Author's response to reviews

Title: Surgery of highly eloquent gliomas primarily assessed as non-resectable: risks and benefits in a cohort study

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Surgery of highly eloquent gliomas primarily assessed as non-resectable: risks and benefits in a cohort study

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REVIEWER COMMENTS TO AUTHOR:

Reviewer #1:

Dear Dr. Pallud, thank you for your inspiring comments.

Concern:

The main idea of this study is that tumor resectability must be decided in conference by neurosurgeons experienced in brain tumor surgery, ideally during dedicated neuro-oncological staff meetings including non-surgeons specialists, but not by individuals. This is not stressed enough in the manuscript in its present form, to my opinion.

Answer: We now stressed this issue in the conclusion (page 21).

Major compulsory revisions:

1. The manuscript does not specifically address the “specialization” of the different neurosurgical departments. There is no detail regarding outside institutions that primarily concluded to the non-resectability. Regarding their own institution, the authors report 51 cases during a 6 to 7-year-long period (2006 to 2012). During the same period, how many diffuse gliomas were operated on and managed? How the tumor respectability was decided? More generally, how one can define the neuro-oncological “specialization” of a neurosurgical department? This is the hot point the authors concluded with in the last sentence of the Conclusions Part: “Moreover, neurosurgical centers with limited expertise on surgery of such highly eloquent lesions should strongly refer their patients for a second opinion to a specialized center”.

Answer: The outside institutions were now described more specific (page 5). Our department resected around 150 gliomas per year during this period as now outlined on page 5. Decision for surgery was made during an interdisciplinary conference including neurosurgeons, neuro-
oncologists, neuroradiologists, neuropathologists, and radiation oncologists. This is now also mentioned on page 5.

How to define neuro-oncological “specialization” is a fairly good question which seems out of the range of this manuscript. However, we now mentioned the availability of a neuro-oncological conference and the whole number of performed glioma surgery in our department, which should be sufficient to prove the extent of specialization at least in our department.

2. Page 4, Method part, lines 4-7: the definition of the tumor location is not detailed enough and is inaccurate as a “perisylvian” location encompasses the other “insular”, “precentral” and “parietal” locations. The authors should use the cerebral sulci to describe the tumor location and should add the tumor volume and the MRI sequence used for the assessment of the tumor location.

Answer: The tumor location and size as well as the used MRI sequences are now specified (page 5).

3. The main findings (clinical, imaging, pathological, treatments, outcomes) for each patient should be summarized in a Table.

Answer: We added this information as table 1 (page 33 & 34).

4. Regarding the clarity of the manuscript:
   - Several redundancies exist between the Method, the Result and the Discussion parts. They should be avoided (for example, see the statistical significance level in each of these parts: “when considering p<0.05 as significant”).
   Answer: These redundancies where deleted throughout the manuscript.

   - The Results part is hard to follow. In addition, several data are already presented in the Method part.
   Answer: We deleted repeated data (page 5).

   - The statistical analyses performed are particularly unclear: they lack for several results and some points are discussed without the ad hoc tests.
The statistical part was specified (page 11).

5. The non-functional surgical morbidity must be addressed in detail: also the authors report 3 cases (6.3%) of postoperative hematomas requiring surgical evacuation, their description is unclear and minimized “However, only 3 out of these 5 cases were rated as significant hemorrhage and underwent revision surgery at the same day”. In addition, the absence of healing problems and of infections must be mentioned.
Answer: We specified these issues in page 12 and 15.

Minor essential revisions:
1. Page 3, Background part, line 5: when detailing diffuse gliomas within eloquent regions, the “peri-sylvian cortex of the dominant hemisphere” should be preferred to the “left-sided peri-sylvian cortex”.
Answer: This issue was changed (page 4).

2. Pilocytic astrocytoma is a very specific glioma. Hence, the unique case reported here should be removed from this series to obtain a homogeneous series dedicated to “diffuse gliomas” in adults.
Answer: As this report wants to draw attention on the resectability of gliomas per se, we strongly advocate to also include pilocytic astrocytomas because especially these tumors should undergo resection. However, we now specifically mentioned this reason (page 6).

3. Page 8, Postoperative evaluation part, line 6: How was defined the “extent of the resection”? Using a quantitative method? Which one?
Answer: This is now described in detail on page 10.

4. The authors report a large panel of preoperative and intraoperative techniques to assess the location of eloquent brain areas and to achieve tumor resection. As these techniques are not used systematically, the authors should explain clearly the reasons of their preferential use and combination. For example, why language cortical and subcortical preoperative mapping under awake condition was performed only in 8 cases (17%), although these
tumors were located in eloquent areas and in the dominant hemisphere in 59% of cases?
Answer: This is now also described in detail on page 7 and 8.

5. The term “significant” should be limited to the description of the statistical analyses that reach statistical significance in the Results part. Most of results are overstated in the Discussion part and qualified as “significant” although the statistical significance was not reached. In addition, sentences such as “cases were rated as significant hemorrhage” should be avoided for a better clarity.
Answer: These confusing parts were modified throughout the manuscript.

