FDG-PET predicts survival in recurrent high-grade gliomas treated with bevacizumab and irinotecan

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Prognosis of recurrent high-grade glioma (HGG) is poor, although bevacizumab has been documented in that context. This study aimed to determine the independent prognostic value of fluorodeoxyglucose (FDG)-PET on progression-free survival (PFS) and overall survival (OS) of recurrent HGG after combined treatment with bevacizumab and irinotecan, compared with other documented prognostic variables. Twenty-five adult patients with histologically proven HGG were included at recurrence. Brain FDG-PET imaging was performed within 6 weeks of starting chemotherapy with bevacizumab and irinotecan. Response based on MRI was assessed every 2 months according to revised assessment in Neuro-Oncology (RANO) criteria. Median PFS and OS were 4 months (range, 0.9–10.4 months) and 7.2 months (range, 1.2–41.7 months), respectively. At 6 months, PFS and OS rate were 16.0% and 72.0%. FDG uptake was the most powerful predictor of both PFS and OS, using either univariate or multivariate analysis, among all variables tested: histological grade, Karnofsky performance status, steroid intake, and number of previous treatments. Moreover, FDG uptake was also prognostic of response to bevacizumab-based therapy. This study provides the first evidence that pretreatment FDG-PET can serve as an imaging biomarker in recurrent HGG for predicting survival following anti-angiogenic therapy with bevacizumab.

Keywords: anti-angiogenic treatment, FDG-PET, prognosis, recurrent high-grade glioma.

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also been recently reported as a strong predictor of survival in 596 recurrent malignant gliomas. On the other hand, a pilot PET study, performed on 19 patients, suggested that a proliferation PET tracer, 18F-3′-deoxy-3′-fluorothymidine (FLT), may be of interest to predict survival after anti-angiogenic treatment. Early changes in FLT uptake between baseline and post-bevacizumab PET examinations predicted OS and tended to predict progression-free survival (PFS). By contrast, isolated baseline uptake ratio had no predictive value on both PFS and OS. Thus, FLT-PET may help in deciding whether to stop or continue bevacizumab, but not to start it. More recently, a PET study using O-2-18F-fluoroethyl-L-tyrosine has suggested that this tracer could be predictive for treatment failure in patients with recurrent HGG who receive anti-angiogenic treatment.

Fluorodeoxyglucose (FDG), a radio-labeled glucose analogue, should also be an appropriate PET tracer to noninvasively assess the biological aggressiveness of tumors in vivo, as previously suggested for many types of cancers, such as lung, breast, head and neck, sarcomas, and lymphomas, because tumoral cells are precisely characterized by increased glycolytic metabolism in parallel with cellular proliferation and loss of differentiation. In neuro-oncology, the prognostic value of FDG in HGG was suggested, including for recurrent HGG. In addition, glucose metabolic rate assessed by FDG-PET has been positively correlated with angiogenesis markers, such as VEGF-R1 in gliomas, and microvessel density in lung adenocarcinomas. These findings suggest that FDG-PET is of specific prognostic interest in such cancers treated with anti-angiogenic therapy. To our knowledge, the prognostic value of baseline FDG uptake has never been addressed in the specific context of recurrent HGG treated with bevacizumab. However, FDG benefits from wide availability, lower cost, and further documented validation regarding prognosis, when compared with recent PET and SPECT amino acid and proliferation tracers, including FLT.

In the present study, we aimed to determine the independent prognostic value of baseline FDG uptake ratio on PFS and OS of recurrent HGG following combined treatment with bevacizumab and irinotecan, in comparison with the most documented prognostic variables.

Material and Methods

Patients

We retrospectively included adult patients with histologically proven HGG who underwent brain FDG-PET at our institution (Timone Hospital, Marseille, France) within 6 weeks before starting chemotherapy with bevacizumab and irinotecan for tumor recurrence. Diagnosis of tumor recurrence was based on sequential MRI. An MRI was performed in the week prior to bevacizumab initiation and then every 2 months up to progression. Time from the end of radiotherapy (with or without temozolomide) to the diagnosis of recurrence exceeded 3 months for all patients to avoid the risk of pseudo-progression. Written informed consent for care was obtained for each patient, and all clinical decisions were based on multidisciplinary consulting meetings.

