Diagnostic Performances of [^{18}F]fluorocholine Positron Emission Tomography in Brain Tumors

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Abstract: 206; Keywords: 5; Main text: 3940; References: 43; Tables: 4; Figures: 2

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Abstract

Aim: Brain tumors characterization by molecular imaging that allow the depiction of brain lesions metabolic pattern is crucial. Our study aimed: (1) to evaluate the diagnostic performances of [^{18}F]fluoroethylcholine positron emission tomography/computed tomography ([^{18}F]FECH PET/CT), and (2) to correlate PET imaging derived parameters of [^{18}F]FECH to survival in brain tumors. *Methods*: from 2009 to 2012, we enrolled 30 patients who underwent [^{18}F]FECH PET/CT. Final diagnosis was established by clinical and radiological follow-up. *Results*: final diagnosis was consistent with tumor disease in 27/30 cases. In 3/30 cases tumor disease was ruled out. [^{18}F]FECH PET/CT resulted true positive and negative in 21/30 and 9/30 patients, respectively. Sensitivity, specificity, positive predictive value, negative predictive value and accuracy of [^{18}F]FECH PET/CT were 78%, 100%, 100%, 33%, and 80%, respectively. Mean and maximum standardized uptake value (SUV_{mean} and SUV_{max}) resulted statistically correlated to histology (*p*-value=0.0255 and =0.0222, respectively). Using a SUV_{max} cut-off of 2.0 or 3.2 we distinguished between low- and high-grade gliomas with a good specificity (70% and 80%, respectively). SUV_{max} and histology resulted correlated to overall survival and disease related survival at multivariate analysis. *Conclusions*: our results, worthy of further investigations, show (1) high diagnostic performances of [^{18}F]FECH PET/CT, (2) a correlation between PET imaging derived parameters and survival.

Keywords: Brain Neoplasm; Glioma; Molecular Imaging; Fluorocholine; Positron-Emission Tomography

Introduction

Glioma accounts for over 60% of primary brain tumors [1] and it was estimated that 22,910 people were diagnosed with and 13,700 patients died of central nervous system tumor in 2012 [2]. Based on histological features gliomas are grouped in different pathological types that represent together with the age at diagnosis and the functional status the most important prognostic factors [3,4]. Although histology remains necessary for glioma grading, magnetic resonance imaging is considered the non-invasive technique of choice for their diagnosis, pre-surgical planning and post-therapeutic monitoring [1,5]. Both histology and magnetic resonance imaging, even with the addition of magnetic resonance spectroscopy, suffer from limitations as a consequence of intrinsic tissue heterogeneity and/or sampling errors. In addition specificity is troublesome significantly reduced especially in the setting of the evaluation of treatment response [1,6]. Therefore, in the era of molecular and cellular cancer biology, the lack of a reliable imaging modality makes the issue of the differential diagnosis between post-treatment changes, and tumor progression a major unmet clinical need in the management of patients with gliomas [7]. In this setting, disease characterization by complementary molecular imaging techniques that allow the depiction of brain lesions metabolic pattern is crucial. Nuclear medicine techniques may be helpful to characterize tumor functional features and many SPECT radiotracers have been employed in brain tumors imaging including [^{123}I]alpha-methyl-L-tyrosine [8], ^{201}thallium [9] and [^{99m}Tc]MIBI [9]. Additionally, since the use of fluorine-18 fluorodeoxyglucose ([^{18}F]FDG) the most widely used PET radiopharmaceutical in oncology, may be limited due to its relatively high physiological grey matter uptake [10], over the past few years, a number of challenger PET biomarkers have been developed and tested in the field of the molecular imaging of gliomas. These challengers include, among others, radiolabeled analogues of acetate, amino acids (FET), nucleosides (FLT), amines (choline), monoamine neurotransmitter precursors (L-DOPA) and nitroimidazoles (F-miso) [11]. Although the application of ^{11}C-methionine in brain tumor imaging from the beginning [12] proved to be a success story [13], other radiotracers have been evaluated in this clinical setting since its use is not practical [11]. In this context, the development of FET [^{18}F]-labeled which offers a number of qualities of the "optimal glioma tracer", has determined its righteously growth in popularity [11]. Choline derivatives radiolabeled with positron emitted isotopes were first pioneered by Hara's et al. [14,15]. The development of a new PET choline derivative, advanced by the introduction of the N-F-18 fluoromethyl labeling group ([^{18}F]fluorocholine, [^{18}F]FCH)] [16,17] with favorable biodistribution profile [6,18], together with the demonstration of choline metabolites in areas of active membrane turnover in World Healt Organization (WHO) grade II and III gliomas [19], represent the rationale for the investigation of this radiopharmaceutical in brain tumors. Surely at present, the main role of choline PET in brain tumors is represented by the diagnosis of recurrences [20]. In fact, despite some disadvantages of radiolabeled choline compared to "optimal glioma tracer" (i.e. [^{11}C]methionine and [^{18}F]FET) [11], it offers well-defined images of brain lesions thanks to the low uptake in normal brain tissue together with its high level of

biological specificity for the proliferative activity of tumor cells [20]. Additionally, although at the present time there's not a reliable parameter or an index (e.g. tumor/background ratio) that allows to distinguish between the various forms of brain tumors, generally higher values of choline uptake correspond to more aggressive forms [20].

