The diagnostic value of dual phase FDG PET CT in grading of gliomas

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Abstract Objective: The purpose of this study was to investigate the correlation between the FDG PET CT and histopathology in grading of gliomas.

Methods: 16 patients with clinically diagnosed glioma performed dual phase FDG PET CT of the brain for staging, and the staging was correlated to the histopathological classification in the surgical specimen.

Results: We found good correlation between the dual phase PET CT grading and the histopathological grading of gliomas, when a 23% increase was used as the cutoff for analysis of the difference in SUVmax of the lesion (L) versus normal gray matter (GM) over time, the sensitivity was 88.9%, the specificity was 85.7%, and the accuracy was 89.4% ($P = 0.003; AUC = 0.94$).

Conclusion: Dual phase FDG PET CT is a reliable predictor of proliferative activity of gliomas and could be used as a method of grading of the tumor.

The World Health Organization (WHO) classification of tumors of the central nervous system is a representative classification system for grading of a brain tumor, and is accepted and used worldwide (2).

Grading is based on the degree of nuclear atypia, mitosis, microvascular proliferation, and necrosis, with increasing anaplasia as tumor grade increases. The histologic features of the tumor and the age and performance status of the patient are major prognostic factors on outcome (3). Furthermore, PET has been introduced as an important tool in the definition of the tumor extent for therapy planning (4).

Dual-time-point 18F-FDG PET has significantly improved the diagnostic sensitivity and specificity for head and neck cancers, breast cancer, malignant lung lesions, and some others (5). Spence et al. (6) have introduced this methodology in
neurooncology and have studied delayed images visually and quantitatively using volumes of interest (VOIs). They investigated the behavior of model-derived kinetic rate constants over time and concluded that 18F-FDG is dephosphorylated faster from normal tissue than from tumor, improving image contrast.

In this study, we correlated the results of the FDG PET CT of the brain glioma with the histopathological classification of the tumor specimen obtained at surgery.

2. Patients and methods

2.1. Study population

Sixteen patients with glioma, 9 men and 7 women, 24 to 60 years old (mean age, 40 years), were examined in the study during the period of July 2014 to March 2015. All patients performed dual phase FDG PET CT in a private center and subsequent surgery for subtotal or total tumor removal. The PET CT study was performed within 2 weeks prior to surgery. The results were correlated to the histological classification in all patients.

2.2. Dual phase PET CT protocol

Patients fasted for at least 8 h before F-18 FDG positron emission tomography with computed tomography (PET/CT). Mean fasting serum glucose of patients was 118–150 mg/dL, and 4 patients had a history of diabetes mellitus. The early PET/CT scans were started 40 to 45 min after the administration of 8–15 mCi F-18 FDG using an hybrid PET/CT system (Ingenuity, TF PET/CT /Philips, the Netherlands), and the delayed PET/CT scans were performed at 75 min after the early scan. The axes of both systems are mechanically aligned to coincide optimally. CT data were acquired first and the following parameters were used: tube rotation time, 0.5 s per revolution; 120 kV; 140 mAs; reconstructed slice thickness, 5 mm. No contrast medium was used for the CT examination. After the acquisition of CT data had been completed, the tabletop with the patient automatically advanced into the PET sensitive field of view and acquisition of PET data was started in 3-dimensional mode with the patient in exactly the same position on the table. Scanning was performed in one bed position for 3 min. The attenuation correction was automatically completed using corresponding CT data.

2.3. Data analysis

Semi-quantitative analysis of PET images was performed, and Maximum and mean standardized uptake values (SUVmax and SUVmean) of the lesion and normal gray matter were measured at early (1) and delayed (2) imaging sessions. Circular regions of interest (0.5–1.0 cm, as appropriate) were used to determine the mean and max SUV of the lesion (L), and of the normal contralateral frontal gray matter (GM) at the level of the thalamus and the centrum semiovale (WM).

Ratios of L SUVmax to GM SUVmax at early and late time points (L1/GM1 and L2/GM2 respectively) were calculated individually, and the change between early and late L to GM ratios was calculated using the formula: [(L2/GM2/L1/GM1)/L1/GM1]. Similar calculations were performed using GM SUVmean, WM SUVmean and WM SUVmax (Fig. 1).