The survival time was defined as from the start of chemotherapy with bevacizumab and irinotecan to the date of death for OS and to the date of relapse or progression for PFS. The follow-up consisted of a monthly clinical examination and a brain MRI every 2 cycles of bevacizumab. Progression was defined on the basis of the first documented evidence of disease progression, based on MRI and/or neurological deterioration and steroid intake, according to revised assessment in Neuro-Oncology (RANO) criteria.

Bevacizumab Administration

Bevacizumab-irinotecan was delivered in a compassionate setting. Each patient received 5 mg/kg bevacizumab intravenously (Avastin; Roche) and 125 mg/m² irinotecan intravenous infusion in 90 minutes (Campto; Pfizer), every 2 weeks until disease progression or development of unacceptable toxicity. In case of progression, the dose of bevacizumab was increased to 10 mg/kg. None of the patients included were receiving liver enzyme-inducing drugs.

PET Methods

FDG-PET was performed on hybrid PET/CT Discovery ST (General Electric Medical Systems) within 6 weeks before starting bevacizumab therapy, to document tumor recurrence. This is a 24-ring tomography machine that simultaneously acquires 47 slices of 3.27 mm thickness, with an intrinsic axial resolution of 5.2 mm (full width at half-maximum). FDG was synthesized according to the Hammacher method. Thirty minutes after intravenous injection of 111 MBq, 3D mode PET was scanned parallel to the orbitomeatal plane. Emission data were corrected for attenuation using a calculated correction-attenuation matrix. Images were reconstructed in axial, coronal, and sagittal planes, using a 3D OSEM iterative algorithm (5 iterations, 32 subsets), and visualized on Xeleris (GE Medical System) and SEGAMI/Mirage workstation.

The uptake of FDG was assessed independently by 2 experienced readers, blinded to clinical data and using 2 different grading methods:

1. the tumor maximal standardized uptake value (SUVMax), determined with a region of interest (ROI) placed in the tumoral area of highest uptake,
2. the T:CL ratio between the tumor and the symmetric contralateral SUVMax. When the tumor crossed the midline, the reference region of interest was determined on the anterior or posterior part of the brain slice, not affected by tumor.
**Statistical Considerations**

The major end point for the study was survival following the start of bevacizumab chemotherapy. PFS and OS were estimated using Kaplan-Meier analysis.

The following variables were tested in univariate analysis using the log-rank test or the Wald test in univariate Cox regression: age, KPS, histological grade (HG), number of previous treatments, corticotherapy (methylprednisolone; yes vs no), frontal localization (yes vs no), time from initial surgery to bevacizumab therapy, the SUVMax, and the T:CL ratio. KPS, in particular, was determined 1 day before starting anti-angiogenic treatment. The SUVMax and the T:CL ratio were dichotomized using the cutoff associated with the highest mean Youden Index for predicting both 6-month death and 6-month relapse. Sensitivity and specificity were calculated.

Then, a multivariate analysis was performed using the Cox regression model to assess survival probability. Variables were included in MVA according to univariate results ($P < .200$) and/or literature data regarding previously reported independent prognostic factors for recurrence (KPS, HG, and treatments). $P$ values <.05 were considered to be significant for each statistical analysis (SPSS, version 17.0, for Windows; SPSS).

**Results**

**Population and Follow-Up**

Twenty-five patients with recurrent HGG were included. According to WHO classification, the distribution of pathologic diagnosis at the time of registration was as follows: 20 GBM (WHO grade IV) and 5 anaplastic gliomas (WHO grade III; 2 of them deriving from a primary WHO grade II), including 4 pure oligodendrogliomas and 1 mixed oligoastrocytoma. The patients' characteristics are summarized in Tables 1 and 2.