In this study, we aimed at evaluating the diagnostic performances of [^{18}F]fluoroethylcholine positron emission tomography/computed tomography ([^{18}F]FECH PET/CT) in patients with brain tumor and determining the possible prognostic role of [^{18}F]FECH PET/CT in this clinical setting.

Materials and methods

Study design

This is a prospective, non-randomized single arm clinical trial performed at the Nuclear Medicine Unit of Santa Maria Nuova Hospital – IRCCS of Reggio Emilia (Italy). The study was conducted in accordance with International Conference on Harmonization Good Clinical Practice guidelines, the Declaration of Helsinki and it was approved by Local and National Authorities (EudraCT number 2009-011380-37). [^{18}F]FECH PET/CT was performed in all patients who presented the following criteria:

- any sex and > 18 years;
- diagnosis of glioma (based on histology or radiological findings) or radiological suspicious of brain tumor recurrence after curative treatment;
- brain magnetic resonance (MR) imaging within 4 weeks;
- signed informed consent;
- no pregnancy, in case of child-bearing female.

Patients were followed for at least 1 year after [^{18}F]FECH PET/CT as required by the study protocol.

Patients

From 2009 to 2012, 30 consecutive patients (15 men and 15 women), underwent [^{18}F]FECH PET/CT either for staging (n = 11/30) or re-staging (n = 19/30). In case of re-staging, the median time between first diagnosis and [^{18}F]FECH PET/CT was of 287.5 days (range 19-1421). Median age at diagnosis was 55 years (range 32-78). Median age at enrollment was 57 years (range 34-79). The primary diagnosis was established with histology in 25/30 patients whereas in the remaining 5 cases it was based on radiological findings (biopsy/surgery was not feasible). Histology was diffuse astrocytoma (WHO II) in 5/25 cases, oligodendroglioma (WHO II) in 4/25 patients, anaplastic astrocytoma (WHO III) in 1/25 patient, anaplastic oligodendroglioma (WHO III) in 4/25 cases and glioblastoma (WHO IV) in the remaining 11/25 cases. According to the WHO classification nine patients had a low grade glioma (LGG) while the remaining 16 cases presented a high grade glioma (HGG). Median time between first diagnosis and [^{18}F]FECH PET/CT was 149 days

(range 30-1166) in case of LGG, 346.5 days (range 25-1421) in case of HGG, and 120 days (range 19-179) in patients without histology.

Twenty patients underwent treatment(s) before [^{18}F]FECH PET/CT (post-surgical staging = 1; re-staging = 19). Previous treatments included surgery (n = 4), radiotherapy (n = ~~5~~ 6) and combined therapy as surgery + radiotherapy + chemotherapy (n = 8) or radiotherapy + chemotherapy (n = 2). All patients presented brain lesion(s) documented by brain MR imaging with the exception of one case in which [^{18}F]FECH PET/CT was performed immediately after curative surgery in order to exclude persistence of disease (post-surgical staging) but in 5 patients (re-staging) all previously treated with surgery alone (n = 3) or surgery plus radiotherapy (n = 2), MRI imaging resulted inconclusive. Totally, 31 lesions documented by brain MRI were evaluable for the study. For [^{18}F]FECH PET/CT results, we used final diagnosis as reference standard. Final diagnosis was achieved by clinical and radiological follow-up in all patients enrolled (median follow-up time = 398 days, range 6-1242). Final diagnosis was consistent with brain tumor in 27/30 cases (first diagnosis = 10/27; re-staging = 17/27), while in the remaining 3/30 patients (post-surgical staging = 1; re-staging = 2) tumor persistence/recurrence was excluded. Survival data were recorded to determine the survival and diagnosis related survival.

Brain MR imaging

MRI acquisitions were performed on a Philips Achieva 1.5T (Philips Healthcare, Eindhoven, The Netherlands) scanner, using the sensitivity encoding (SENSE) 8-channel head coil provided by the scanner manufacturer.
The standard protocol used in our institution included in particular the following sequences:

- fluid attenuated inversion recovery (FLAIR): slice thickness 3.5 mm (gap 0), acquisition plane axial;
- diffusion weighted imaging (DWI): echo planar imaging (EPI) sequence, slice thickness 3 mm (gap 0.4 mm), acquisition plane axial, b-value: 0, 1000 s/mm^2;
- T1-weighted after contrast agent administration (T1C): 3D Turbo Field Echo sequence, slice thickness 0.9 mm (gap 0). The acquisition was performed in sagittal plane and the images were reconstructed in axial plane setting slice thickness 3 mm (gap 0). The sequence was acquired after injection of 0.2 ml/kg of gadolinium contrast agent (DOTAREM, Guerbet, Roissy, France) followed by saline flush.

