Author’s response to reviews

Title: Central nervous system Gadolinium accumulation in patients undergoing periodical contrast MRI screening for hereditary tumor syndromes

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Author’s response to reviews:

Dear Professor Lubinski and Professor Scott,

We appreciate the opportunity to submit a revised version of our article "Central nervous system Gadolinium accumulation in patients undergoing periodical contrast MRI screening for
hereditary tumor syndromes”. We have carefully read the reviewers comments. Please find written below our point-by-point response. Revisions in the manuscript are mentioned below and are also highlighted in the manuscript using 'track changes'.

Reviewer 1

1. Quality of written English: needs some language corrections before being published.

We have reflected on several language issues and have adjusted them by using 'track changes' in the manuscript.

2. Not reported are clinical signs of toxicity; this is seemingly absent but should be added.

We have indeed not mentioned any side effects of Gadolinium accumulation in our patients. To date there is limited knowledge on this subject. First, we have thoroughly screened our VHL and TSC patients' electronic files for clinical signs of toxicity immediately after Gadolinium administration. None of the patients experienced any documented side-effects.

Second, we have screened the patients’ electronic files for long term neurological signs that could not be explained by VHL or TSC disease progression. We did not find any documented signs of inexplicable neurological deterioration.

However, assessing neurological side-effects in patients who already suffer from space occupying central nervous system lesions, is difficult. Especially in VHL patients: not only do they have hemangioblastomas in the cerebellum, but these tumors can also be totally or partially located in the dentate nucleus, where Gadolinium accumulation is most visible.

We have added our observations to the revised manuscript: Methods (p.5, end of 2nd paragraph), Results (p.8, end of paragraph), Discussion (p.17, 3th paragraph), Conclusions (p.18, middle of paragraph).

3. Methods regarding Gadolinium uptake are clear. Unclear remains the number of injections of Gadolinium. At least the number of MRI dates should be given. Most patients know that quite exactly, in others the intervals may allow to conclude how many MRIs have been done.

Our original intention was indeed to use our own estimation of the number of MRIs, based on the available MRIs in the patients' electronic files of the hospital. We compared our own estimation to the postulated formula of 1 MRI per year. (We also corrected a writing error in the
manuscript. On p.5 we wrote: "… average of 2 Gd enhanced MRIs per year of screening." This is incorrect: on average, patients only undergo 1 MRI per year, for brain, spine or abdomen.)

For VHL patients, the estimation almost exactly corresponded to the formula of 1 MRI per year.

For TSC patients, the estimation clearly differed. After discussing this with the physicians of the TSC patients, it was clear that TSC patients underwent at least one MRI scan with Gadolinium per year and that the estimated numbers were an underestimation. The explanation was that, compared to the VHL patients, more TSC patients were followed in other hospitals in the past.

We would like to retain the formula instead of the estimation, because we believe that it is more accurate. Nevertheless, to avoid confusion among the readers, we have replaced ‘years of screening’ by ‘number of MRIs’ throughout the revised manuscript and the tables (blue frames).

We have written the rationale more clearly in the revised manuscript (Methods p.5, 2nd paragraph).

4. We must be aware that patients with VHL may have lost one kidney because of cancer and that TSC patients may have lost a kidney because of angiomyolipomas. Also we need to know if more than the mentioned TSC case has polycystic kidney disease. This must be reported

The analysis of our patient data does not show a clear relationship between renal function and Gadolinium accumulation. As you have suggested, we have now reported kidney function and its influence on Gadolinium accumulation more clearly and extensively in the revised manuscript. First, we have emphasized the need of evaluating kidney function in VHL and TSC patients (Methods p.5, end of 1st paragraph). Second, we have added ‘kidney disease’ and 'kidney function' to Table 1 (Orange frame, Results, p.9). There was only one patient with polycystic kidney disease, together with TSC ('contiguous gene syndrome': the genes lie close to each other on chromosome 16). Most of the VHL and TSC patients had multiple renal cysts, but not related to polycystic kidney disease. Third, the kidney function, including stage 2 and stage 3, and its effect on Gadolinium accumulation were mentioned in more detail (Results p.13-14 and Discussion p. 16 last paragraph, p.17 1st paragraph)

5. Regarding kidney function measurement according to the MDRD formula, this is ok. But it has to be mentioned that normal function is 90 ml/min and more. 60-90 ml/min is so-called stage 2 and means already impaired renal function. We need to know how many cases had stage 2. They should also say that stage 3 is 30-59 and that the given case had stage 3 of chronic renal failure.
We have changed the cut-off for normal kidney function throughout the revised manuscript. We have also mentioned how many cases had stage 2 and stage 3 (Orange frame, Table 1: Results, p.9).

