Author's response to reviews

Title: Impairment of intellectual functions after surgery and posterior fossa irradiation in children with ependymoma is related to age and neurologic complications

Authors:

Katja von Hoff (hoff_k@klinik.uni-wuerzburg.de)
Virginie Kieffer (kieffer@igr.fr)
Jean-Louis Habrand (habrand@igr.fr)
Chantal Kalifa (kalifa@igr.fr)
Georges Dellatolas (dellatolas@vjf.inserm.fr)
Jacques Grill (grill@igr.fr)

Version: 2 Date: 2 October 2007

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Responses to the reviewers

Reviewer Cornelia E. Catsman-Berrevoets

Major Compulsory Revisions

1. The authors state that hydrocephalus at presentation showed a trend to negatively influence the intellectual outcome in their ependymoma patients. In the methods they however do not describe their definition of hydrocephalus, how it was measured, if different degrees of severity influenced the results. In addition the presence or absence of periventricular lucencies as a measure of severity of hydrocephalus cq ICP is not mentioned at all.

Reviewer one highlights and interesting point of the study. Indeed patients with hydrocephalus seem to have a worse outcome. We indicate how hydrocephalus was analysed in the legend of a table that we added to the manuscript. This table 3 summarizes the medical history of the 23 patients of the study. Indeed, we choose to consider the hydrocephalus as a binary variable defined by the association of clinical signs of raised intracranial pressure with enlarged lateral ventricles and/or bulging of the third ventricle. Our series was too small to split the data according to the degree of hydrocephalus. In addition, depending on the speed of constitution of the hydrocephalus, patients could experience minimal enlargement and severe symptoms or vice et versa. We do not have FLAIR sequences at diagnosis for most of the patients to detect periventricular lucencies. The oldest patients had even only CT scan available before treatment of the hydrocephalus.

We agree however that in future prospective studies of the outcome of posterior fossa tumors, one should try to grade the severity of the hydrocephalus both in terms of volume of the ventricles relative to the size of the brain and in terms of duration.

2. Authors state that cerebellar damage strongly correlates with the IQ measurements. As measure of cerebellar damage they consider cerebellar symptoms. However, no attempt was made to correlate the neuropsychological results with the site and size of the cerebellar lesion. The absence of this information makes this paper rather superficial, which is a great pity because for the authors this information should not be hard to obtain and could ameliorate the quality of the paper considerably. Taking into account the site of the lesion the discussion why PQ was so much lower than VIQ would become more relevant.

In the table 3 that we added to the manuscript, we have described the site of the primary lesion. As it can be seen, most of the tumors were located in the fourth ventricles some extending either in the lateral recesses or downwards in the cervical region. This is expected with this diagnosis on the contrary to other posterior fossa tumors like pilocytic astrocytoma or medulloblastoma that are not always median. We could therefore not define different type of presentation. Regarding size, the range of size was narrow and we could not find any influence of size on the outcome. This may be also explained by the fact that size itself is not a sufficient measure since volume of the posterior fossa should also be considered. We could not reconstruct this data a posteriori.

We consider that cerebellar damage measured clinically post-operatively is a better predictor than any information that could be obtained pre-operatively. Indeed, cerebellar damage results from both the tumor and the operation (surgical route, contusion, resection, potential vascular damage…). The decrease in IQ is more pronounced for PIQ has it has been previously demonstrated by several papers, including ours (Grill et al, J Neurosurg 2004). We do not
have a definite explanation for this finding and further studies are needed to rule out the possible causes such as processing speed for example.

**Minor essential revision**

French terms have been translated into English when feasible. The text of allouette is referenced as such and is a standardized text to measure reading abilities in French.

**Reviewer Eirik Helseth**

**Major Compulsory Revisions**

1. **Important information about the patients on an individual basis are missing**: surgical complications, grade of resection (verified with postoperative MR), tumor status at the time of cognitive testing (no tumor detectable, residual tumor, recurrent tumor), shunt or endoscopic third ventriculostomy, number of shunt failures and shunt infections. All these factors may influence cognitive function. This information should be given in a table together with main cognitive scores. The reader will then be able to study each patient.

   As requested by the reviewer we added a table (number three) to describe the history of the disease and its treatment on an individual basis together with the full scale IQ. As stated in the methods section all patient were in complete remission at the time of the evaluation (but one who had a treated spinal relapse with no incidence on cognitive functioning). None of the patients shunted had a shunt failure or infection during follow-up.

**Minor Essential Revisions**

1. **Short observation time for some patients**

   We agree with the reviewer that for some patients the follow-up is short but the range of period at which the last evaluation was performed is large (up to 15 years). The median delay of 4.5 years is a period where significant decline in IQ is already seen in patients with medulloblastoma.

2. **Radiation policy**

   As this series consist in patients irradiated to the posterior fossa, the readers may thought that it is our policy for all patients. The table 3 gives now data of individual patient history and one can see that some of the patients were not irradiated upfront and received irradiation at the time of further progression, explaining why some patients had more than one surgery also. However, this case was rather unusual since most of the patients were older than 3 at the time of diagnosis and did therefore receive upfront irradiation. The chemotherapy approach was reserved to children below the age of three at diagnosis.

   We consider that it is beyond the scope of this paper to discuss the merits or drawbacks of radiation in this population of patients. Considering the limited effects of irradiation on cognition in older children (ie above the age of 5), the benefit in terms of survival certainly outfits the risk of the treatment. Our paper is just an argument in favor of a wider use of irradiation, provided the child is old enough. Indeed, we can not be completely sure that
irradiation would be safe in young children since they represent only a minority of the patients in the study.