[^{18}F]FECH synthesis

Radiopharmaceutical synthesis was performed with a one step reaction as previously reported by Asti et al.[21]. Briefly, batches of 48 GBq (1.3 mCi) [^{18}F]fluoride were produced by irradiating O-18 water with a MINItrace cyclotron (GE Medical system, Uppsala, Sweden) by using a 50 A current for about 60 min. At the end of bombardment, the activity was transferred to a Fx-FN Tracer Lab synthesizer (GE Medical System, Uppsala, Sweden) and trapped in a light QMA cartridge. F-18 fluoride was then desorbed from the cartridge by using a 0.075 M TBA bicarbonate solution (600 L) and directed into the reactor vessel. The reaction mixture was heated to dryness at 60°C for 7 minutes and then at 120°C

for 5 minutes. The nucleophilic substitution and the alkylation reactions were performed simultaneously by adding 0.3 mL of a 45 mg/ml 1,2-bis(tosyloxy)ethane solution in acetonitrile and 0.05 mL of N,N-dimethylaminoethanol dissolved in 0.1 mL acetonitrile to the F-18 fluoride anhydrous residue. The reactor was heated at 95°C for 10 minutes and then cooled to 50°C. The reaction mixture was recovered by rinsing the reactor with 10 mL water. The washing solution, containing [^{18}F]FECH, was filtered through two plus C-18 connected with two plus QMA cartridges and collected in a bulb vessel. [^{18}F]FECH pre-purified solution underwent a second purification being transferred in a plus CM cartridge. The cartridge was washed out with 10 ml water and 5 mL ethanol and subsequently eluted with 3 mL 0.9% NaCl water solution. The [^{18}F]FECH was collected in a product vial and diluted to a 16 mL volume with injectable water. Radiochemical purity was always >99%.

PET/CT imaging

PET/CT images were acquired 60 minutes after the administration of [^{18}F]FECH (about 3.7 MBq/kg or 0.1 mCi/kg) with patient in supine position by using a head holder on a GE Discovery™ STE scanner (GE Healthcare). The following parameters were settle: CT field of View (FOV) 300x300 mm^2, tube voltage 120 kV, tube current 100 mAs, slice thickness 3.75 mm, pixel dimension 0.59x0.59 mm^2, matrix size 512x512; PET FOV 300 mm, slice thickness 3.27 mm, matrix 256x256, pixel dimension 1.17x1.17 mm^2, acquisition time 3 minutes 50 seconds/bed, 47 slices (1 bed). CT acquisition was used both for attenuation correction (after rescaling at ^{18}F photon energy) and for anatomic localization. PET images were reconstructed using an iterative algorithm for the CT attenuation correction (VUEPoint). All studies were visually and semiquantitatively assessed by a panel of 2 board-certified nuclear-medicine physicians. PET-VCAR™ (GE Healthcare) was used to analyze tumor lesions. Semi-quantitative analysis was performed by drawing a region of interest (ROI) comprising the whole uptake of the lesion. A similar ROI was drawn in the controlateral healthy white matter. Attention was paid to avoid non-pathologic uptaking regions in ROI drawing (e.g. ventricles). PET/CT was considered positive when the choline uptake was higher in the problem area than in surrounding tissue (qualitative analysis) and it could not be considered physiological [22]. In case of negativity, the ROI was drawn in the anatomic area identified by brain magnetic resonance imaging and suspected for presence of disease. Using PET-VCAR™ we calculated the mean and maximum standardized uptake value (SUV_{mean} and SUV_{max}), the functional volume (FV) and the total lesion proliferation (TLP). The FV was determined using a fixed threshold method (threshold of 40%) [23]. The TLP was determined by multiplying the FV by the SUV_{max} in the considered area. TLP corresponds to total lesion glycolysis (TLG) using fluorine-18 fluorodeoxyglucose PET/CT ([^{18}F]FDG PET/CT). The same parameters (SUV_{mean}, SUV_{max}, FV, and TLP) were also calculated in healthy brain parenchyma (background). Values of each parameter considered was reported as absolute value. A tumor/background ratio (T/B) was also calculated for SUV_{max}.

Statistical analysis

Sensitivity, specificity, accuracy, positive predictive value and negative predictive value of [^{18}F]FECH PET/CT in final diagnosis prediction was calculated by the Clopper-Pearson technique considering 95% two-sided confidence intervals (CI). The choice of this method was determined based on the small number of patients.

The relationship between [^{18}F]FECH-PET/CT and MRI findings (on patient basis) was assessed calculating the exact *p*-value for chi-square test and measured by Cramer's V. The choice of the exact calculation of *p*-value, instead of the asymptotic one, was due to the observation that 67% of cells in the table had an expected frequency <5.

The Clopper-Pearson technique was also used to determine the diagnostic performance measures of dichotomized SUV_{max} for histology grade prediction. In this case we included in the analysis only the patients having histology (n = 25 patients for a total of 27 lesions).