7. Regarding postoperative deficits:
- The detailed assessment of postoperative language deficit is lacking.
Answer: On page 13 postoperative changes in language function is outlined in detail:" After awake craniotomy on 8 patients, 6 patients (75%) showed a new aphasia at the first postoperative day but only 1 patient (13%) experienced a permanent surgery-related aggravated aphasia during long-term follow-up." Moreover, such information is now given in table 1 (page 33 & 34).

- Page 17, Recurrent gliomas part, line 4: the statement that “this high rate of GTR resulted in a higher rate of very relevant postoperatively new permanent deficits” is not correct if the authors actually performed functional-based resection.
Answer: You are right. We changed this sentence (page 19).

- Page 13, Postoperative MRI scans, line 8: the statement “2 (cases) showed resection within motor eloquent regions” is strange. Do the authors explain the postoperative deficit by a partial removal of the primary motor cortex? How the authors explain this at the light of the use of pre and intraoperative functional mapping?
Answer: No, we do not explain these deficits as partial removal of the primary motor cortex – however, this is the only explanation, which can be observed on postoperative MRI. To outline this issue clearly, we added some clarifying comments (page 19).

- Page 16, Correlation of tumor type and location to postoperative motor deficit, lines 9-11: the authors should discuss that adjuvant oncological treatments (chemotherapy and radiotherapy) may alter brain and vessels and may reduce postoperative plasticity. This may
participate to a higher risk of postoperative deficit after surgical resection of a recurrent glioma.
Answer: We added this important point to our discussion and emphasized with a newly published report (page 18).

8. Page 19, Authors’ contributions: who performed the statistical analyses?
Answer: This was performed by SK and FR. We added this issue to the manuscript (page 22 & 23).

Discretionary revisions:
1. All along the manuscript: the authors should prefer “WHO grade X” than "WHO°X".
Answer: This was changed throughout the manuscript.

2. Page 7, Awake monitoring part: the operative position of the patient should be mentioned.
Answer: The patient was positioned supine and 45° to the right side. Now mentioned on page 9.

3. Page 4, Tumor resection part, lines 2-3: The statement “Upon any amplitude loss or decline of more than 50%” should be referred to the monitoring technique parameter.
Answer: Now mentioned on page 9.

4. All along the manuscript: the authors should prefer “chemotherapy” than “chemo”.
Answer: We changed this issue throughout the manuscript.

5. In the Results part: regarding statistical analyses, the exact p-value should be preferred to a standard “p<0.05”.
Answer: We changed this issue throughout the manuscript.
6. Table 1 (now table 2):
- The case of pilocytic astrocytoma should be removed.
Answer: as mentioned above, this report wants to draw attention on the resectability of gliomas per se, we strongly advocate to also include pilocytic astrocytomas because especially these tumors should undergo resection. However, we specifically mentioned this reason (page 6).

- Why the estimation of the overall survival was limited to the population of deceased patients?
Answer: When patients are alive, mean overall survival equals to mean follow-up. We added this information to page 37.

7. Table 3: this table is not necessary and should be converted in a simple sentence.
Answer: This was changed (page 16, 34).

8. Regarding Figures:
- The histogram layouts should be changed to simple greyscale colors such as white/grey/black.
Answer: This was changed (now Fig. 2-5).

- The authors should reduce the thickness of the drawing lines.
Answer: This was changed (now Fig. 2-5).
Reviewer #2:

Dear Professor Schaller, below, we reply to your seminal notes and very helpful suggestions:

I like the concept that patients with particularly complex or eloquently located gliomas should be evaluated in all respects in a dedicated center, and be treated accordingly. Infrastructure of such centers is important and requires particular personnel (i.e. neuropsychologists, intraoperative neurophysiologists), high-end imaging (including metabolic imaging), navigation, intraoperative imaging, and particular expertise (i.e. for awake craniotomy). This has been accepted for other pathologies as well, such as for complex spinal or neurovascular disease, or for pediatric neurosurgery, to name a few. The authors have well demonstrated that such a (desperate) cohort of patients can still be treated with acceptable and good outcomes under ideal circumstances. I would thus accept this manuscript for publication - after revision.

Concerns:
1. The paragraph on the correlation between postoperative deficits and primary vs. recurrent tumors needs clarification (p11): They start with the statement that postoperative worsening was more frequent in recurrent tumors, and then they continue with a long sentence with a lot of numbers - for primary tumors. Then, they return to the recurrent tumors and their respective numbers. This should be presented in the reverse order and made more understandable.
   Answer: Primary as well as recurrent tumors are now mentioned in separated subsections and we tried to emphasize the different tumor types under discussion (page 13-16).

2. It is not easy to understand what the authors mean with "without the influence of IOM" (p12)? I would assume that MEPs remained unchanged during the course of surgery, but this should be explained/clarified.
   Answer: We clarified this aspect (page 14).

