Added value of 18F-FDOPA PET to the management of high-grade glioma patients after their initial treatment: a prospective multicentre study

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Abstract

Background. Diagnostic value of 18F-fluoro-L-dihydrophenylalanine (18F-FDOPA) PET in patients with suspected recurrent gliomas is recognised. We conducted a multicentre prospective study to assess its added value in the practical management of patients suspected of recurrence of high-grade gliomas (HGG).

Methods. Patients with a proven HGG (WHO grade III and IV) were referred to the multidisciplinary neuro-oncology board (MNOB) during their follow-up after initial standard of care treatment and when MRI findings were not fully conclusive. Each case was discussed in 2 steps. For step 1, a diagnosis and a management proposal was made only based on the clinical and the MRI data. For step 2, the same process was repeated considering the 18F-FDOPA PET results. A level of confidence of the decisions was assigned to each step. Changes in diagnosis and management induced by 18F-FDOPA PET information were measured. When unchanged, the difference in the confidence of the decisions was assessed. The diagnostic performances of each step was measured.

Results. 107 patients underwent a total of 138 MNOB assessments. The proposed diagnosis changed between step 1 and step 2 in 37 cases (26.8%) and the proposed management changed in 31 cases (22.5%). When the management did not change, the confidence in the MNOB final decision was increased in 87 cases (81.3 %). Step 1 had a sensitivity, specificity and accuracy of 83%, 58% and 66% and step 2, 86%, 64% and 71% respectively.

Conclusion. In case of equivocal MR findings, 18F-FDOPA PET adds significant information for the follow-up of HGG patients in clinical practice.

Introduction

High-grade gliomas are the most frequent malignant brain tumors in adults [1]. There is a consensus on the initial treatment based on surgery, radiotherapy and chemotherapy. Unfortunately, the responses to this standard-of-care are not durable and additional treatments are necessary and can involve re-irradiation, alternative chemotherapy, clinical trials for innovative drugs and/or re-resection. Standard-of-care in this setting of recurrence is far less well defined [2] and the prognosis remains poor with rare long term survival [3].

During follow up of initially treated patients and when recurrence is suspected, individual decisions about continuation, modification or discontinuation of treatment are usually based on MRI imaging. However, the initial therapeutic strategies, beside their effectiveness on the tumours, also induce effects on the surrounding tissues. These posttreatment changes are responsible for complex MRI modifications, in particular on contrast enhancement which was the core of the initial structural Macdonald criteria [4]. Therefore, new criteria have been proposed to cope with these phenomena [5], but it is clear that structural imaging alone is limited in that setting and that advanced multimodal imaging is important to improve the non-invasive characterisation of post-therapeutic changes in brain tumours [6, 7]. Advanced

MRI techniques including perfusion weighted diffusion weighted imaging and spectroscopy are very helpful but suffer yet from a lack of standardization [8, 9] [10]. Despite these difficulties, MRI remains the corner stone of high-grade gliomas patients follow-up but additional work is needed to improve response assessment [11].

PET using radiolabelled amino-acids analogues is a recommended complementary method as proposed by Albert et al. [12]. In the setting of posttreatment evaluation, amino acid PET has demonstrated a high sensitivity and specificity for the differentiation between progression and treatment-related changes. This is true for the 3 mostly used labelled amino acid and analogues: 11C-methyl-methionine, 18F-fluoroethyl-L-thyrosine (18F-FET) and 18F-fluoro-L-dihydrophenylalanine (18F-FDOPA). The increased of amino acids in brain tumours is related to the over-expression of the amino-acid transporter LAT-1 in tumour cells and their vasculature [13, 14]. Since LAT-1 is normally expressed at the blood brain barrier, these compounds do not need blood brain barrier breakdown like contrast media to be taken up by brain lesions. The use 11C-methyl-methionine is limited to the centres with onsite cyclotrons. Amino acids labelled with 18F-fluorine were developed in order to be distributed more widely. 18F-FET and 18F-FDOPA have shown very similar behaviour and usefulness in brain tumour imaging as 11C-methyl-methionine. The main difference between 18F-FET and 18F-FDOPA is the physiological striatal uptake for the latter. This normal striatal uptake of 18F-FDOPA is a significant advantage since it gives an internal normal reference. Its drawback is the potential difficulty to separate this activity from tumour uptake when the tumour is adjacent to the striatum.