Relationship among the histological grade and SUV_{mean}, SUV_{max}, FV and TLP was assessed by univariate and multivariate logistic models. For each independent variable the subsequent statistics were calculated: Wald chi-square *p*-value, c statistic (interpretable as area under ROC in univariate settings), Odds Ratio and 95% two-sided CI using the Wald method. Univariate and multivariate Cox proportional hazard models was used to determine the relationship among overall survival/diagnosis related survival and SUV_{mean}, SUV_{max}, FV, TLP, histological grade and age at diagnosis. The survival models were estimated on patient basis: for the 2 patients having 2 lesions, only the lesion with the highest SUV_{max} was considered for each patient. For each independent variable the subsequent statistics were calculated: Wald chi-square *p*-value, Hazard Ratio and 95% two-sided CI using the Wald method. The Hazard Ratio for histological grade was calculated taking the low level as reference. Clinical consideration further than statistical one supported the choice of these parameters [4]. A *p*-value less than 0.05 was considered significant (two-side).

Results

[^{18}F]FECH PET/CT diagnostic performances

[^{18}F]FECH PET/CT was feasible in all patients enrolled (n = 30).

[^{18}F]FECH PET/CT clearly ~~depict~~ depicted site of increased uptake in 21/30 patients (Figures 1 and 2). In 9/30 patients no site of significant uptake was detected. According to the final diagnosis [^{18}F]FECH PET/CT resulted true positive in 21/30 cases, true negative in 3/30 cases and false negative in 6/30 cases. No cases of false positive [^{18}F]FECH PET/CT results were found in our series of patients. In LGG [^{18}F]FECH PET/CT resulted true positive in 5 cases (staging = 3; re-staging = 2), true negative in 1 patient (re-staging) and false negative in 3 cases (staging = 1; re-staging = 2). In all patients affected by HGG [^{18}F]FECH PET/CT results were consistent with final diagnosis resulting true positive in 16 cases (staging = 3; re-staging = 13) and true negative in one case (re-staging). In patients without histology, [^{18}F]FECH

PET/CT was true positive (re-staging) and negative (staging) in 1 case each, while in 3 patients resulted false negative (staging = 3).

The overall sensitivity, specificity, positive predictive value, negative predictive value and accuracy of [^{18}F]FECH PET/CT, calculated on patient basis, were 78% (CI: 58-91), 100% (CI: 29-100), 100% (CI: 84-100), 33% (CI: 8-70), and 80% (CI: 61-92), respectively.

[^{18}F]FECH-PET/CT and MRI resulted concordant in 20 cases (19 both positive and 1 both negative). Based on final diagnosis MRI resulted true positive and true negative in 24/30 (staging = 10; re-staging = 14) and 1/30 (post-surgical staging) patients, respectively. In the 5 cases of inconclusive MRI (all re-staging), [^{18}F]FECH-PET/CT resulted true positive in 2 cases (both HGG), true negative in 2 cases (LLG and HGG each) and false negative in the remaining case (LGG).

A significant correlation between [^{18}F]FECH-PET/CT and MRI findings was found (Cramer's V=0.4257 and *p*-value=0.0492).

[^{18}F]FECH PET/CT semiquantitative parameters (SUV_{mean}, SUV_{max}, FV, and TLP)

Table 1 summarizes the main [^{18}F]FECH PET/CT derived parameters for each lesion (Table 1a) and for healthy brain parenchyma (Table 1b). We didn't observed difference in background values (SUV_{mean}, SUV_{max}, FV, and TLP) among brain lobes (e.g. frontal *versus* temporal). We not found any statistical difference in background values (SUV_{mean}, SUV_{max}, FV, and TLP) among LGG, HGG and patients without histology while SUV_{mean}, SUV_{max}, and FV, differed in patients with positive and negative [^{18}F]FECH PET/CT (*p*-value = 0.0182, = 0.0108, and = 0.0152, respectively). In patients who presented positive [^{18}F]FECH PET/CT results SUV_{mean}, and SUV_{max} of healthy brain parenchyma resulted lower compared to negative ones (0.13±0.3 *versus* 0.2±0.3, and 0.22±0.5 *versus* 0.33±0.5, respectively).

The absolute value of SUV_{mean}, SUV_{max}, FV, and TLP of the lesion were lower in patients with LGG as compared to high grade ones. In the 25 patients with available histology both the SUV_{mean} and the SUV_{max} resulted statistically correlated to histology (*p*-value = 0.0255 and = 0.0222, respectively) at logistic univariate analysis (Table 2). However, at the multivariate model no significant correlation among any of the variables was demonstrated (Table 2). Of notice, at the multivariate analysis we removed the variable of SUV_{mean} due to its high correlation with SUV_{max} (r = 0.9951).

The T/B ratio resulted higher (*p*-value = 0.0125) in patients with HGG (22.6±14.3) compared to patients affected by LGG (5.6±5.1).