3. In the same paragraph they refer to "significant MEP loss". It would be important if there was real "loss", or if there was significant deterioration (i.e. by amplitude decreases of >50%), as this is misleading in the present form.
   Answer: We changed these points to “MEP decline” (page 14).
4. How do they position themselves to the value of intraoperative monitoring as, in their study cohort, the rates of neurological deficits did not differ among the two groups, those with, and those without intraoperative MEP worsening?
Answer: MEP was only used when the operating surgeon considered MEP monitoring to be important during surgery, which means proximity to the rolandic cortex or the corticospinal tract. We clarified this issue on page 7. There was only one patient without MEP monitoring who suffered from new postoperative paresis but due to secondary hemorrhage rather than intraoperative issues.

5. On p 15 they compare overall survival of their GBM patients with "the non-surgical series". Which series? A series from the literature? What does that have to do with table 1?
Answer: The cited series (reference 7-9, 37) investigated non-surgical treatment. We changed the position of the reference to table 1 (now table 2) to clarify this sentence (page 17).

6. It seems that none of their patients who underwent resection of a recurrent tumor had combined radiochemotherapy previously (table 2). I find this highly unusual in view of the (supposed to be) rather standardized treatment regimens for adjuvant GBM therapy. Can they comment on that? Is this another argument in favor of centralization of (eloquent) glioma treatment, where patients can be discussed in pluri-disciplinary tumor boards and are then treated according to dedicated (study) protocols?
Answer: Actually, as mentioned in table 2, 2 patients with recurrent gliomas (not only GBM) underwent both modalities. However, this number is still small and we added your arguments to our discussion and conclusion paragraphs because you pointed out a very important issue (page 20 & 21)!

7. They have not really spent much time and energy on their legends. These would merit some work in making them more explanatory.
Answer: We now increased the information given in the legends (page 32-36).
Reviewer #3:

Dear Professor Duffau, thank you for your helpful comments, which enabled significantly improvement of our manuscript.

Major revisions
The authors report a series of 47 gliomas, which were initially considered as inoperable in another institution, due to their location in eloquent areas. Thanks to the use of intrasurgical mapping and monitoring techniques, gross total resection was finally achieved in 74% of cases, with 8.5% of permanent neurological worsening. This is an interesting article. The rationale of this study is original. The results are well presented and well discussed. These data support the fact that neurosurgeons should be careful before to tell that a tumor cannot be removed. Thus, this paper may be useful for the neuro-oncological community.

1) However, the recent article by Chang EF et al., J Neurosurg 2011 should be cited and discussed, because it previously showed that the use of intrasurgical mapping allowed the resection of gliomas which involved areas wrongly considered as being crucial - and resulted in an improvement of overall survival.
Answer: Thank you for this important comment! We added this crucial work to the manuscript (page 17).

2) In addition, the authors cannot write that "The nTMS data regarding language mapping offered valuable information for the surgeon in advising our patients and planning the surgery" (page 15). Indeed, there are no data in this article demonstrating such an assertion.
Answer: You are right. We deleted this sentence but added a reference with fits nicely to this subchapter (page 18).
Reviewer #4:

Dear Dr. Kaloshi, we thoroughly considered all your comments. Below you will find our answers to your concerns.

There is a clear need to find more effective ways to perform as maximal resection as possible for patients with gliomas. Unfortunately, given the very heterogeneous group of patients, it is difficult to draw any meaningful conclusions from this report. Therefore, while the issue is interesting, the gain of knowledge is limited.

Concerns:
1) Abstract page: there are some lacking or unclear data
   - Results paragraph. Since it is one of the most important prognostic factors and could therefore influence survival times, the median Karnofsky Performance Score of the study population should be described in this section.
   Answer: KPS is now mentioned (page 2).

   - Results paragraph. Line 19-20. in the sentence, the ranges of median survival are “4 weeks – 64.5 months” seem to be erroneous because in the results section of the article are “4 weeks – 20.5 months”
   Answer: You are right (page 2).

   - Data on histology and extent of resection are missing.
   Answer: We added the histology part to the abstract. However, extent of resection was already within the manuscript (page 2).

2) Methods section;
   - Patients paragraph, line 18-19. the sentence “twenty-nine patients… (the sum of the number of patients is 28 (3+8+17).
   Answer: You are right. There were 9 cases of gliomas with WHO grade III (page 6).

3) Results section:
   - Line 1-2: the sentence “awake surgery was performed in 8 cases, whereas 38 cases were performed…” It remains one patient (out of 47) without a defined approach?
   Answer: No, there were 8 awake cases and 38 MEP cases, whereas 3 cases had both. Thus, 4 cases underwent surgery without MEP or awake monitoring. However, we added this information to clarify this point (page 12).
- The median KPS and the range should be specified and described in this section.
  Answer: It is now mentioned within the text on page 16.

- It is not clear if a previous therapy (i.e. temozolomide) had an impact in making possible the GTR in primarily evaluated non-resectable glioma.
  Answer: No, the patients presented after non-resectability was noted after any adjuvant therapy. We added this information to page 36.

- It would be of great interest to know the prognostic impact of the maximal resection in grade II, III and IV gliomas.
  Answer: With regard to the number of patients in each group, the subgroups are too small for such a statistical analysis. Thus, this study has to be considered as a pilot study. Yet, we added this very important aspect to page 17.

4) An example of a gross total resection is not provided.

  Answer: We added such an example (Fig. 1).