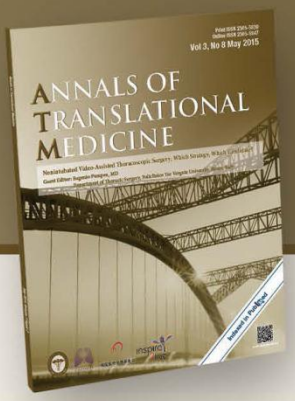
ANNALS OF TRANSLATIONAL MEDICINE



Peer Review File

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Reviewer A

The manuscript needs more careful re-editing (special care for acronyms, spaces for brackets and units, 'difference in').

Reply: The manuscript had been re-edited as advised by reviewers.

Methodological information relevant to reproduce the results of the study is missing.

Reply: This content had been added at Method section as advised (see page 7, line 136-145).

DW-MRI metrics are derived from a 2D region, which is known to depend on the contour. It is not very clear how these contours are then evaluated.

Reply: The ROIs were manually drawn on the greatest axial slice, to cover the slice as large as possible, the values were documented. The ROIs were drawn twice at a one-month interval. The average values of two times were recorded. These were added as advised by the reviewer (see page 7, line 136-145).

Referencing to DW-MRI parameters is sometimes inaccurate.

Reply: These were corrected as advised by reviewer.

The statistical analysis is mostly appropriate, but some additional information is needed.

Reply: Additional information was added as advised by reviewer (see page 7-8, line 154-155).

The discussion section should be expanded.

Reply: The discussion section was expanded as advised by the reviewer (see page 11-13).

Here a line by line analysis follows.

Abstract

line 1: 'mon-exponential' should be 'mono-exponential'

Reply: This mistake was corrected as advised by the reviewer (see page 2, line 31).

line 39: introduce acronyms with a uniform style (i.e. intravoxel incoherent motion (IVIM))

Reply: This was corrected as advised by the reviewer (see page 2, line 37).

line 41: it is not clear to which values you are referring to

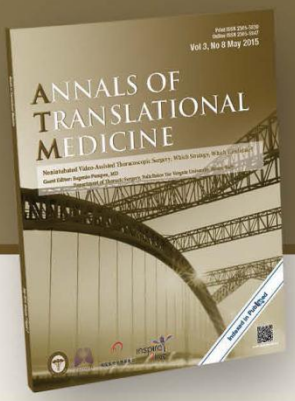
Reply: This has been corrected as 'The differences of apparent diffusion coefficient (ADC), true diffusion coefficient (D), pseudodiffusion coefficient (D*), perfusion fraction (f), mean diffusivity (MD), and mean kurtosis (MK) values', following the reviewer's advice (see page 2, line 40-42).

line 45: consider specifying what ICC is and changing 'values' to 'parameters'

Reply: These changes have been made following the reviewer's advice (see page 3, line 46).

line 45: you do not specify what ADC, D, f, MD, MK are. Consider stating the full name of the parameters or rephrasing to avoid using the short names, if you reached a word limit. For example, you could remove the cut-off values from the abstract.

Reply: the full names were added 'The differences of apparent diffusion coefficient (ADC), true diffusion coefficient (D), pseudodiffusion coefficient (D*), perfusion fraction (f), mean diffusivity (MD), and mean kurtosis (MK) values', and the cut-off values were removed following the reviewer's advice (see clean manuscript page 2,



line 40-42).

line 46 and others: 'difference on' should be 'difference in'

Reply: These were corrected as advised by the reviewer (see page 3, line 48).

line 51: in differentiating two groups

Reply: This has been corrected as advised by the reviewer (see page 3, line 50).

line 57: does it really matter if they 'provide more quantitative values for differentiation'? I would focus more on the informative value of the parameters than on their number.

Reply: This content was deleted as advised by the reviewer.

Introduction

line 62: reference 1 reports epidemiological data from the UK or other nations. I suggest going to the original source of information and better specify the epidemiological context of the numbers provided.