Table 3 shows diagnostic accuracy of [^{18}F]FECH PET/CT in differentiating LGG and HGG using a threshold for SUV_{max} of 2 and 3.2, respectively. A threshold for SUV_{max} = 2.0 resulted in 70% specificity (CI: 35-93) and 88%

sensitivity (CI: 64-99). Increased specificity up to 80% (CI: 44-98) was achieved increasing the SUV_{max} cut-off to 3.2, with a corresponding loss in term of sensitivity that decreased to 71% (CI: 44-90).

[^{18}F]FECH PET/CT and patients survival

During follow-up, 17/30 patients died for disease-related complication (n = 14/17), ab-ingestis pneumonia or sepsis (n = 3/17). Death occurred with a median time of 468.5 (range 90-1792) and 222 (range 6-664) days after first diagnosis and [^{18}F]FECH PET/CT, respectively.

At univariate analysis (patient based, n = 30) all the [^{18}F]FECH PET/CT derived parameters were statistically related to both overall survival and disease related survival. No relation between either histology or age at diagnosis and survival was demonstrated (Table 4).

At the subsequent multivariate survival analysis that was limited to the subset of patients with all the covariate available (n = 25), only SUV_{max} and histology (as in the case of the previous multivariate model, SUV_{mean} was dropped out) maintained a significant correlation with both overall survival and disease related survival (Table 4).

Discussion

Molecular imaging procedure holds the unique propriety of exploiting biochemical features of cancer cells through the use of suitable radiolabeled molecular probes, therefore providing a powerful technique for in vivo characterization of tumor lesions. Due to favorable biodistribution profile, radiolabeled choline has shown intense uptake in primary brain tumor as compared to normal brain tissue [14,24], resulting in clear delineation of tumor lesion as observed in all the patients we evaluated in the present study. Indeed in our experience, [^{18}F]FECH PET/CT presented extremely high specificity for malignant brain lesion presenting an overall diagnostic accuracy of 80%. However, the highest accuracy was obtained when [^{18}F]FECH PET/CT was used in the re-staging setting to identify or exclude tumor recurrence (89%). Particularly, if we consider only patients with inconclusive MRI findings (n = 5), [^{18}F]FECH PET/CT was able to confirm (n = 2) or exclude (n = 2) disease recurrence in the majority of cases. Despite the proportion of inconclusive MRI in our population was lower compared to others [25,26] [^{18}F]FECH PET/CT resulted of value in these cases similarly to what has already been reported for LGG [26]. In case of staging, accuracy of [^{18}F]FECH PET/CT slightly decreased (63%) mainly as a consequence of higher number of false negative findings (n = 6) observed in patients with ~~low grade~~ LGG (n = 3) or in cases of lesion with unknown histopathology (n = 3). However, if we consider only patients with HGG, [^{18}F]FECH PET/CT sensitivity was 100%, confirming the existence of increased uptake of choline derivatives in malignant lesions with worst histopathology parameters i.e. histological grade and proliferation index [27].

At the semiquantitative analysis of PET derived parameters we found a significant correlation between SUV and histology (*p*-value = 0.0255 for SUV_{mean} and = 0.0222 for SUV_{max} and at the logistic univariate analysis). It should be

mentioned that value of SUV_{max} of lesions, obtained in our patients resulted higher (almost twice) as compared to data previous reported in brain primary lesions [24,28-32]. This fact may be related to the use of [^{18}F]fluoroethylcholine instead of [^{18}F]fluoromethilcholine which is most common employed in literature, the intrinsic variability of SUV_{max} (i.e. protocol of images acquisition, time elapsed between radiopharmaceutical injection and scanning) and the high proportion of patients with gliomas HGG in our population. In addition, in our statistical analysis SUV_{mean} was removed at multivariate analysis because of its high correlation with SUV_{max}. Therefore, we decided to retain SUV_{max} based on the clinical significance and on its lower standard error for the regression coefficient (0.4515 *versus* 0.8330 of SUV_{mean}) that resulted in narrower CI.

Based on the evidence of low values of background for all parameters considered and the absence of statistical difference among background uptake and LGG, HGG and patients without available histology, we preferred to use the absolute value of SUV_{max} instead of the T/B. The lower background [^{18}F]FECH uptake (in terms of SUV_{mean} and SUV_{max}) in healthy brain parenchyma in case of positive PET/CT compared to negative ones could be a consequence of the choline "trapping" from lesions (i.e. well-defined images of brain lesions), however the small number of cases prevent further speculations.

Setting the SUV_{max} cut-off at ≥ 2.0 we have a differentiation between LGG and HGG with a specificity of 70% that increase to 80% if we set the cut off for SUV_{max} at ≥ 3.2. These data are worthy of further investigations since could be have a crucial clinical significance especially in patients in which biopsy or surgery are not feasible, in order to identify the best treatment option.

