

- **Baseline ADC**

Mean baseline ADC (0.86 ± 0.26) was comparable to previously reported values (0.70 – 0.90 × 10^{-3} mm^2/s)[2,4,5].

- **Post-treatment ADC**

Mean post-treatment ADC (1.62 ± 0.84) was slightly higher than previously reported study means (0.71–1.54 × 10^{-3} mm^2/s) [2,4,5]. Our greater variability may reflect the small sample size (n = 6), differences in treatment timing, tumor heterogeneity, and ROI placement.

- **Change over time**

ADC increased in 3/4 patients with paired examinations, consistent with some previously reported trends[4,5].

Study	N	Baseline	Post-treatment	Main finding
Demir (2015)[4]	11	0.74*	1.05*	Significant increase
Neubauer (2017)[5]	29	0.90 ± 0.23**	1.54 ± 0.33**	Significant increase
Peschmann (2019)[2]	19	0.70 ± 0.08	0.71 ± 0.25	Low baseline ADC in relapsing NB

ADC ×10^{-3} mm^2/s; mean ± SD unless indicated. *Median; **Combined NB/GNB cohort.

Discussion: Objective 2.3

Baseline ADC and Clinical Outcomes

- **Limited prognostic discrimination**: Baseline ADC did not clearly distinguish favorable from adverse outcomes, with adverse outcomes observed both below and above the proposed threshold[2] of 0.80×10^{-3} mm²/s.
- **Comparison with previous literature**: Peschmann et al.[2] reported that all relapsing neuroblastomas had baseline ADC below 0.80×10^{-3} mm²/s, a pattern not clearly reproduced in our cohort.
- **Future directions**: Image-defined risk factors (IDRFs) were not assessed in the present study. Larger studies are needed to evaluate the association between baseline ADC, IDRFs, and clinical outcomes.

Interpretation and Clinical Implications

ADC may complement conventional response assessment, but its prognostic utility remains uncertain.

Baseline ADC and Prognosis

- Baseline ADC values did not consistently distinguish patients with favorable versus unfavorable outcomes.
- Both low and relatively high ADC values were observed in patients who subsequently relapsed.
- These findings highlight the limited prognostic reliability of ADC alone in this small cohort.

Longitudinal Variability

- ADC generally increased following treatment, although heterogeneous longitudinal patterns were observed.
- Variability may reflect treatment timing, tumor heterogeneity, necrosis, and ROI placement.
- Differences in MRI timing after treatment make direct comparisons of ADC changes challenging.

Clinical Implications

- Previous studies have demonstrated significant ADC increases following chemotherapy in neuroblastoma.
- ADC may complement conventional size-based assessment by providing information on tumor microstructure and treatment response.
- Larger prospective studies with standardized imaging protocols are needed to validate proposed ADC thresholds (including 0.80×10^{-3} mm^2/s) and establish their clinical utility for risk stratification.

Limitations

Study Design & Cohort

- Small, retrospective, single-centre cohort (n = 13; 4 paired examinations).
- Limited clinical outcome data, precluding robust statistical analyses.
- Heterogeneous treatment regimens and follow-up intervals.

Imaging & Measurements

- Non-standardized DWI acquisition protocols.
- ROI-based sampling may not capture whole-tumor heterogeneity.
- Interobserver and test–retest reproducibility not assessed.
- No systematic histopathological or molecular correlation.

Conclusions

1. Feasibility

ADC measurement was feasible in all included patients, with high within-tumor reproducibility.

2. Treatment response

ADC increased after treatment in 3 of 4 patients with paired imaging.

3. Prognostic value

Baseline ADC did not consistently distinguish clinical outcomes but remains a promising complementary quantitative tool to help clinicians guide treatment.

Next Steps

- Standardized MRI protocols
- Larger cohort
- Multicentre validation
- Histopathological, molecular and image-defined risk factors (IDRFs) correlation
- Long-term outcome assessment

References