Reply: We retrieved the original source the article 'Brewer P, Riddell Z, Grimer RJ, Jeys L. Perioperative mortality following above-knee amputations indicated for bone and soft tissue tumours. *European Journal of Surgical Oncology*'. No specific number of incidences were reported in this article, but it reported the five-year survival rate. We have cited in the text as advised by the reviewer (see page 3, line 63).

line 64: what do you mean with 'probability of resection'? Probability that surgery would be performed?

Reply: The same as the reviewer's thought, it means the probability that surgery could be performed.

line 73: wrong surname of the author

Reply: We have corrected the surname of the author as advised by the reviewer (see page 4, line 77).

line 75: I believe it should be 'lower b-values'

Reply: This mistake has been corrected as 'lower b-values' as advised by the reviewer (see page 4, line 79).

line 75: the b-value threshold of <200 is defined for brain. Also for STN?

Reply: In the reference 14 'van Rijswijk CS, Kunz P, Hogendoorn PC, Taminiau AH, Doornbos J, Bloem JL. Diffusion-weighted MRI in the characterization of soft-tissue tumors. J Magn Reson Imaging.' They used 200 s/mm^2 as the threshold. We followed their approach.

line 77: I suggest writing 'true diffusion coefficient (D)'

Reply: We have corrected the D values as 'true diffusion coefficient (D)' following reviewer's advice (see page 4, line 81).

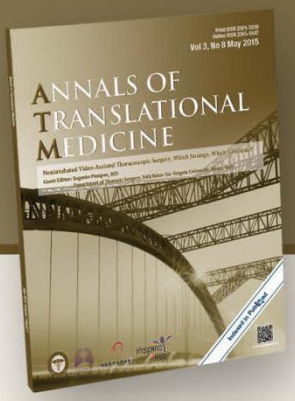
line 78: I thing that the perfusion status can be assessed with injection of external CA, but not the diffusion one. You cite 4 refeerences for this statement: where was this written?

Reply: This content has been revised as' It was reported that D* and f values were correlated well with microvessel density of colorectal cancer animal models, IVIM parameters were also correlated cerebral blood volume in gliomas (13, 19, 20). ', following the reviewer's advice (see page 4, line 82-84).

line 80: DKI is first named without full name

Reply: The full name has been added as advised by the reviewer (see page 4, line 85).

line 86-87: RSTN, PSC and DWI are reported for the first time without full name



Reply: The full name of RSTN, PSC and DWI have been added as advised by the reviewer (see page 4, line 91-93).
line 88: ADC, D, D*, f, MD and MK, are reported for the first time without full name

Reply: The aim of this article was shortened, and these were deleted as advised by the reviewer.
line 89: typo in 'bio-exponential'

Reply: This mistake has been corrected as advised by the reviewer (see page 4, line 94).
line 86-91: the three sentences describing the aim are equivalent and should be shortened
general comment: The rational of the study is stated at the beginning. However, I think that a broader description of the features of STN should be provided.
general comment: references related to the specific pathology are to be preferred.
Reply: The aim of the article has been shortened, and the comment on the description of PSC and RSTN has been added as advised (see page 5, line 91-96)
Materials and methods
line 98: histologically-proven

Reply: This change has been made as advised by the reviewer (see page 5, line 106).
line 99: State explicitly that the study involves only 27 (not 43) subjects.

Reply: This change has been made as advised by the reviewer(see page 5, line 107-109).
line 101: what do you mean by 'previous histology'? histology of primary tumors.

Reply: We mean the histology of primary tumors, it was corrected as advised by the reviewer (see page 6, line 111).
line 105-115: the main details of the sequences are reported, but they should be presented as sentences or reported in a table.

Reply: The sequences are reported as sentences as advised by reviewer (see page 6, line 113-129).
line 105-115: in-plane resolution and acquisition time should also be reported.

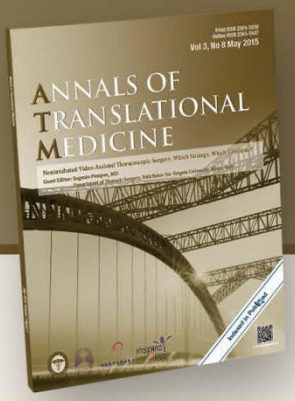
Reply: The resolution and acquisition time was added as advised by the reviewer (see page 6, line 113-129).
line 110: which is the MRI sequence that was acquired after Gd injection?