As for other radiotracers such as [^{18}F]DOPA [33,34] and [^{18}F]FLT [35] a correlation between radiolabeled choline [32] and survival has been reported in HGG. Similarly, we found a correlation between PET/CT findings and survival in all patients enrolled. Particularly, all [^{18}F]FECH PET/CT parameters, SUV_{mean}, SUV_{max}, FV and TLP, resulted statistically related to both overall survival and disease related survival at univariate analysis whereas the clinical prognostic factors (histology and age at diagnosis) failed to demonstrate correlation to survival. This might be due to the high percentage of gliomas HGG with a long-survival at enrollment (median 346.5 days, range 25-1421) as compared to data in literature [1].

Interestingly, in our series of patients also FV and TLP resulted statistically correlated to survival. Many studies with [^{18}F]FDG PET/CT reported that both FV and TLG enclose more informative data compared to SUV values [36], and they have been used to predict therapy response in different types of cancer [37-43]. Our application of a similar concept (TLP) is new and seems promising. The choice to introduce the concept of TLP, has been made in an attempt to take into account much metabolic data as possible deriving from PET/CT images. Among all the variables evaluated at the multivariate analysis, both SUV_{max} and histology resulted correlated to overall survival (*p*-value = 0.0044 and = 0.0073,

respectively) and disease related survival (p-value = 0.0023 and = 0.025, respectively) while the remaining parameters (including age at diagnosis) were not statistically significant.

Limitations of the study and conclusions

Despite our promising results, our study is affected by some limitations, mainly represented by patient population. First the number of subjects enrolled is limited and histology was not available in all patients. Our population was constituted by a high percentage of HGG with a long-survival at enrollment. Patients enrolled were naïve or previously treated and PET/CT was performed with different clinical purpose (staging and re-staging) and thus at different stage of disease. Not all patients were followed for the same time after [^{18}F]FECH PET/CT. Finally, in this series of patients we observed only false negative cases using [^{18}F]FECH PET/CT however, also false positive results can occur.

Our results suggest a promising role of [^{18}F]FECH PET/CT in brain tumor due to its high diagnostic accuracy. Additionally, [^{18}F]FECH PET/CT resulted able distinguish between LGG and HGG with a good specificity. Finally, PET imaging derived parameters, correlate to overall and disease related survival. All these data are worthy of further investigations in larger series of patients, eventually compared to magnetic resonance imaging, since could have a crucial clinical significance impacting in management of patients affected by primary brain tumors.

Acknowledgement

We thank all general practitioners who contributed to patients' management.

Founding: none; Conflict of interest: none

Paper has been presented as poster at SNMMI Annual Meeting 2014 (J Nucl Med Meeting Abstract, May 2014;55:1902)

Tables

Table 1: [^{18}F]FECH PET/CT parameters provided by PET-VCAR™ based on PET/CT results in all lesions and based on histology types (lesion basis).

Table 2: Results of statistical analysis (lesion basis) performed on the 25 patients with available histology.

Table 3: Diagnostic performances of [^{18}F]FECH PET/CT to differentiate low from high grade gliomas using different cut-offs of SUV_{max}.

Table 4: Results of statistical survival analysis (patient basis).

Figures Legends

Figure 1: Axial T1 weight magnetic resonance imaging MRI (A), [^{18}F]FECH PET/CT (B), and fused [^{18}F]FECH PET/MRI (C) images of a patient with glioblastoma that recurred after surgery, chemotherapy and radiotherapy. MRI panel shows a lesion in left occipito-temporal region. [^{18}F]FECH PET/CT images (PET left, CT middle and fused PET/CT right) show an area of intense [^{18}F]FECH uptake. [^{18}F]FECH-PET/MRI slide confirms that the [^{18}F]FECH uptake coincides with the lesion identified by MRI.

Figure 2: Axial T1 weight MRI (A), [^{18}F]FECH PET/CT (B), and fused [^{18}F]FECH PET/MRI (C) images of a patient with high grade glioma. MRI panel shows a lesion in left temporal-insular region. [^{18}F]FECH-PET/CT images (PET left, CT middle and fused PET/CT right) show an area of intense [^{18}F]FECH uptake. [^{18}F]FECH-PET/MRI slide confirms that the FECH uptake coincides with the lesion identified by MRI.

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Table 2: Results of statistical analysis (lesion basis) performed on the 25 patients with available histology.

Type of statistical analysis	Correlation with	[^{18}F]FECH PET/CT parameter	*p*-value	c statistic	OR 95% CI Lower limit	OR	OR 95% CI Upper limit
Univariate	**Histology**	**SUV_{mean}**	*0.0255*	0.841	1.173	3.676	11.520
		SUV_{max}	*0.0222*	0.844	1.113	2.111	4.006
		FV	0.0697	0.747	0.979	1.302	1.732
		TLP	0.1012	0.791	0.977	1.126	1.298
Multivariate*	**Histology**	**SUV_{max}**	0.0758	0.847	0.920	2.229	5.401
		FV	0.4574		0.771	1.172	1.781
		TLP	0.3553		0.843	0.947	1.063

[^{18}F]FECH PET/CT: [^{18}F]fluoroethylcholine positron emission tomography/computed tomography; OR: odd ratio; CI: confidence interval; SUV_{max}: maximum standardized uptake value; SUV_{mean}: mean standardized uptake value; FV: functional volume; TLP: total lesion proliferation.