6. Table 1: show only the line 28 VHL and 24 TSC cases. Under the line: seemingly no signs of symptomatic toxicity, but clear signs of accumulation of Gadolinium by time.

We have removed the first row "total patients" in Table 1 (Orange frame, Results, p.9). To the second row we have added "Clinical signs of Gadolinium toxicity" and in the third row "Radiological signs of Gadolinium accumulation".

7. These results lead to reconsideration of the policy of prevention medicine in VHL and TSC. So far, patients felt comfortable, if they had regular screening, and best quality of imaging, and best method for detection of tumors is contrast enhanced MRI. Where should we go? This paper says that all sites of potential tumors should be documented after a single shot of gadolinium. That is fine and important. But we must reconsider the length of intervals and potential alternatives of imaging.

a. The authors should comment, if gadolinium-free MRI is diagnostic for CNS lesions. Regarding intervals of imaging, it must be considered how many operations the patients had and if based on these, as I think, astonishing low numbers of operations the intervals of imaging can be stretched.

To date, there are no validated guidelines evaluating the best screening protocol for VHL and TSC patients. Institutions tend to implement screening protocols based on their own experience with VHL disease.

We are the first to suggest an abbreviated MRI screening protocol, simultaneously screening for brain, spine and abdomen. We also consider to lengthen screening intervals on an individual basis if there is no disease progression since the last screening and if there are no lesions close to the limit of treatment. Furthermore, for VHL and TSC patients without central nervous system involvement, we suggest limiting MRI brain and spine screening to only once in two years. We have added this to Conclusions p. 18 (end of paragraph).

The extent and progression of hemangioblastomas and tubers/white matter lesions may not be accurately assessed using non-contrast enhanced MRIs. ELST tumors in VHL disease can only be seen on MRI with contrast. Furthermore, according to the guidelines of the American College of Radiology, MRI with Gadolinium contrast is more sensitive for the diagnosis of renal cell carcinomas and angiomyolipomas than unenhanced MRI. CT should be avoided for diagnosis of
all lesions, given the irradiation exposure. We have also added this to Conclusions p. 18 (end of paragraph).

b. For visceral tumors, ultrasonography should be considered as a relevant alternative.

In our hospital, we use an abbreviated MRI protocol using only one injection to screen for all lesions together (brain, spine, abdomen). Therefore, as the diagnosis of new renal cell carcinomas mostly relies on MRI with Gadolinium, we believe that renal cell cysts, pheochromocytomas and pancreatic cysts may as well be simultaneously screened for. The measurement of renal and pancreatic cysts using ultrasound is operator-dependent and therefore the assessment of growth is difficult. Furthermore, patients with only cysts do not need to be treated. For patients with an eGFR of < 30, one may opt to use non-contrast MRIs with T1, T2, and fat suppression sequences, however, with inferior results. We have added an abbreviated summary of these ideas to the revised manuscript (Conclusions p. 18, last paragraph).

Reviewer 2
1. Quality of written English: acceptable

We have reflected on several language issues and have adjusted them by using 'track changes' in the manuscript.

2. Important observation. Please convince me that the exclusion of a control group has not confounded the results. If patients having single scans for other diseases were included randomly in the assessment, that would have been a better design. But I agree the dose/time relationship is convincing given the scans were read blinded to the duration of screening.

We did not use a control group because we thought it would confuse the results, rather than clarify them. In fact, the aim of our study was (1) to study the prevalence of Gadolinium accumulation in VHL and TSC patients (for which no control group is needed) and (2) to compare the amount and rate of Gadolinium accumulation between the two groups. We hypothesized that the type of disease influences the amount and rate of Gadolinium accumulation.

In the past, Multiple Sclerosis patients were often used as a control group with serial Gd-MRI screening and without neoplasia. We originally used MS patients as a control group for this study. However, it was recently recognized that dentate nucleus enhancement in MS patients is
rather due to disease progression than to the accumulation of Gadolinium. We have also considered using a control group of patients who were free of disease. However, we could not find healthy patients who underwent such large amounts of MRI scans in our hospitals database. Furthermore, the serial administration of Gadolinium to healthy patients without diagnostic purpose, was not very feasible on ethical grounds (due to uncertainty about long term toxicity and the deleterious effect on kidney function).

Therefore, as you say, the readers of MRI were blinded to duration of screening, to compensate for the absence of a control group and to reduce bias.

With kind regards,

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