Reply: The sequence of enhancement was elucidate as advised (see page 6, line 114).
line 116-117: which methods were used? Which optimization? Without such information the results are not reproducible. Report the information at least in some supplementary material.

Reply: MR Body Diffusion Toolbox (www.siemens.com/syngo.via-frontier) was developed by Siemens, mainly for scientific research. If necessary, we can attach instructions on how to use it.
line 120: what do you mean by 'referenced'? Was image registration performed? If no registration was performed, what is the idea behind avoiding partial volume effects on DWI by looking at a different image?

Reply: When we selected the ROIs, the T1WI/T2WI/enhanced T1WI imaging were reviewed to identified necrotic, hemorrhagic, and cystic area, we avoid these areas. And we didn't draw ROI too close to the margin to avoid partial volume effect. These steps were done at the one-month interval. And the average of two times was documented.
line 121: ADC is not a parameter from IVIM or DKI, but from conventional MRI. Specify the difference between the two ADCs (only b-values used? which ones?) and mark each with a tag (e.g. ADC + IVIM as a superscript/subscript)

Reply: ADC_IVIM mapping was generated by 9 b values that were the same as IVIM, but with a mono-exponential decay model. While ADC_DKI mapping was generated by 5 b values that were the same as DKI, but with a mono-exponential decay model.
line 123: it is good that multiple contours were evaluated. Was the re-contouring performed by the same radiologist? What do you mean by 'the mean values were recorded'? Which contours were actually used for



the analysis? Did you compare only the volumes or did you compute a mean region by averaging the contours?

Reply: The contours were varied with the morphology of the lesions; the greatest axial slice was selected. ROI were drawn as large as possible while avoiding the avoid necrotic, hemorrhagic, and cystic areas, and partial volume effect, the ADC of every ROI was measured. The ROIs were drawn twice at the one-month interval, the mean value of ADC of two times was calculated and recorded.

line 126: I believe it is 'normality test'

Reply: It has been corrected as 'normality test' following the reviewer's advice (see page 7, line 148).

line 126-127: state the acronym ICC. Specify which type of repeatability you are accounting for. Specify the type of ICC you are computing.

Reply: ICC (Intra-class correlation coefficient). The repeatability of ADC values was calculated between two times.

line 129: how is the optimal cut-off generated?

Reply: The cut-off value was calculated by ROC analysis by MedCalc software.

line 130: citation to the work describing the DeLong test is missing

general comment: since you are performing multiple comparisons, did you apply correction for multiple testing?

general comment: how do you justify using the same b-values for different anatomical sites (head, trunk, extremities)?

Reply: The citation of the Delong test has been added(reference 28). We used the Delong test three times for AUCs of ADC, D, and f values comparison, so we use $\alpha=0.05/3$ for correction. We used the same b-values in different locations for further comparison.

Results

line 136: 'extremities'

Reply: This mistake has been corrected as advised by the review (see page 8, line 160).

line 144-146: add space before bracket (e.g. 'sarcoma (n=4),'). This results could also be reported in a tabular form.

Reply: The spaces were added as advised by review (see page 8, line 168-171) and wasn't reported in table form for the number limitations of the table.

line 149: how do you assess this repeatability? It is not clear to me. If it is related to multiple contouring, you should also report the overlapping regions of the contours.

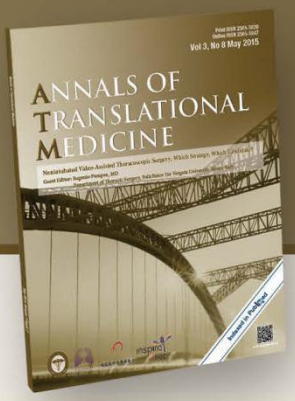
Reply: The repeatability was assessed for values measurement at the one-month interval. We assessed the repeatability of values of two times.

line 151-154: in my opinion this should be states in the Materials and methods section

Reply: These sentences were moved to the Methods section as advised by review (see page 6, line 131- page 7, line 135).

line 156: I believe you should report metrics evaluating the fit, depending on the fitting method employed. In Figure 2b, the IVIM model seems not to fit well the low b-values region, which is where the model should work better. I suspect the fit quality of D to be higher than for D* and f. How would you assess this?