*The variable of SUV_{mean} was removed due to its high correlation with SUV_{max}.

Table 3: Diagnostic performances of [^{18}F]FECH PET/CT to differentiate low from high grade gliomas using different cut-offs of SUV_{max}.

SUV_{max} cut-off	**Sensitivity**	**Specificity**	**Positive predictive value**	**Negative predictive value**	**Accuracy**
≥2.0	88% (CI: 64-99)	70% (CI: 35-93)	83% (CI: 59-96)	78% (CI: 40-97)	82% (CI: 62-94)
≥3.2	71% (CI: 44-90)	80% (CI: 44-98)	86% (CI: 57-98)	62% (CI: 32-86)	74% (CI: 54-89)

[^{18}F]FECH PET/CT: [^{18}F]fluoroethylcholine positron emission tomography/computed tomography; CI: confidence interval; SUV_{max}: maximum standardized uptake value.

Table 4: Results of statistical survival analysis (patient basis).

Type of statistical analysis	Correlation with	[^{18}F]FECH PET/CT parameter	*p*-value	Lower limit 95% HR	HR	Upper limit 95% HR
Univariate	**Overall survival**	**SUV_{mean}**	*0.0019*	1.189	1.599	2.149
		SUV_{max}	*0.0025*	1.096	1.297	1.535
		FV	*0.0274*	1.010	1.091	1.179
		TLP	*0.0038*	1.007	1.023	1.039
		Histological grade^	0.2934	0.192	0.562	1.647
		Age at diagnosis	0.3540	0.980	1.019	1.059
	Disease related survival	**SUV_{mean}**	*0.0010*	1.262	1.776	2.497
		SUV_{max}	*0.0013*	1.136	1.384	1.688
		FV	*0.0252*	1.012	1.101	1.199
		TLP	*0.0038*	1.008	1.025	1.042
		Histological grade^	0.6744	0.221	0.766	2.652
		Age at diagnosis	0.2390	0.983	1.026	1.072
Multivariate^	**Overall survival**	**SUV_{max}**	*0.0044*	1.143	1.535	2.061
		FV	0.7230	0.807	1.048	1.362
		TLP	0.8330	0.944	0.994	1.047
		Histological grade^	*0.0073*	0.036	0.147	0.596
		Age at diagnosis	0.4468	0.974	1.017	1.063
	Disease related survival	**SUV_{max}**	*0.0023*	1.223	1.761	2.537
		FV	0.8656	0.751	1.027	1.405
		TLP	0.8066	0.934	0.993	1.054
		Histological grade^	*0.0250*	0.029	0.152	0.789
		Age at diagnosis	0.3134	0.975	1.027	1.081

[^{18}F]FECH PET/CT: [^{18}F]fluoroethylcholine positron emission tomography/computed tomography; HR: hazard ratio; SUV_{max}: maximum standardized uptake value; SUV_{mean}: mean standardized uptake value; FV: functional volume; TLP: total lesion proliferation.

^Histological grade analysis concerned only the 25 patients with available histology.

*The variable of $SUV_{mean}$was removed due to its high correlation with SUV_{max}.

Table 1a: [^{18}F]FECH PET/CT parameters calculated for each lesion by PET-VCAR™.

[^{18}F]FECH PET/CT parameters for each lesion considered		All patients			Low grade glioma			High grade glioma			No histology		
		All (n=31)	[^{18}F]FECH PET/CT		All (n=10)	[^{18}F]FECH PET/CT		All (n=17)	[^{18}F]FECH PET/CT		All (n=5)	[^{18}F]FECH PET/CT	
			Positive (n=23)	Negative (n=9)		Positive (n=6)	Negative (n=4)		Positive (n=16)	Negative (n=1)		Positive (n=1)	Negative (n=4)
SUV_{max}	Mean	3.1	4.21	0.33	1.5	2.3	0.3	4.2	4.4	0.5	0.8	2.8	0.3
	Median	2.4	3.4	0.3	0.9	2.0	0.3	3.6	3.7	0.5	0.4	2.8	0.3
	Range	0.2-13.6	0.8-13.6	0.2-0.5	0.2-4.7	0.8-4.7	0.2-0.4	0.5-10.2	1.2-10.2	n.a.	0.2-2.8	n.a.	0.2-0.4
	SD	3.2	3.1	0.1	1.5	1.5	0.08	2. 7	2.6	0.0	1.1	0.0	0.1
SUV_{mean}	Mean	1.7	2.3	0.2	0.9	1.3	0.2	2.3	2.5	0.3	0.4	1.5	0.2
	Median	1.4	1.9	0.2	0.5	1.2	0.2	2.0	2.0	0.3	0.2	1.5	0.1
	Range	0.1-7.2	0.4-7.2	0.1-0.3	0.2-2.5	0.4-2.5	0.2-0.2	0.3-6.3	0.6-6.3	n.a.	0.1-1.5	n.a.	0.1-0.3
	SD	1.8	1.8	0.1	0.8	0.8	0.0	1.6	1.5	0.0	0.6	0.0	0.1
FV	Mean	4.8	6.6	0.4	2.6	4.0	0.5	6.0	6.4	0.2	4.6	21.5	0.4
	Median	3.3	4.8	0.4	1.0	3.9	0.5	3.9	4.0	0.2	0.4	21.5	0.3
	Range	0.2-21.5	0.5-21.5	0.2-0.7	0.3-7.5	0.5-7.5	0.3-0.7	0.2-20.1	0.9-20.1	n.a.	0.3-21.5	n.a.	0.3-0.5
	SD	5.5	5.6	0.2	2.8	2.9	0.2	5.3	5.2	0.0	9.4	0.0	0.1
TLP	Mean	13.4	18.7	0.1	4.3	7.0	0.1	18.0	19.2	0.1	6.6	32.8	0.2
	Median	5	9.3	0.1	0.5	5.9	0.1	8.1	9.3	0.1	0.1	32.8	0.1
	Range	0.1-125.7	0.2-125.7	0.1-0.1	0.1-18.7	0.2-18.7	0.1-0.1	0.1-125.7	1.8-125.7	n.a.	0.1-32.8	n.a.	0.1-0.3
	SD	24.9	27.8	0.0	6.4	7.2	0.0	30.3	31.0	0.0	14.6	0.0	0.1