18F-FDOPA PET has demonstrated a higher accuracy than MRI in the differentiation of glioma recurrence from treatment-induced changes [12]. However, in practice, MRI remains the necessary first performed study and 18F-FDOPA PET is used in association. Its added value ultimately lies in its capability of changing treatment decisions [15]. Therefore, prospective studies assessing its impact on patients' management in those conditions are necessary.

Two monocentric studies have addressed this issue. Walter et al. [16] first studied 58 patients with high and low grade brain tumors in different settings and found that 18F-FDOPA changed the intended management in 41% of the cases. However, the study did not include MRI in the decision process. More recently Humbert et al. [17] studied the impact of the 18F-FDOPA results along with MRI, on a multidisciplinary brain tumor board decisions. They studied 56 glioblastoma patients and 41 with brain metastases in the setting of residual disease and recurrence. Treatment plans were changed in 33.3% of the glioblastoma patients and in 17% of the metastatic ones.

We conducted a multicentre prospective study to assess the added value of 18F-FDOPA PET to conventional clinical and MRI based decision making in the specific setting of posttreatment evaluation of patients with high-grade gliomas in daily practice, namely in the differential diagnosis between recurrence/progression and treatment-induced changes.

Materials And Methods

Patient selection criteria

It was a multicentre, open, uncontrolled and non-randomized study designed to evaluate the added value au 18F-FDOPA to the conventional management of high-grade glioma patients.

The study (N° ID-RCB: 2015-A00520-4) was conducted prospectively in 5 French University Hospitals from January 2016 to February 2019 under the leadership of the Centre Antoine Lacassagne. Each case was discussed during each institution weekly Multidisciplinary Neuro-Oncology Board (MNOB) meetings.

The study was approved by the Ethic Committee, the Agence Nationale de Sécurité du Médicament (ANSM) and registered (https://clinicaltrials.gov/ct2/show/NCT02631655) in 2015.

Inclusion criteria were (i) histopathologically proven high-grade gliomas (WHO grade III and IV); (ii) age more than 18 years; (iii) signed informed consent; (iv) patients referred to the multidisciplinary neuro-oncology board (MNOB) of each institution in the setting of decision making in the follow-up after initial standard of care treatment (surgery and radio-chemotherapy) and (v) patients for whom MRI findings were not leading to a high confidence level in the decision to be made by the MNOB.

Study design (Fig. 1)

Each patient's case was presented and discussed during the weekly meetings of the MNOB of each institution. The MNOB included neuro-oncologists, neurosurgeons, radiologists, pathologists and radiotherapists. The presence of a nuclear physicians was not mandatory.

The review process included systematically 2 steps. During step 1, the MNOB discussion was only based on the clinical data and the MRI findings (including all available sequences) without knowledge of the 18F-FDOPA results. This discussion led to a first diagnostic and a first management proposal. The possible diagnostic proposals were: complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD). The possible management proposals were: continuation of the same treatment modality or change of treatment modality. Changes in treatment modalities included, surgery, re-irradiation, different chemotherapy or treatments stop (supportive care). The confidence level of this first proposal was assessed using a 3 level confidence score.

During step 2, the same case was discussed again by the MNOB including, that time, the 18F-FDOPA PET images. With this additional information, a second diagnostic and management proposal were made. The same proposals as in step 1 were possible and a new confidence level was attributed.

The step 1 and step 2 proposals were compared and when unchanged, the levels of confidence were taken into account.

Patients had a systematic clinical follow-up at 3 months after the MNOB. If appropriate, the same patient could be studied again within 12 months from his/her inclusion. Therefore, the same patient could

undergo several MNOB reviews during his follow-up period. Clinical data and, if surgery occurred, pathological data were collected.