Reply: We share a similar view with the reviewers. We did not evaluate the fit quantitatively. When the measured value is closer to that of a curve, we assume that the curve has a better fit. The area under the curve of D value was also found to have better discriminative performance than that of D* and f values.



line 165: you report one p-value but DeLong comparison is done between pairs of curves. You need to better detail this result. See also my previous comment about multiple comparisons.

Reply: We compared AUC three times, so we set the alpha level at 0.05/3 as advised by reviewer (see page 7, line 154-155).

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line 173: strange dot at the end of the line. Typo?

Reply: This mistake has been corrected as advised by reviewer.

line 181: typo in mon-exponential

Reply: This mistake has been corrected as advised by the review (see page 10, line 206).

line 182: it is not clear which parameters were included in the mono- and bi-exponetial models. Is it ADC vs D,D*,f? If so, why did you include D*? Please specify which parameters you use here or in the materials and methods section.

Reply: Because there was no statistical difference in the D* value between these two groups, it was excluded when the model was built. These were included as advised by reviewer (see page 10, line 205-207).

Table 1: are you reporting mean and standard deviation? State it in the caption and state somewhere that the parameters followed a normal distribution (if they did). Where the p-value is 0.000, I would prefer to read its real value as 1.7e-5, for example. In the note, what IU stands for? Specify the acronym or re-phrase it.

Reply: These were revised as advised by the reviewer (see page 19, table 1).

Figure 1b: the image is difficult to read.

Reply: Figure 1b has been re-edited as advised by reviewer.

Figure 2: pay attention that panel b and d are still readable once the figures are resized for publishing. In panel b the label of the y axis is cut.

Reply: Figures 2b and d have been re-edited as advised by reviewer, and the label of the y-axis can be seen now.

Figures: what is the difference between the green dots and the green line for IVIM or DKI? The main question is: what do the green dots represent?

Reply: The green dots represent the measured values. The green line was the generated decay curve of bi-exponential and non-Gaussian distribution by software respectively.

Table 2 and 3: ADCs needs to be marked at two different ones.

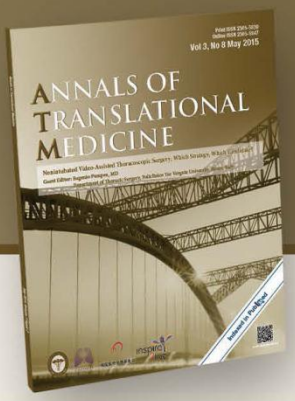
Reply: ADCs had been marked separately(ADC_IVIM and ADC_DKI) as advised by the reviewer (see page 19-20, table 2 and 3).

general comment: specify if parametric or non-parametric statistical tests were used for each p-value, since in the Materials and methods section you present both of them. You can do it in the tables presenting results.

Reply: This content had been added as advised by the reviewer (see page 19, table 1).

general comment: from the tables it is clearer how you compute the ADC (b-values for IVIM and DKI). I believe you should report this information in material and methods and you should mark the ADC_IVIM and the ADC_DKI in the results, to allow the reader to distinguish them.

general comment: why are you not comparing IVIM and DKI models but only IVIM-mono(0,800) and DKI-mono(0-2100)?



Reply: ADCs had been marked separately (ADC_IVIM and ADC_DKI) as advised by the reviewer.

general comment: I think the confidence intervals of the estimated AUC should be reported

Reply: 95% confidence intervals of AUC had been added as advised by the reviewer (see page 19-20, table 2 and 3).

Discussion

line 192: how did you decide that an ICC>0.8 detects 'great' repeatability? Provide a citation for this statement.

Reply: The citation had been added, where ICC>0.8 was thought as great repeatability, as advised by the reviewer (see page 11 line 225).

line 202-204: why are reference 11 and 12 relevant to the discussion of soft tissue neoplasm?

