MS ID#: 1504

MS TITLE: Detection and differentiation of paediatric renal tumours with diffusion-weighted imaging: an explorative retrospective study

Reviewer 1:

This interesting manuscript evaluates the diagnostic value of DWI for the diagnosis of pediatric renal tumors. Although the authors were not able to characterize renal tumors based on ADC values, their results are valuable since they highlight the potential of DWI for the detection of renal tumors. Especially the promising results in detection of NBS or nephrogenic rests represent a major strength of this manuscript.

However, there are some issues that have to be addressed:

- Introduction p. 3: If a patient has bilateral Wilms tumor, what difference does it make if NBS is detected in addition. This required further discussion.

- Methods p.4:The authors should discuss their choice of b-values. Would biexponential DWI lead to better results?

- Methods p.4:more details on the DWI sequence are required; did they authors use respiratory triggering? Did they use coregistration?

- Methods p.4: How did the authors calculate ADC values? Where did they draw the ROIs?

Results, p.8: The authors should provide the mean ADC value for the NBS foci

Discussion, p.9: "DWI signal is related to cellularity". This should be discussed more in detail. The authors should also discuss T2-shine through effects.

Discussion, p.9: as both cancer and NBS were detected by DWI, I do not think that the results of this study confirm the high sensitivity (or at least specificity) of DWI for malignant disease; the authors should moderate their claims.

Discussion, p.10: The authors should also provide changes in size (not only in ADC) of tumors during chemotherapy. This is essential in order to understand the meaning of DWI for treatment monitoring. Furthermore, the conclusions on the value of ADC for response assessment should be more moderate due to the small number of patients.

- General remark: English editing is required (e.g. p.6 "hepatic metastasis at initial diagnosis" or "the fourth patient had three ipsilateral....").

Reviewer 2:
This paper investigates the usefulness of diffusion-weighted MRI and in particular ADC for detection and differentiation of paediatric renal tumours. This retrospective study used data from 11 patients with histologically proven renal tumours. The results show that ADC is unable to differentiate benign from malignant renal tumours, however it helped locating the tumours with more confidence than when not used in combination with the rest of the clinical MRI. Also DWI helped identification of nephroblastomatosis foci that were undetectable with ce-T1w. The authors go in great detail describing each WT case making this paper very clinically relevant.

Specific Comments:

Page 5: It would be nice the explanation/justification of the additional ROI to be accompanied by a figure demonstrating the different ROI methods (showing the restricted diffusion area, cystic areas etc).

Page 7: spelling mistake “…spread at nine months”.

It is not a big surprise that such a simple model (ADC) cannot perform better in distinguishing difficult pathologies. It would be something worth mentioning in the limitations and that the field is now looking into alternative models for investigating cancer such as the IVIM, the Kurtosis and the VERDICT models.

References: I find the reference list a little bit out of date, and I would suggest including a few more recent papers on renal tumour investigation with DWI.

Reviewer 3:

Interesting paper assessing benefit of DWI in paediatric patient with renal tumors. Nevertheless, few aspects of the study should be more clarified or corrected before publication.

1. The signal intensity ratio (tumor vs. adjacent tissue) is not a standard method to assess the detectability. I would suggest that authors provide contrast to noise ratio (CNR) which is often employed as an index for contrast.

2. Please add more information about "two experienced observers", e.g. radiologists or physicists with # years experiences.

3. Scan parameters of ce-T1w should be provided for the SI ratio comparison.

4. Please provide the ROI definition (tumor and adjacent tissue; large and heterogeneous tumors) in figures as examples of the SI ratio measurements.
Reviewer 4:

Abstract:

• Well written and concise.

• Patients and Methods section: I think the description of the DWI sequence is too detailed and a little redundant for the abstract (length). The abstract already stated that images were acquired on a 1.5 T, so I would remove this statement. I would consider removing the b-value information (from the abstract). This is important, but can be stated with greater detail and at leisure in the body of the manuscript.

• As per journal requirements and formatting, it may be helpful to spell out abbreviations in the abstract.

BODY OF THE MANUSCRIPT:

Introduction:

• Well written, with no comments or concerns.

Patients and Methods:

• Please spell out all abbreviations upon first time use. Examples include: Magnetic Resonance (MR), Diffusion-weighted images (DWI), Turbo Spine-echo (TSE), T2-weighted (T2w).