Objectives of the study

The primary objective was to measure the changes in diagnosis and management proposed by the MNOB induced when taking into account the 18F-FDOPA PET information by comparing diagnostic proposals and management proposals 1 and 2.

The secondary objectives were: (i) to measure the difference in the confidence of the decisions when diagnostic and management were not changed by comparing the confidence levels in those cases and (ii) to evaluate the diagnostic performances of 18F-FDOPA in terms of sensitivity, specificity and accuracy for the diagnosis of progression or recurrence when compared to pathology when available or to the radiological and clinical follow-up. The radiological and clinical data used as diagnostic reference were those collected during the systematic 3 months visit after the MNOB decision.

PET imaging

18F-FDOPA PET static acquisitions were started between 10 to 20 minutes post injection [18] (mean acquisition delay 18 ± 5 min) of 3 MBq/kg of 18F-FDOPA (mean 173.8 ± 41.7 MBq). Image reconstructions were performed using OSEM methods including the conventional corrections [18].

For analysis by the MNOB, PET images were co-registered to post-contrast T1-weighted MR images obtained within 28 days from the PET study. Other MRI sequences were used for the first diagnosis and management procedure including T2-weigheted FLAIR. Diffusion and perfusion imaging as well as proton-spectroscopy were not performed systematically but used when available.

PET images were displayed using a colour scale which maximum was set on the striatal region. The criteria for 18F-FDOPA PET analysis were only visual according to the following 4-point scale [19, 20]: 0, no detectable lesion uptake; 1, detectable lesion uptake but less than striatum uptake; 2, lesion uptake equivalent to striatum uptake and 3, lesion uptake greater than striatum uptake. 18F-FDOPA was considered positive in favour of recurrence or progression if the visual scale score was equal or greater than 2.

Statistical analysis

The required number of patient cases to be evaluated was calculated prior to the start of the study to be 110 (taking into account 10% of wrongly included patients, lost to follow-up or withdrawn from the study). Data entry and management were performed on the capture system (Ennov Clinical). Categorical data are shown as counts and percentages and continuous variables as means with standard deviations. Comparisons were evaluated using χ^2 test or Fisher's exact test for categorical data and Student's test or Wilcoxon's test for continuous variables. Statistical analyses were performed with SAS software version 9.4 (SAS Institute Inc) and R 3.6.0 (R Foundation) on Windows® and the caret and DTComPair packages. Results were considered statistically significant at a p value of less than 0.05 (two-sided).

Results

Patient population

One hundred and ten patients were included. Three of them did not meet the inclusion criteria (Fig. 2) leading to a studied population of 107 patients (62 males and 45 females) of median age 56 years (range 19–83). Patients' characteristics are given in Table 1. Ninety-one patients (85%) had a glioblastoma and 16 a WHO grade III glioma (15%). IDH1 was mutated in 13 patients (12.1%), wild-type in 73 patients (68.2%) and NOS in 21 patients (19.6%).

Table 1
Patients' characteristics

Variables	Values
Age, median (range)	56 (19–83)
Sex, n (%)	
Male	62 (57.9)
Female	45 (42.1)
Initial surgery, n (%)	
Biopsy only	38 (35.5)
Partial resection	31 (29.0)
Subtotal resection	33 (30.8)
Unknown	5 (4.7)
Pathology, n (%)	
Glioblastoma (WHO grade IV)	91 (85.0)
WHO Grade III	16 (15.0)
IDH status, n (%)	
IDH-Wild type	73 (68.2)
IDH-mutated	13 (12.1)
NOS	21 (19.6)
MGMT promoter status	
Methylated	23(21.5)
Unmethylated	13(12.1)
Unknown	71(66.4)
Treatment prior to MNOB, n (%)	
Surgery and radio-chemotherapy	89 (83.2)
Surgery and chemotherapy	10 (9.3)
Surgery and radiotherapy	3 (2.8)
Radio-chemotherapy	2 (1.9)
Others	3 (2.8)

In the majority of the cases, patients were studied after having undergone surgery and received radiotherapy and concurrent adjuvant temozolomide (Stupp) (89 patients; 83.2%).