After initial surgery, all patients underwent external radiation therapy and 1–3 different lines of chemotherapy before bevacizumab: temozolomide ($n = 25$), including first-line concomitant radiochemotherapy with temozolomide according to the Stupp regimen ($n = 18$); carmustine ($n = 3$), carmustine-impregnated

**Table 1. Individual characteristics of patients**

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Abbreviations: KPS, Karnofsky performance status; OS, overall survival; N/A, not available; PD, progressive disease; PFS, progression free survival; PR, partial response; SD, stable disease.

*PR (not confirmed at 2 months).
wafers mostly administered at time surgery for recurrence \( (n = 11) \); procarbazine-vincristine-lomustine polychemotherapy \( (n = 2) \); enzastaurin \( (n = 1) \); or carboplatin-etoposide \( (n = 1) \). The mean number of previous treatments was 1.8 (range, 1–3) for chemotherapy regimen and 1.4 for surgery (range, 1–2).

Patients received a median of 8 injections of bevacizumab (range, 2–16), corresponding to a median duration of treatment of 4 months. For 2 patients, bevacizumab treatment was interrupted because of severe toxicity (1 intracerebral hemorrhage and 1 intestinal perforation). However, all included patients received a minimum of 2 injections (1 month) of bevacizumab therapy.

The median follow-up period from the start of bevacizumab was 7.2 months (range 1.2–41.7).

Twenty-four patients (96%) progressed or relapsed after bevacizumab treatment. They were treated as follows: temozolomide \( (n = 6) \), carboplatin-etoposide \( (n = 6) \), lomustine \( (n = 1) \), procarbazine \( (n = 1) \), carmustine-temozolomide \( (n = 1) \), and no further treatment \( (n = 9) \).

At the end of the follow-up period, all 25 patients had died.

**Pretreatment FDG-PET Assessment**

PET was performed an average of 18.2 days (range, 2–42) before the start of bevacizumab therapy (Tables 1 and 2). The mean SUVMax was 9.4 g/mL (range, 2.3–28.9 g/mL), and the mean T:CL ratio was 1.6 (range, 0.6–3.6) (Tables 1 and 2). The mean SUVMax and the T:CL ratio did not significantly differ between histological grade III and IV \( (P = .736 \text{ and } .514, \text{ respectively}) \).

**MRI Response**

According to RANO criteria, 36 patients had partial response (PR), 7 had stable disease (SD), and 10 had progressive disease (PD) (Table 1). Analysis of variance showed statistically significant differences among these 3 groups of patients for the SUVMax \( (P = .0409) \) and with a trend for the T:CL ratio \( (P = .0695) \). Post-hoc least significant difference analysis showed a statistically significant difference between PR and PD and between PR plus SD and PD for the SUVMax and the T:CL ratio \( (P < .05) \) (Fig. 1).

**Survival and Prognostic Factors**

Median PFS and OS were 4 months (range, 0.9–10.4 months) and 7.2 months (range, 1.2–41.7 months), respectively. At 6 months, PFS and OS rate were 16.0% and 72.0%, respectively.

The results of univariate and multivariate analysis for PFS and OS are summarized in Tables 3, 4, and Fig. 2. Two examples of PET and MRI findings before bevacizumab are also reported in Fig. 3. The SUVMax and the T:CL ratio were dichotomized using the cutoff associated with the highest mean Youden Index for predicting both 6-month death and 6-month relapse (7.0 and 1.348, respectively).

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The results of univariate and multivariate analysis for PFS and OS are summarized in Tables 3, 4, and Fig. 2.