• The second sentence of the second paragraph of the Patients and Methods section could be edited for clarity. It states: “seven patients below aged 0 to 6…”. I would simplify the wording to state that n (number of; age range) patients were sedated.

• The manuscript states that the DWI was acquired in the transverse plane. Is this the axial plane? This is minor linguistics but would be helpful for clarity.

• If possible, please include the type of fat suppression used.

• I understand and support the rational that the authors have used, comparing signal intensity (SI) in a lesion to SI in the background parenchyma. However, I would STRONGLY encourage the use of a more widespread metric such as contrast to noise ratio (CNR). This metric is well known in the abdominal MRI literature, and incorporates pure image noise into the calculation.

• Please provide additional details about the interpretation of these studies. Were the DWI and the conventional images interpreted simultaneously? Was there an interval (to avoid recall bias) between interpretation of DWI and conventional images?
• Also please state what images of the DWI acquisition were analyzed (b=800 only, b=50 and b=800, trace diffusion map). Please state if these were reviewed in default window setting, or “inverted gray scale” which the authors have chosen for the figures.

• Results:

• Sample size is small, which makes interpretation of results challenging. Also, it limits applicability of these results.

• Typographical error: “Juvenil” renal cell carcinoma, as opposed to “Juvenile”.

• In the section “Patients with primary diagnosis of Wilms Tumor”: I understand the observation that NBS was better seen in DWI, and I sympathize with the statement. However, this remains subjective. Could the authors be more explicit and say how many lesions were seen only on DWI, and how many lesions were seen on DWI and conventional images, but were better seen on DWI.

Discussion:

The first two paragraphs summarize findings and critically appraise observations. The third paragraph is long, and should be shortened. I would suggest shortening information on ADC values and their usefulness in other tissues. I believe all the references the authors cite are pertinent and establish a precedent for the use of ADC to differentiate benign vs. malignant lesions. I’m not opposed to mentioning the quantitative thresholds (from literature) they reported to distinguish benign vs. malignant lesions, as they provide a general “framework” of magnitudes observed in different tissues. However, I would refrain from comparing the results of these references between each other (references 17, 19, 23). There are several sentences discussing how reported ADC in musculoskeletal neoplasms compares to regenerative nodules in cirrhotic liver. These sentences should be deleted, as they are discussing results from work that is not part of this submission. Also, comparing diffusivity between musculoskeletal neoplasms and HCC adds little to the discussion of diffusion in renal neoplasms.

Good discussion of volume averaging, and how it may relate to differences in ADC. I would make a little more emphasis on great quality of images on free breathing DWI.

Limitations:

In general, its well drafted. There is a sentence that states, “The scanning protocols were designed with a particular emphasis on comparability and our results in previous studies did not show any substantial inconsistencies”. I find this sentence confusing, as the authors are referring to prior studies, and not data from this study. I don’t think prior results increase validity or reliability of the observations in this manuscript, unless the other studies pertain
directly to renal masses with this protocol (ref would need to be included). Overall I would favor deleting it.

Tables:

• The units of ADC and the exponents (mentioned in the abstract), need to be mentioned again in the caption.

Figures and legends:

• Figure 1. Image quality is good. I’m a little bit surprised by the decision to depict the DWI images on inverted gray scale. While I consider this a valid approach that can be helpful (different window settings have proven useful in adult stroke literature), I’d be curious to hear why the authors chose to do so, and if they do it in routine clinical practice. While only a minor concern, I think most people look at the DWI/ADC in the standard display settings, and interpretation of the images provided in this manuscript may be less intuitive.

• Figure 2. Excellent demonstration of the principle the authors are trying to convey. Lesions are conspicuous; some were not seen on CET1w.

• Figure 3, no comments to add.

• Figure 4. I would slightly edit the caption, which currently states "MRI showed a small focal signal increase". This goes back to the use of inverted gray scale. Although I believe that the lesion has decreased diffusivity the display gets confusing since the caption says high signal intensity and the image (arrow) demonstrates a dark focus (inverted scale). The focus of high signal on DWI is as a matter of fact not displayed. If the authors choose to maintain this display, they probably should refer to these foci as areas of decreased/restricted diffusion.

(end)