Seventy-six patients (71%) completed 12 months follow-up, 31 (29%) had incomplete follow-up due to patient's death in 25 cases, lost of site in 5 and unknown reason in one case.

Results of 18F-FDOPA on Multidisciplinary Neuro-Oncology Board decisions

The 107 patients underwent a total of 138 18F-FDOPA PET studies leading to 138 MNOB assessments (Fig. 2). Eight patients (7.5%) underwent 3 18F-FDOPA PET studies and 3 MNOB evaluations; 15 (14%) 2 and 84 (78.5%) one. Therefore, the value of 18F-FDOPA PET could be evaluated in 138 instances.

The proposed diagnosis was unchanged between step 1 and step 2 of the MNOB assessment in 101 cases (73.2%): 3 CR, 7 PR, 26 SD and 65 PD. It was changed in 37 cases (26.8%) to disease downstaging in 23 cases (16.7%) and upstaging in 14 cases (10.1%) (Table 2).

Table 2
Diagnostic proposals for step 1 and step 2

		Step 1 (MR) diagnosis			
		CR	PR	SD	PD
Step 2	CR	3	2	7	2
(18F-FDOPA + MR) diagnosis	PR	1	7	4	0
	SD	0	0	26	8
	PD	2	1	10	65

The proposed management between step 1 and step 2 (without and with 18F-FDOPA PET data) was unchanged in 107 cases (77.5%) and changed in 31 cases (22.5%). 18F-FDOPA PET data led the MNOB to change his management proposal in favour of introducing a new chemotherapy in 14 cases, continuing the same treatment in 10 cases, surgery in 3 cases, radiotherapy in 2 cases and to stop any treatment in 2 cases (Table 3).

Table 3
Management proposals for step 1 and step 2

		Step 1 (MRI) management proposals				
		Continue same treatment	Surgery	Re-irradiation	New chemotherapy	Stop treatments
Step 2 (18F-FDOPA + MR) management proposals	Continue same treatment	47	1	0	7	2
	Surgery	2	3	0	1	0
	Re-irradiation	2	0	8	0	0
	New chemotherapy	11	0	2	34	1
	Stop treatments	0	0	1	1	15

When the proposed management was unchanged, 18F-FDOPA PET increased the confidence in MNOB's decision in 87 cases (81.3%), did not change it in 16 cases (15.0%), decreased the confidence in 1 case (0.9%) and was not evaluated in 3 cases (2.8%).

Diagnostic accuracy of each step

Considering as gold standard the results of surgery in five cases and the 3 months radiological and clinical follow-up for the rest, step one of the process including only clinical and MR data diagnosed PD (progression/recurrence) with a sensitivity of 83% [IC95%: 82–85], a specificity of 58% [IC95%: 57–59] and an accuracy of 66% [IC95%: 57–74].

Step 2, including 18F-FDOPA PET results diagnosed PD (progression/recurrence) with a sensitivity of 86% [IC95% : 85–88], a specificity of 64% [IC95% : 63–65] and an accuracy of 71% [IC95% : 63–78].

Discussion

To our knowledge, this is the first prospective multicenter study of the impact of 18F-FDOPA PET on the clinical management of high-grade gliomas in the setting of suspicion of recurrence after initial treatment. In the framework of effectiveness of diagnostic imaging [21], it corresponds to a level 3 type study of "diagnostic efficacy thinking" assessing the post-test changes induced by 18F-FDOPA PET imaging. It shows that 18F-FDOPA changed the MRI based intended management in 31 cases (22.5%) and increased the confidence in the initial decision when unchanged in 87 cases (81.3%).

