Peer Review File

Reviewer A

Comment 1: Overall a good analysis; would like to see some discussion on how to address the controversy surrounding the use of Ki67 in prognostication that might strengthen a case for wider use.

Reply 1: We added a discussion considering the use of Ki-67 in prognostication.

Literature data considering prognostic value of Ki-67 remains controversial. In a retrospective study including 30 atypical meningioma, Ki-67 rate was not significantly an unfavorable factor of recurrence (p=0.58) (Kim et al., 2012). Yang et al. observed similar result regardless of histological grade (Yang et al., 2008). In both studies, Ki-67 cut-off was low (8% and 3.2%, respectively). On the other hand, several retrospective studies including between 50 and 205 atypical meningiomas reported a statistically significant correlation between Ki-67 rate and recurrence (Barrett et al., 2019; Champeaux et al., 2017; Choi et al., 2015; Kim et al., 2012; Nanda et al., 2016; Yamaguchi et al., 2014). Except Kirn *et al.* study, all those studies had a Ki-67 threshold between 10 and 15%. Considering literature data, Ki-67 rate seemed to be an unfavorable factor of recurrence in atypical meningioma with elevated expression of this proliferative index. The lack of a consensus definition of cut-off value is the main contributor toward heterogeneity.

Changes in the text: Discussion section: Line 192 – 202

Comment 2: Line 104: What were the radiation therapy procedures used in the other 24 patients?

Reply 2: Data considering radiation therapy procedure used in the other 24 patients are missed data.

Changes in text: Results section: Line 113-114

Comment 3: Line 137: Contradicts info given in lines 128-135; please clarify.

Reply 3: We clarified the information given in lines 128-135.

Extent of surgery had no significant impact on PFS (p=0.4) and on OS (p=0.5) for patients with a Ki-67>17.5% while it significantly improved PFS (p=0.05) and tended to improve OS (p=0.06) for patients with a Ki-67<17.5%. Considering patients with a Ki-67>17.5% and who received adjuvant radiotherapy, PFS (14.8 vs 2.8 months, p=0.4) and OS (p=0.7) times were longer but significance was not reached.

Changes in text: Results section: Line 141 – 145

Comment 4: Line 156: Was the Simpson grading system used to evaluate extent of resection for patients analyzed in your study? If so, please include a discussion of this in the Methods and Results sections.

Reply 4: We included a discussion considering Simpson grading system used to evaluate extent of resection.

The quality of surgery was defined according to the Simpson classification. Total resection was defined as Simpson grade 1, 2 and subtotal resection was defined as Simpson grade 3, 4, 5.

Change in text: Methods section: Line 82 – 84

Comment 5: Line 222: The use of progesterone expression rate in the prognostication of meningioma is controversial, and the manuscript would benefit from a discussion on this and its potential relationship to somatic mutations such as PIK3CA. Perhaps this is something to explore in a future analysis.

Reply 5: We added a discussion considering use of progesterone expression in the prognostication of meningioma.

Several studies reported an impact of progesterone receptor expression in the prognostication of meningioma. Hsu et al. observed a correlation between negative PR expression and a higher Ki-67 index ($p<0.0001$). In this retrospective study including 70 meningiomas all grade, OS was statistically lower for patients with a negative expression of PR ($p<0.0001$) (Hsu et al., 1997). In a prospective study including 90 meningioma all grade, Mukhopadhyay et al. reported a correlation between high proliferation index, negative PR expression and histological grade II or III (Mukhopadhyay et al., 2017). Roser et al. reported the association Ki-67>4% and negative PR expression as an unfavorable prognostic factor in totally removed meningiomas (Simpson I and II) (Roser, 2004).

Change in text: Discussion section: Line 203 – 213

Reviewer B

Major comments:

Comment 1: It is unclear how PFS and OS were defined. Is PFS the time to re-intervention? Why is death of any cause a definition of PFS? These patients should be censored, also in the OS graph. How can median OS be >20 years (line 138) if patients were diagnosed 2008-2018? A flow chart defining screening and inclusion/exclusion of patients should be added.

Reply 1: We clarified PFS and OS definition. We clarified the result reported in line 138. We added a flow chart defining inclusion/exclusion of patients.

Progression-free survival (PFS) time was defined from the disease diagnosis to progression confirmed by brain RMI.

Overall survival (OS) time was defined from the diagnosis to the date of death or last report.

We retrospectively included 216 patients treated for a grade II meningioma in six centers in France between January 2008 and December 2018. Among them, 25 recurrent grade II and 10 grade I transformed into grade II meningiomas were diagnosed at first time between 1988 and 2007.

Change in text: We clarified PFS and OS definition in Methods section: Line 86 - 88. We added a flow chart in Results section. We clarified inclusion period in Result section: Line 104 - 107.