With regard to PFS and FDG uptake, the SUVMax and the T:CL ratio significantly predicted PFS \((P < .001, \text{ HR} = 8.09; \text{ HR} = 3.64, \text{ respectively})\). None of the other variables were significant prognostic factors on PFS in univariate analysis. In multivariate analysis,
the SUVMax and the T:CL ratio were the most powerful independent predictors of PFS ($P = .001$, HR = 8.41; $P = .004$; HR = 4.56, respectively) among all variables tested: the histological grade, KPS, corticotherapy, and the number of previous treatments. Sensitivity and specificity for relapse at 6 months were 66.7% and 100%, respectively, for the SUVMax and 61.9% and 100%, respectively, for the T:CL ratio.

With regard to OS and FDG uptake, the SUVMax and the T:CL ratio ($P = .005$, HR = 3.86; $P = .018$, HR = 2.85, respectively) were the most significant prognostic factor on OS. Among clinical variables, corticotherapy (yes vs no) was also significant in univariate analysis ($P = .048$, HR = 2.64), and the histological grade was nearly significant ($P = .097$), with a trend toward longer survival in grade III cases (median PFS = 8.7 months vs 6.9 months for grade IV). In multivariate analysis, the SUVMax and the T:CL ratio were the most powerful independent predictor of OS ($P = .038$, HR = 3.28; $P = .001$, HR = 5.96, respectively) among all variables tested: the histological grade, KPS, and the number of previous treatments. Corticotherapy (yes vs no) was also statistically significant in multivariate analysis ($P = .034$, HR = 3.22).
Sensitivity and specificity for death at 6 months were 87.5% and 58.8%, respectively, for the SUVMax and 87.5% and 64.7%, respectively, for the T:CL ratio.

**Discussion**

To our knowledge, this retrospective study provides the first evidence that glucose metabolic rate as assessed by FDG-PET could be used as an imaging biomarker in recurrent HGG for predicting survival following antiangiogenic therapy with bevacizumab. The SUVMax and the T:CL are better prognostic indicators for both PFS and OS than are the histological grade, KPS, corticotherapy, and the number of previous treatments. Moreover, our study showed that FDG uptake may predict MRI response (RANO criteria) to bevacizumab-based treatment.36

In addition to its retrospective design, the main limitations of our study are the sample size of our population and the lack of consensus on the optimal method to measure FDG uptake.29,39,40 We chose the SUV ratio method, which was the most pertinent to predict survival in HGG in our previous report.26 This method provides easy semi-quantitative analysis31 and is well-adapted for daily clinical practice. However, it probably needs to be further improved and validated. Indeed, the metabolic activity of the tumor may be underestimated in the case of a small focus of activity or extensive necrosis because of partial volume effect.28 In addition, the choice of contralateral symmetric brain parenchyma as the region of reference has not been standardized thus far, and it was reported to affect reproducibility because of the high dependence on the location of the lesion.29,41 In our experience, reader reproducibility was improved by the morphological additional data of hybrid PET/CT.

Our PET findings agree with previous physiopathological data on the increased glycolytic metabolism of...
tumoral cells mediated by overexpression of GLUT1 transporter\textsuperscript{42} and increased hexokinase activity\textsuperscript{43} in parallel with cellular proliferation and loss of differentiation.\textsuperscript{23,44} In many types of cancers, such as lung, breast, head and neck, sarcomas, and lymphomas, the prognostic impact of baseline FDG-PET is well-documented and has been applied in clinical practice.\textsuperscript{22} In neuro-oncology, the prognostic value of FDG-PET was based on the previously reported correlation between tumoral grade and FDG-assessed glycolytic metabolism\textsuperscript{25} and on the results of numerous subsequent clinical studies.\textsuperscript{18,24–32} In the specific context of recurrent HGG, the prognostic value of FDG-PET was reported mostly in heterogeneous populations.\textsuperscript{18,28,30,45–48} Only one study has looked at the relationship between FDG-PET and histological tumor grading in recurrent HGG.\textsuperscript{18} Similar to our series, they did not find a significant difference in FDG uptake between patients with grade III or grade IV tumors but confirmed the outcome predictive value of FDG-PET in the group of patients with use of multivariate analysis.\textsuperscript{18} This suggests that glucose metabolic rate provides additional early prognostic information independently of the histological grade in recurrent HGG.