In her study, Walter et al. [16] first studied 58 patients with high and low grade brain tumors in different settings and found that 18F-FDOPA changed the intended management in 41% and the management changes were actually implemented in 31% of the cases. Unlike in our study, the clinical situations of 18F-

FDOPA PET indications were diverse and PET data were not analyzed back to back or coregistered with MRI. However, the majority of the patients were studied in the context of suspected recurrence and MRI changes; the reported impact on the intended management in this subgroup was also 41%. This study included 38% of non WHO III or IV grades. The specific impact in low versus high-grade brain tumor management or in initial versus follow-up setting is unknown. This higher impact of 18F-FDOPA is probably mostly due to the study design based on a 3 questionnaires survey sent to the referring physician in Walter's study whereas in our case these changes were decided on multidisciplinary bases in a directly operational setting. Walter et al. reported a possible bias toward favoring 18F-FDOPA PET in their study since the referring physicians were convinced 18F-FDOPA PET users. This was not the case in our study.

Humbert et al. [17], addressed a similar issue using 18F-FDOPA PET. The design of the study was the same as our, however this was a prospective monocentric study which included brain metastases as well as high-grade gliomas during the follow up after initial treatment. Furthermore, within the high-grade glioma patients, only 12 were studied for the diagnosis of tumor recurrence. In that subgroup the management was changed in one third of the case. Our study found a smaller percentage of 22.5% which is likely to be more realistic since obtained on 138 studied cases studied in 5 different institutions.

Other studies addressed a similar issue using other radiopharmaceuticals. Hillner et al. [22] investigated a large series of 367 patients with primary brain tumors from the National Oncological PET registry who underwent 18F-FDG brain PET. They analyzed pre and post PET forms filled by the referring physician and found 38.2% of intents of management changes in light of the 18F-FDG PET findings. However, the article could not document if the planned management changes were actually completed.

Yamane et al. used 11C-methionine PET to separate recurrence from radiation necrosis in brain tumors and its clinical impact based on retrospective questionnaires to the referring physicians. Twenty PET studies were performed for initial diagnosis of brain tumors and 69 for differentiating tumor recurrence from radiation necrosis. In this last subgroup which included various grades of primary brain tumors and metastases, intended management was confirmed in 42 cases and a significant management change due to PET results was found in 18 cases (42.9%).

Brendle et al. very recently published a study that addressed a similar issue using 18Ffluoroethyl-tyrosine (18F-FET) and multiparametric simultaneous PET-MR [23]. In their subgroup of 131 patients studied during the disease course, they demonstrated a changed in patients' management in 53% of the cases. However, this was a monocentric retrospective study which, by design, did not separate MR form PET induced changes. Nonetheless, it brings forward the interest of PET/MR in that indication as well as the value of dynamic PET data which was not evaluated in our study.

Overall, our study performed prospectively in 5 different centers, shows a slightly inferior rate of changes of patients' management induced by 18F-FDOPA PET than reported in the literature. However, this is more likely to be generalizable. Furthermore, our study also shows that, when the decision itself was not modified, 18F-FDOPA results increased the confidence of the decision in more than 80% of the cases.

In the literature, the performances of 18F-FDOPA are generally reported as superior to MRI for the diagnosis of HGG recurrence [12, 24, 25]. However, it should be pointed out that, in our study, we measured the performances of step 2 process. 18F-FDOPA performances were not assessed independently from those of MRI since both information were taken into consideration at this step. This correspond to daily practice in which 18F-FDOPA is usually not interpreted without the MRI findings. However, we observe a sensitivity and a specificity of 86% and 64% which are rather in the lower range of the generally reported values for 18F-FDOPA PET alone in that indication [19, 24–26] reflecting the multicenter design of our study.

One limitation of the study concerns the diagnostic performances which were evaluated on surgical confirmation in only 5 cases. Furthermore, our study did not consider the use of a semi-quantitative analysis of 18F-FDOPA images. However, the visual analysis reflects the most common daily practice and neither quantitative static analysis [19] nor dynamic analysis [27] has been shown to be superior to visual analysis in that setting. The only exception is very recent the Brendle study [23]in which maximum Tumor to Background Ratio on static 18F-FET and the presence of a washout curve in the kinetic PET analysis appeared as an important parameter. Lastly, the study evaluated the changes in the management induced by the 18F-FDOPA PET without assessing the impact on patient survival. A prospective study comparing the prognosis and the quality of life of patients who benefited from 18F-FDOPA PET information to patients treated without this additional information is necessary to fully answer this question.