[^{18}F]FECH PET/CT: [^{18}F]fluoroethylcholine positron emission tomography/computed tomography; n.a.: not applicable; SUV_{max}: maximum standardized uptake value; SD: standard deviation;

SUV_{mean}: mean standardized uptake value; FV: functional volume; TLP: total lesion proliferation.

Table 1b: [^{18}F]FECH PET/CT parameters calculated for healthy brain parenchyma by PET-VCAR™.

[^{18}F]FECH PET/CT parameters for healthy brain parenchyma		All patients			Low grade glioma			High grade glioma			No histology		
		All (n=31)	[^{18}F]FECH PET/CT		All (n=10)	[^{18}F]FECH PET/CT		All (n=17)	[^{18}F]FECH PET/CT		All (n=5)	[^{18}F]FECH PET/CT	
			Positive (n=23)	Negative (n=9)		Positive (n=6)	Negative (n=4)		Positive (n=16)	Negative (n=1)		Positive (n=1)	Negative (n=4)
SUV_{max}	Mean	0.25	0.22	0.33	0.23	0.18	0.3	0.25	0.24	0.5	0.28	0.1	0.33
	Median	0.2	0.2	0.3	0.2	0.15	0.3	0.2	0.2	0.5	0.3	0.1	0.35
	Range	0.1-0.5	0.1-0.5	0.2-0.5	0.1-0.4	0.1-0.4	0.2-0.4	0.1-05	0.1-0.5	n.a.	0.1-0.4	n.a.	0
	SD	0.12	0.11	0.1	0.11	0.12	0.08	0.12	0.11	0	0.13	0	0.1
SUV_{mean}	Mean	0.15	0.13	0.2	0.15	0.12	0.2	0.15	0.14	0.3	0.16	0.1	0.18
	Median	0.1	0.1	0.2	0.15	0.1	0.2	0.1	0.1	0.3	0.1	0.1	0.15
	Range	0.1-0.3	0.1-0.3	0.1-0.3	0.1-0.2	0.1-0.2	n.a.	0.1-0.3	0.07	n.a.	0.1-0.3	n.a.	0.1-0.3
	SD	0.07	0.06	0.07	0.05	0.04	0	0.08	0.1-0.3	0	0.09	0	0.1
FV	Mean	1.01	1.24	0.41	1.08	1.47	0.5	1.11	1.17	0.2	0.5	1	0.38
	Median	0.8	1	0.4	0.65	1.1	0.5	0.8	0.85	0.2	0.4	1	0.35
	Range	0.2-4.2	0.2-4.2	0.2-0.7	0.3-4.2	0.4-4.2	0.3-0.7	0.2-3.5	0.2-3.5	n.a.	0.3-1	n.a.	0.3-0.5
	SD	0.89	0.95	0.16	1.09	1.39	0.18	0.82	0.81	0	0.29	0	0.1
TLP	Mean	0.15	0.17	0.1	0.14	0.17	0.1	0.17	0.18	0.1	0.1	0.1	0.1
	Median	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
	Range	0.1-0.6	0.1-0.6	n.a.	0.1-0.4	0.1-0.4	n.a.	0.1-0.6	0.1-0.6	n.a.	n.a.	n.a.	n.a.

	SD	0.11	0.13	0	0.09	0.12	0	0.13	0.13	0	0	0	0

[^{18}F]FECH PET/CT: [^{18}F]fluoroethylcholine positron emission tomography/computed tomography; n.a.: not applicable; SUV_{max}: maximum standardized uptake value; SD: standard deviation; SUV_{mean}: mean standardized uptake value; FV: functional volume; TLP: total lesion proliferation.