Reply: Although the article 'Qi LP, Yan WP, Chen KN, Zhong Z, Li XT, Cai K, Sun YS, Zhou XJ. Discrimination of Malignant versus Benign Mediastinal Lymph Nodes Using Diffusion MRI with an IVIM Model' didn't focus on STN. We just wanted to illustrate that IVIM can be used to differentiate benign from malignant lesions. So we cited it.

line 205: at low b-values, f and D* are more important than D.

Reply: As the reviewer said, D*and f values are more significant at low b-values. We have revised this sentence as advised by the reviewer (see page 13, line 243-244).

line 209: did you assess the cellular density of the tumours in your cohort or are you stating a known fact (i.e. PSC has higher density than RSTN)? In the latter case, specify the source.

Reply: We did not evaluate the cell density quantitatively, and we couldn't retrieve relevant literature either. We speculated that it may be due to a higher cell density in RSTN than that of the PSC.

line 214: molecules

Reply: This has been corrected as advised by the reviewer (see page 12, line 255).

line 215: probably you are missing an 'is' in this sentence, which in my opinion can be omitted as it does not add information about your study.

Reply: This has been corrected as advised by the reviewer (see page 12, line 252).

line 213: feature

Reply: This has been corrected as advised by the reviewer (see page 12, line 256).

line 218: brain tumours

Reply: This has been corrected as advised by the reviewer (see page 12, line 259).

line 221-222: more comments and/or reference to this statement should be provided. Also considering the wide range of tumour types included in this study.

Reply: These have been corrected as advised by the reviewer (see page 12-13, line 264-266).

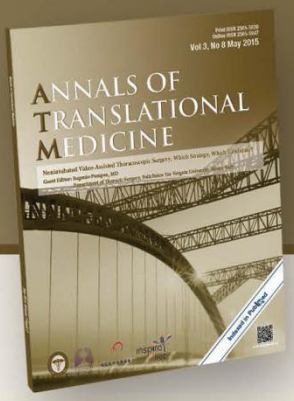
line 226: was the slice axial?

Reply: it was the axial slice, and this was added as advised (see page 14, line 287).

general comment: technical discussion of the DW-MRI methods employed is missing.

Reply: This was added as advised by the reviewer (see page 11, line 234-237).

general comment: as the authors state in the limitation, there are many confounding factors and sources of variability that were not evaluated. Given the small sample size, such analysis would not be very robust and



probably not worth doing. However, I believe that results for different locations should be shown (e.g. boxplots) or at least discussed.

Reply: This was added as advised by the reviewer (see page 11, line 232-233).

general comment: IVIM and DKI works in different b-values regions (low and high respectively), thus referring to different tissue properties. A discussion of such aspect is missing.

Reply: These were added as advised by the reviewer (see page 13, line 281-282).

general comment: discussion on specificity and sensitivity of the logistic regression models is missing.

Reply: These were added as advised by the reviewer (see page 13, line 278-279).

general comment: the references in the discussion (and in the introduction) do not specifically refer to STN. I think literature more relevant to the study should be provided (for example "Evaluation of response after pre-operative radiotherapy in soft tissue sarcomas; The European Organisation for Research and Treatment of Cancer - Soft Tissue and Bone Sarcoma Group (EORTC - STBSG) and Imaging Group recommendations for radiological examination and reporting with an emphasis on magnetic resonance imaging" by Messiou C et al.; "Detection of Soft-Tissue Sarcoma Recurrence: Added Value of Functional MR Imaging Techniques at 3.0 T" by Del Grande F. et al., "Development and Validation of Nomograms for Malignancy Prediction in Soft Tissue Tumors Using Magnetic Resonance Imaging Measurements" by Hyun Lee et al.). These references are purely reported to support my comment.

Reply: "Detection of Soft-Tissue Sarcoma Recurrence: Added Value of Functional MR Imaging Techniques at 3.0 T" by Del Grande F. et al., "Development and Validation of Nomograms for Malignancy Prediction in Soft Tissue Tumors Using Magnetic Resonance Imaging Measurements" by Hyun Lee et al were cited as advised by the reviewer (see reference 10 and 11).

general comment: there is no comparison with current clinical practice. What is currently done to distinguish RSTN and PSC? What is the added value, if any, of DW-MRI?