Conclusion

In high-grade gliomas patients suspected of recurrence, 18F-FDOPA PET adds information, which helps distinguishing between true tumor progression and therapy-related alterations when MRI findings are not straightforward. It demonstrates a clinical benefit that can accelerate changes in management's decision in patients with reduced life expectancy.

Statements And Declarations

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Competing interests

The authors have no relevant financial or non-financial interests to disclose

Author contributions

Study design and writing – original draft preparation: Jacques Darcourt, Antoine Verger. Patients inclusions and data acquisitions: Jacques Darcourt, Véronique Bourg, Marie Blonski, Fabien Almeirac, Lidiane Mondot, Florence Le Jeune, Laurent Colombier, Aurélie Kass, Luc Taillandier, Antoine Verger. Data management: Renaud Schiappa. Statistical analysis: Jocelyn Gal. Writing - review and editing: All authors read, edited and approved the final manuscript.

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Figures

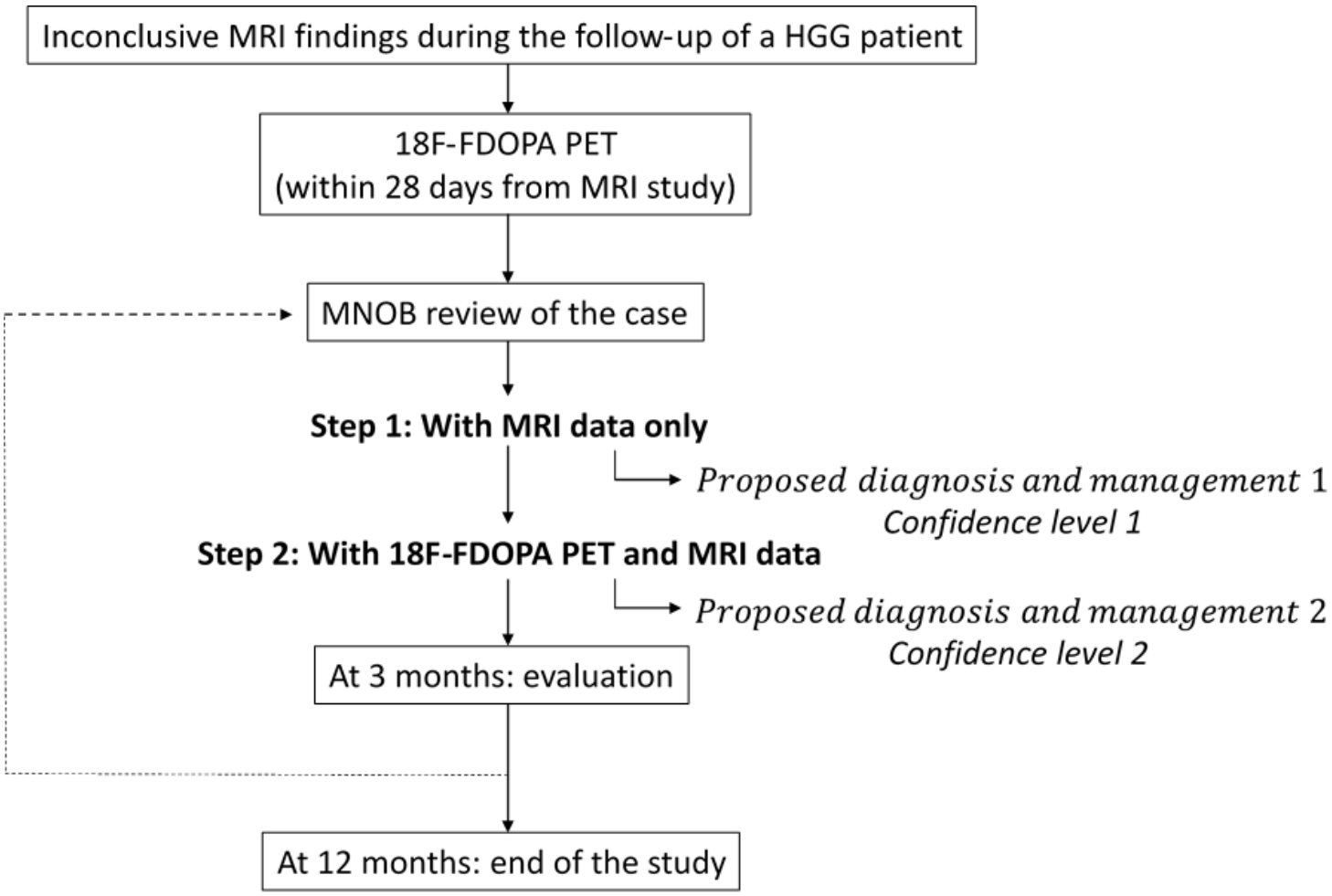

Figure 1

Study design

Abbreviation: MNOB = Multidisciplinary Neuro Oncology Board

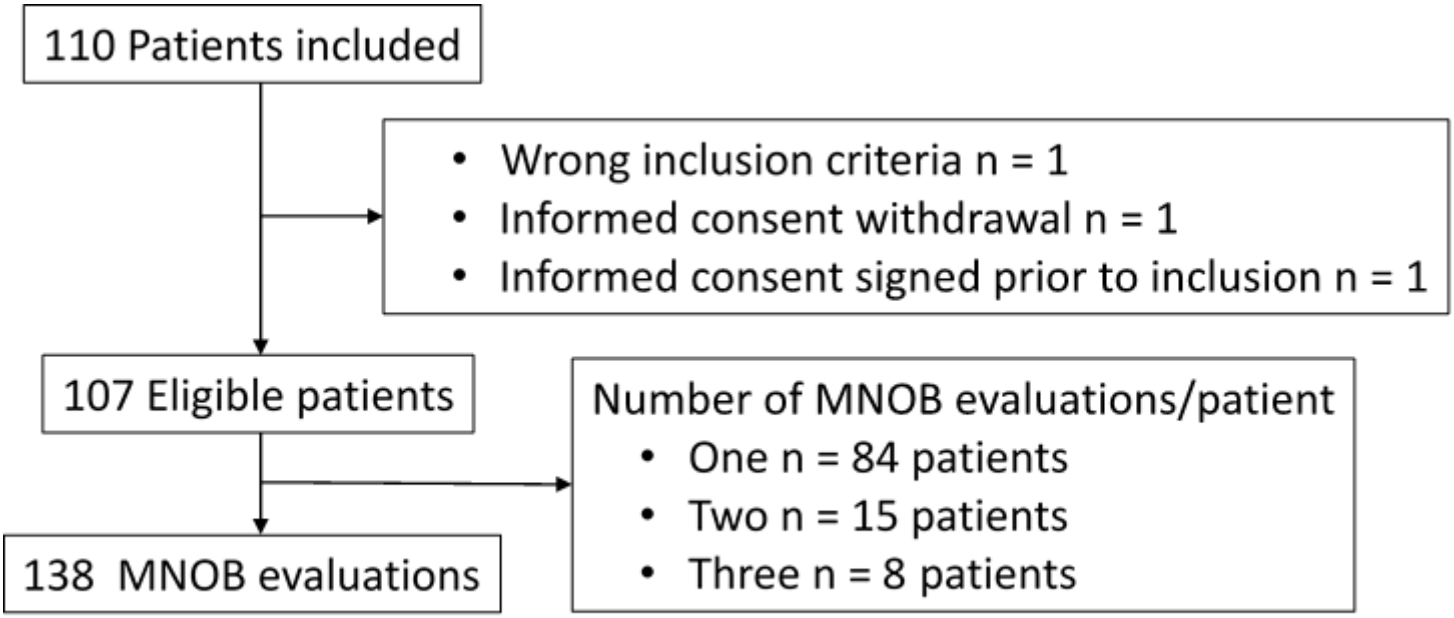

Figure 2

Patient's Inclusion/exclusion criteria and follow-up

Abbreviation: MNOB = Multidisciplinary Neuro Oncology Board