In our study, we focused on recurrent HGG treated with anti-angiogenic bevacizumab therapy. One recent PET study focused on such a population but with a different tracer, FLT.\textsuperscript{19} Twenty-one recurrent HGGs (17 grade IV and 4 grade III) were prospectively treated with biweekly cycles of bevacizumab and irinotecan. FLT-PET was performed at baseline, after 1–2 weeks, and after 6 weeks from start of treatment. Both early and later FLT-PET metabolic responses (defined by more than 25% reduction in the tumor SUV) were more significant predictors of OS, compared with MRI responses. However, isolated baseline FLT SUVs did not predict patient survival,\textsuperscript{19} contrary to baseline FDG uptake ratio in our study. The lack of a baseline FLT SUV in predicting outcome in Chen’s bevacizumab study might be explained by the different molecular processes reflected by the 2 tracers. Indeed, FLT images cellular proliferation, which correlates with KI-67 proliferation index and therapeutic response.\textsuperscript{46} By contrast, FDG explores tumoral cell glycolytic metabolism, which was shown to correlate well with prognosis\textsuperscript{25} and with angiogenesis markers.\textsuperscript{24,34}

By contrast, with newly diagnosed HGG, the prognostic factors at recurrence are still discussed.\textsuperscript{5–7,17–19} Wong’s meta-analysis of prognostic factors at recurrence\textsuperscript{5} was based on 8 consecutive phase II trials including 225 recurrent GBM and 150 recurrent anaplastic astrocytomas. Histology was the most robust prognostic factor on OS and PFS (significantly poorer outcome in GBM) and independently persisted in multivariate analysis. To a lesser extent, a KPS greater than 80 and salvage treatment (defined by more than 2 prior chemotherapies and/or more than 2 prior surgeries) were associated with poorer outcomes, whereas age had no predictive value.\textsuperscript{5} Carson et al. found that temozolomide, in addition to KPS and histology, age, time since initial diagnosis, tumor location (frontal vs other), and corticosteroid use were of prognostic value to survival in their study of 333 patients with recurrent glioma enrolled in phase I and II clinical trials for temozolomide treatment.\textsuperscript{6} In agreement with these findings,\textsuperscript{5,6,17} histological grade IV tended to independently predict shorter OS in our population, whereas corticosteroid intake retained its prognostic value both in univariate and in multivariate analysis. The lack of prognostic value on PFS and OS observed in our study for age, number of previous treatments, or time from initial
surgery to bevacizumab therapy may be explained by the small sample size of our population. However, these findings are in agreement with other analyses performed in patients treated with bevacizumab for recurrent glioma. In a phase II trial of single-agent bevacizumab, KPS and the number of prior chemotherapy regimens had no effect on PFS, whereas older age was associated with better PFS. In the BRAIN study, the number of previous lines of chemotherapy did not significantly affect PFS. In the study by Chen et al., age, number of recurrences or number of prior treatments, tumor grade, and steroid intake did not predict outcome after bevacizumab. Taken together, these results may also suggest that the impact of established prognostic factors in recurrent HGG may be decreased with bevacizumab therapy. In contrast and despite the small sample size of our population, FDG uptake was the most powerful prognostic factor, regardless of the histological grade for both PFS and OS. Baseline FDG uptake could therefore be more relevant in the specific context of recurrent HGG treated with anti-angiogenic therapy.

**Conclusion**

This retrospective study provides the first evidence that glucose metabolic rate as assessed by FDG-PET can serve as an imaging biomarker in recurrent HGG for predicting tumor control and survival following anti-angiogenic therapy with bevacizumab. Furthermore, because of the wide availability of FDG, the role of FDG-PET to monitor response by sequential examination should be explored. Future studies are needed to determine whether FDG-PET could overcome morphological imaging limitations in this context.

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**References**


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