2.4. Statistical analysis

The diagnostic accuracy of PET derived indices was calculated using Receiver Operating Curve (ROC) analysis. The cutoff values were determined automatically by the ROC analysis program. The optimal cutoff value for these variables was defined as the point on the ROC curve with minimal distance from

![Fig. 1](image-url) 50 years old patient with left frontal low grade glioma by noncontrast CT (a), early (b) and late (c) PET images showed: early SUVmax of the lesion = 6 and 4.7 in the late scan, difference of −21.7%, the GM early SUVmax was 7.8 and 5.9 in the late scan, difference of about −24.4%, and the ratio between the lesion and gray matter uptake was 0.77 in the early and 0.80 in the late phase with L/GM difference of 3.6%.
100% sensitivity and 100% specificity (i.e., 0% false-positive rate and 0% false-negative rate). The area under the ROC curve (AUC) was determined with its corresponding 95% confidence interval. The cutoff values obtained were further tested to determine the sensitivity, specificity, and accuracy. \( P < 0.05 \) was used to define statistical significance.

3. Results

Dual phase FDG-PET/CT imaging was performed on 16 consecutive patients (9 men and 7 women, 24-60 years old) based on histopathological data of the 16 patients included in our study, 7 patients had low grade gliomas (L) while 9 had high grade gliomas (H). All patients did not receive chemotherapy or radiotherapy at the time of examination.

Table 1 shows SUVmax early and SUVmax late of the lesions (L) and gray matter (GM), as well as the percent change over time, and ratios of L SUVmax to GM SUVmax at early and late time points, and the percent change in L/GM over time as well as the corresponding PET CT and histopathological grading. SUV mean data trends (not shown) were similar to SUVmax trends, but the latter were more accurate at predicting the diagnosis. The most accurate parameter of all variables analyzed, the ratio of the change of the lesion to GM ratios over time \((\text{L}2/\text{GM}2 - \text{L}1/\text{GM}1)/(\text{L}1/\text{GM}1)\) was the most sensitive and specific predictor of outcome. When a 23% increase was used as the cutoff for analysis of the difference in SUVmax of the lesion (L) versus normal gray matter (GM) over time, the sensitivity was 88.9%, the specificity was 85.7%, and the accuracy was 89.4% \((P = 0.003; \text{AUC} = 0.94)\). Other parameters such as the mean SUV, early SUV ratios, and SUV at early or late time points were less accurate. The change in SUVmax of lesion to gray matter over time was clearly the most accurate parameter. In some cases, delayed images demonstrated tumor activity much more convincingly than the early images did. This was most notable in cases of high grade glioma in areas of functionally active brain (Fig. 2).

4. Discussion

According to the classification of the World Health Organization (WHO), gliomas are of 3 main types: astrocytomas, oligodendrogliomas, and mixed oligoastrocytomas which can usually be distinguished by their histologic features. These tumors are typically heterogeneous in that different levels of malignant degeneration can occur in different regions within the same tumor. Analysis of the most malignant region of the tumors establishes grading: low-grade, or WHO grades I and II, and high-grade, or WHO grades III and IV. Grading is based on the degree of nuclear atypia, mitosis, microvascular proliferation, and necrosis, with increasing anaplasia as tumor grade increases. The histologic features of the tumor and the age and performance status of the patient are major prognostic factors on outcome (7).

Several studies have explored the usefulness of dual time point F-18 FDG positron emission tomography imaging (DTPI) in improving detection of brain metastases and tumors outside the brain, distinguishing malignant from benign lesions or distinguishing malignant from inflammatory lesions (8). Several investigations of delayed or DTPI F-18 FDG PET of tumors have focused on measurements of SUV or tumor-to-non tumor ratios and have shown that F-18 FDG uptake does not plateau until well after the duration of standard F-18 FDG PET studies (60 min after administration of F-18 FDG) (9). Spence et al. (6) had reported that F-18 FDG uptake of a malignant brain lesion was gradually increased until 180 min after administration. As a result, DTPI may show better performance to grade of brain tumors. F-18 FDG PET is a technique that permits measurement of regional cerebral glucose metabolism. It provides a unique opportunity for the study of physiological processes and is useful in the differentiation of low-grade and high-grade gliomas (10). However Kaschten

<table>
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et al. (11) and Sasaki et al. (12) reported that F-18 FDG uptake did not allow differentiation between grade III and grade IV gliomas.

Cutoff values for tumor-to-normal brain ratios have been proposed by different authors, but the methodology and references must be analyzed carefully. For prediction of prognosis inside high-grade gliomas, Patronas et al. (13) used a cutoff value of 1.4 for FDG tumor to contralateral region ratio, but their results are not transposable because most of their 45 cases were recurrences. Delbeke et al. (14), on 58 untreated gliomas studied with FDG, found that optimal cutoff value for differentiation between low- and high-grade gliomas was 0.6 for tumor-to-fronto-parietal cortex ratio and 1.5 for the T/WM ratio. No cutoff level was proposed between Grades III and IV gliomas.