Comment 2: "According to national laws, approval from the ethics committee was not mandatory." Approval from a local ethics committee is mandatory, or the respective legislation should be cited. Why was informed consent sought from all patients if no ethics approval is required?

Reply 2: We clarified the information considering ethics committee.

Considering the retrospective nature of the study, no ethics committee was mandatory. No patients written consent are needed.

Change in text: Methods section: Line 88 - 90

Comment 3: The description of results should be more precise. E.g., line 99 "median age at diagnosis"; line 105-112: is "adjuvant radiotherapy" first-line? Adjuvant means that there is residual tumor, but do the authors really refer only to patients with incomplete resection? Do the authors refer to radiotherapy at recurrence? How can radiotherapy be performed "more often" – more patients received radiotherapy, correct? How many patients received which systemic therapy?

Reply 3: We make a more precise description of results. We clarified "median age" line 99, adjuvant radiotherapy line 105-112, and radiotherapy at recurrence. We added the number of patients which received systemic therapy.

"median age" was changed into "median age at diagnosis"

Adjuvant radiotherapy means radiotherapy after the first surgery regardless of extent of surgery.

At time of recurrence, use of radiotherapy was higher for patients who did not receive radiotherapy after the first surgery.

Fifteen patients received systemic therapy mainly based on bevacizumab (7), sunitinib (2) chemotherapy (hydroxyurea (2) and temozolomide (1) or somatostatin analog (3).

Change in text: We clarified the data considering median age, adjuvant radiotherapy, radiotherapy at recurrence and systemic therapy in Methods section (Line 81 - 82) and Results section (Line 114 - 119).

Comment 4: Discussion: A few other factors could be discussed. What about molecular prognostic factors, e.g., methylation classes – could such be associated with Ki-67? What about pre-operative embolization, which was suggested to be associated with inferior PFS? Limitations could be discussed in more detail

Reply 4: We added a discussion about molecular prognostic factors, mainly methylation classes and pre-operative embolization. We discussed limitations in more detail.

Few others factors have a prognosis value. Sahm et al. described 6 distinct methylation classes of meningioma using genomic analysis. This molecular classification had high prognosis power (Sahm et al., 2017). In a large retrospective study, recurrence rate was statistically higher for grade II/III (p=0.029) or intermediate/malignant methylation subtype (p=0.005) meningioma treated with pre-operative embolization compared to those without (Wirsching et al., 2018).

Retrospective nature of this cohort is the main limitation. Moreover, definition of Ki-67 was not similar between the 6 centers, there was a heterogeneity about Ki-67 value. Criteria to use adjuvant radiotherapy are not similar between the 6 centers, there was no consensus.

Change in text: We added a discussion considering molecular prognostic factors in Discussion section (Line 238 - 240). We added a discussion about pre-operative embolization in Discussion section (Line 240 - 242). Limitations were discussed in more detail in Discussion section (Line 243 - 245)

Minor comments:

Comment 1: 1. Abstract: line 50 – "did not reach statistical significance" should state the p value and read "was associated with XYZ by trend only"

Reply 1: We changed "did not reach statistical significance into "was associated with XYZ by trend only". We added p-value.

Progression-free survival (p=0.3) and overall survival (p=0.7) were associated with adjuvant RT by trend only.

Change in text: in the Abstract: Line 50 - 51

Comment 2: 2. Abstract: conclusion first sentence – please reword "the only significant recurrence prognosis."

Reply 2: We reworded "the only significant recurrence prognosis"

Ki-67 proliferative index was significantly associated with recurrence.

Change in text: in the Abstract: Line 55

Comment 3: Line 69: please refer to the EANO guideline (Goldbrunner et al. Lancet Oncol)

Reply3: Line 69, we referred to EANO guideline.

Change in text: in Introduction section: Line 70

Comment 4: Line 78: if available, Simpson grade should be added

Reply 4: We added Simpson grade.

The quality of surgery was defined according to the Simpson classification. Total resection was defined as Simpson grade 1, 2 and subtotal resection was defined as Simpson grade 3, 4, 5.

Change in text: in Methods section: Line 82 - 84

Comment 5: Line 94/95: How were cutoffs by ROC curve analysis defined? This sentence is incomprehensible, please reword.

Reply 5: The ROC curve was used to define the Ki-67 threshold value.

Change in text: in Methods section: Line 100 - 101

Comment 6: Line 103: "grays" shoud read Gray or Gy

Reply 6: We changed "grays" into Gy.

Change in text: in Results section: Line 111

Comment 7: How were HR calculated? Cox regression?

Reply 7: HR was calculated with a Cox regression

Change in text: in Methods section: Line 98