Reply: Since few literatures focused on the assessment of IVIM and DKI in STN. We have only made a brief comparison with the literature as advised by the reviewer (page 13, line269- 280).

Conclusion

line 235: see comment for the abstract

The conclusions are balanced and do not over-estimate the results of the study.

Reply: This had been corrected as that of the abstract.

Reviewer B

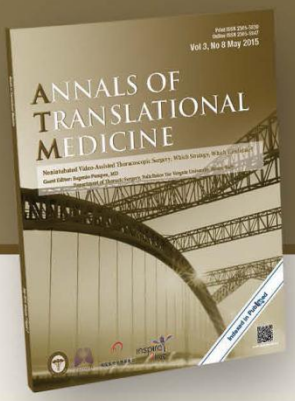
Major comments:

In this study, the authors focused on the value of bi-exponential and non-Gaussian DWI in the application of Recurrent Soft Tissue Neoplasns and Post-Surgey Changes. It is an interesting work. I recommend it can be accepted after major revision. There are several comments needed to be concerned as follows.

1. The manuscript needs careful editing by someone with expertise in technical English editing, so that the goals and results of the study are clear to the reader. Some sentences contain grammatical and/or spelling mistakes.

Reply: This article had been revised by expertise as advised.

2. In the result section, when you described the results, and compared the results, you should also add the values, P value, Chi-square value, confidence intervals….



Reply: These had been added as advised by the reviewer (see page 8-10, result section and page 19-20, table 1-3).

3. In the method section, the authors should describe the inclusion and exclusion criterion of the patients and controls. Forty-three patients were enrolled in this study, among them, 15 were RSTN and 12 were PSC, it meant that 16 of them was control group? but in the result section, the author just compared the values between RSTN and PSC group. Please confirm the data in the results.

Reply: Sixteen cases were excluded according to histology results. These have been revised' Inclusion criteria: ① all patients with complete clinical history; ② all the masses were histologically-proven by surgery or fine-needle aspiration biopsy. Twenty-seven cases (34 masses) were histologically-proven and included. They were divided into RSTN and PSC groups, 15 cases (22masses) were recurrences and 12 cases (12 lesions) were PSC.' as advised by the reviewer (see page 5, line 105-109).

4. In line 138, the authors described "There were 15 histologically proven RSTN (22 masses)." And in the abstract, the authors referred 34 masses. But the authors did not describe it in detail.

Reply: These have been revised' Twenty-seven cases (34 masses) were histologically-proven and included. They were divided into RSTN and PSC groups, 15 cases (22masses) were recurrences and 12 cases (12 lesions) were PSC.' as advised by the reviewer (see page 5, line 105-109).

Minor comments:

1. In Line 32, "May researches focused on the quantitative mon-expomential DWI…", if you want to describe "Many researches focused on the quantitative mon-expomential DWI…" Please confirm it.

Reply: These have been revised 'Many researches focused on the quantitative mon-exponential DWI…" as advised by the reviewer (see page 2, line 31).

2. In Line 39 and Line 96, "Methods the clinical, IVIM (Intravoxel incoherent motion) and DKI…" The first letter of a sentence should be capital. And if you want to describe "Methods The clinical data/infromation, IVIM (Intravoxel incoherent motion) and DKI…"Please confirm it.

Reply: These have been revised 'the clinical, IVIM and DKI imaging of a cohort of 27 patients (15 RSTN (22 masses), and 12 PSC(12 lesions)) with 34 masses, from Nov.1 2017 to Sep.30 2018, were reviewed.' as advised by the reviewer (see page 2, line 37 and page 5, 102-104).

3. In Line 141-142, the authors described "Five of them were found with metastases, 4 in lung, 1 in liver and 1 in bone". Please confirm it is five or six.

Reply: This has been revised' Five of them were found with metastases, 4 in the lung (1 coexisted with liver metastasis), and 1 in the bone.' as advised by the reviewer (see page 8, line 165-167).