It is clear that increasing 18F-FDG-avid lesion SUVmax values, decreasing background SUVmax values, and increasing lesion-to-background SUVmax ratio, support the potential utility of delayed phase and dual-time-point diagnostic 18F FDG PET/CT imaging. This suggests that delayed scans performed at an appropriately selected extended injection-to-scan acquisition time intervals can potentially minimize or alleviate the issue of overlap in the pattern of 18F-FDG uptake between benign tissues versus malignant tissues, as well as between background tissues versus malignant tissues. However, further investigations are warranted to better assess this phenomenon and to formally evaluate the clinical usefulness of extended injection-to-scan acquisition time intervals in various diagnostic 18F-FDG PET/CT oncologic imaging applications (15).

Di Chiro and coworkers (16) pioneered the application of FDG-PET to gliomas. High-grade gliomas contained regions of high FDG uptake and lower grade gliomas lacked these regions. Patients with grade III or IV astrocytic gliomas tumor uptake of FDG greater than the cortex were associated with a median survival of about 10 months (17). More recently, Padma et al. (18) reported 331 cases assessed by tumor/reference region ratios: 0 = no uptake, 1 ≤ normal white matter (WM), 2 normal WM < lesion < normal cortex, and 3 ≥ normal cortex. In categories 0 and 1 combined, 86% of the tumors were grade I or II by pathology grading, with a median survival of 2.3 years. In categories II and III combined, 94% were grade III or IV, with a median survival of 11 months.

Whereas several factors influencing survival have been identified in patients with high-grade astrocytoma, the prognostic factors in adult low-grade gliomas remain poorly defined (19). Therefore, management of low-grade gliomas is still a subject of controversy. Low-grade gliomas may present histological features of benign tumor but 20–25% per year undergo malignant transformation. Low-grade gliomas may show histological features of a benign tumor, but it is well known that this may not be reflected in their long-term clinical course. The 5 year survival has been reported to range from 15% to 62%. The average survival ranges between 23 and 63 months. These figures vary with tumor location, patient’s age, surgical intervention and radiotherapy. The natural history of a low-grade glioma is not predictable from the histological picture in an individual case. Muller et al. (20) studied 137 recurrent low-grade gliomas and found that of grade I tumors, 56% progressed to grade II and 31% to GBM over a period of 5 years. It has been shown that increased FDG uptake in histologically proven low-grade glioma predicts in most cases a deleterious evolution. This metabolic feature, detectable with a non-invasive procedure, may provide a clue to cellular changes announcing malignant transformation in a tumor which keeps histological features of a low-grade glioma (17). Such data indicate that PET may help in the stratification of patients entered in protocols which evaluate therapeutic strategies in brain tumors. In high-grade gliomas, Barker et al. (21) studied the prognostic value of FDG PET in 55 patients with malignant glioma. In univariate analysis, the FDG PET score was a significant predictor of survival time after FDG PET scanning (P = 0.005). Median survival was 10 months for patients with FDG PET high uptake scores of 2 or 3 and 20 months for
those with low uptake scores of 0 or 1. In multivariate proportional hazards analysis the FDG PET score was a significant predictor of survival ($P = 0.019$) in a model that included patient’s age and FDG PET.

Our study results correlated with the results done by Delbeke et al. that showed sensitivity of 94% and specificity of 77% of dual phase PET CT in grading of gliomas, while Kim et al. showed good correlation between dual phase PET CT grading and histological grading of gliomas with $P < 0.035$ compared to $P < 0.003$ in our study; however, our statistics identified the L/GM ratio as the most accurate parameter correlated with pathological results for grading of glioma. Kim et al. showed that SUVmax in the delayed images is the best parameter for grading, while Delbeke et al. showed that Cutoff levels of 1.5 for the T/WM FDG uptake ratio and 0.6 for the T/C ratio are useful in the differentiation of low-grade from high-grade gliomas with PET, and these differences could be attributed to low number of cases studied as well as the small low group glioma patients.

Our study had some limitations, the study population was small, and no correlation with other imaging modalities and large prospective investigations are needed to support our data.

In conclusion dual phase FDG PET CT has been proved to be a reliable predictor of the proliferative activity of gliomas when compared to histopathological classification and can be used for preoperative grading and as a prognostic factor of gliomas.

**Conflict of interest**

The authors declare that there is no conflict of interest.

**References**


(15) Povoski SP, Murrey Jr DA, Smith SM, Martin Jr EW, Hall NC. 18F-FDG PET/CT oncologic imaging at extended injection to scan acquisition time intervals derived from a single institution 18 F-FDG directed surgery experience: feasibility and quantification of 18 F-FDG accumulation within avid lesions and back ground tissues. BMC Cancer 2014 Jun;14(14):453.


