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Comparison of dual-time point ^{18}F-FDG PET/CT tumor-to-background ratio, intraoperative 5-aminolevulinic acid fluorescence scale, and Ki-67 index in high-grade glioma

Yong-il Kim, MD, PhD[a], Kyung Gi Cho, MD, PhD[b], Su Jin Jang, MD, PhD[c,*]

Abstract

The aim of this study was to compare preoperative dual-time point ^{18}F-fluorodeoxyglucose (FDG) uptake pattern with intraoperative 5-aminolevulinic acid (5-ALA) fluorescence in high-grade gliomas. In addition, we assessed for possible associations with a pathologic parameter (Ki-67 index).

Thirty-one patients with high-grade glioma (M:F = 19:12, mean age = 60.6 ± 11.2 years) who underwent dual-time point ^{18}F-FDG positron emission tomography (PET)/computed tomography (CT) scan before surgery were retrospectively enrolled; 5-ALA was applied to the surgical field of all these patients and its fluorescence intensity was evaluated during surgery. Measured ^{18}F-FDG PET/CT parameters were maximum and peak tumor-to-background ratio (maxTBR and peakTBR) at base (-base) and delayed (-delay) scan. The intensity of 5-ALA fluorescence was graded on a scale of three (grade I as no or mild intensity, grade II as moderate intensity, and grade III as strong intensity).

Seven of the patients had WHO grade III brain tumors and 24 had WHO grade IV tumors (mean tumor size = 4.8 ± 1.8 cm). MaxTBR-delay and peakTBR-delay showed significantly higher values than maxTBR-base and peakTBR-base, respectively (all $P < .001$). Among the ^{18}F-FDG PET/CT parameters, only maxTBR-delay demonstrated significance according to grade of 5-ALA ($P = .030$), and maxTBR-delay gradually decreased as the fluorescence intensity increased. Also, maxTBR-delay and peakTBR-delay showed significant positive correlation with Ki-67 index ($P = .011$ and .009, respectively).

Delayed ^{18}F-FDG uptake on PET/CT images could reflect proliferation in high-grade glioma, and it has a complementary role with 5-ALA fluorescence.

Abbreviations: 5-ALA = 5-aminolevulinic acid, CT = computed tomography, FDG = fluorodeoxyglucose, IHC = immunohistochemistry, PET = positron emission tomography, SUV = standardized uptake value, TBR = tumor-to-background ratio, TOF = time-of-flight, VOI = volume of interest.

Keywords: 5-aminolevulinic acid, dual-time PET, fluorescence, fluorodeoxyglucose, glioma, Ki-67 index

1. Introduction

High-grade glioma is an aggressive tumor with a poor prognosis; one-year survival is approximately 30%.[1] Cytoreductive surgery is known to prolong the survival of patients with high-grade glioma and is thought to be essential for successful adjuvant treatment.[2] However, complete resection of high-grade glioma is difficult because viable tumor tissue is sometimes hard to distinguish from brain tissue.[3]

Recently, 5-aminolevulinic acid (5-ALA) has emerged as a metabolic marker of malignant cells that can be used intraoperatively to identify tumor tissue.[4] 5-ALA is a natural biochemical precursor of hemoglobin that demonstrates synthesis and accumulation of fluorescent porphyrins in malignant cells.[5] A previous study showed that a significantly larger number of complete resections can be achieved using 5-ALA fluorescence-guided tumor resection compared with conventional white light-guided microsurgery.[6]

Positron emission tomography (PET)/computed tomography (CT) with radiolabeled glucose analog (^{18}F-fluorodeoxyglucose [FDG]) is widely used for tumor initial staging, treatment response evaluation, detection of recurrence, and prognosis.[7] In brain tumors, ^{18}F-FDG PET/CT is known to be useful for characterization and prognosis prediction of glioma.[8] Furthermore, the dual-time point PET/CT protocol, which includes both base and delayed imaging, is known to be useful for accurate tumor identification and characterization in brain tumor,[9,10] lung cancer,[11,12] breast cancer,[13] and other solid tumors.[14,15] Previous studies for brain tumor reported that base PET/CT scan was done in 45–60 min. And delayed PET/CT scan was performed in 180–360 min with more than 10% of uptake ratio increase than base PET/CT scan.[9,10]

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The authors declare that they have no conflict of interest.

[a] Department of Nuclear Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, [b] Department of Neurosurgery, CHA Bundang Medical Center, CHA University, Seongnam, [c] Department of Nuclear Medicine, CHA Bundang Medical Center, CHA University, Seongnam, Republic of Korea.

[*] Correspondence: Su Jin Jang, Department of Nuclear Medicine, CHA Bundang Medical Center, CHA University, 59 Yatap-ro, Bundang-gu, Seongnam-si, Gyeonggi-do, 13496, Republic of Korea (e-mail: jsjnm07@cha.ac.kr).

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The aim of this study was to find the difference and identify the relationship between dual-time point ^{18}F-FDG PET/CT uptake and intraoperative 5-ALA fluorescence in high- grade glioma. In addition, we examined the association of dual-time point ^{18}F-FDG PET/CT uptake and intraoperative 5-ALA fluorescence with a pathologic parameter (Ki-67 index).

2. Materials and methods

2.1. Patients

From January 2011 to December 2016, 336 patients had dual-time point brain ^{18}F-FDG PET/CT (base and delayed scan) performed at our institution. Among them, 134 patients who underwent brain tumor surgery with intraoperative 5-ALA imaging were retrospectively identified. Patients were further selected with the following inclusion criteria:

(1) Pathologically confirmed high-grade glioma,
(2) preoperative brain ^{18}F-FDG PET/CT performed less than 2 months before surgery, and no previous treatment, and
(3) ^{18}F-FDG PET/CT imaging with the same machine.

The study design and waiver of informed consent were approved by the Institutional Review Board (IRB) of our institution (No. 2017–09–041).

2.2. ^{18}F-FDG PET/CT protocol

After the patient fasted for at least 6 h, 5 mCi (185 MBq) of ^{18}F-FDG was injected intravenously, and imaging was performed using a fusion PET/CT scanner 1 h later as base scan (Biograph mCT 128; Siemens Medical Solutions, Knoxville, TN, USA). CT images were acquired from the vertex to skull base area for determination of the attenuation map and lesion localization (120 kV, 120 mA, 3 mm section width, 3 mm collimation). PET images of the same area were acquired after the CT scans, in 3-dimensional mode (7 min per bed position, 21.6 cm increments). Delayed scan was performed 3 h after ^{18}F-FDG injection using the same methods. Images were reconstructed on 400 × 400 matrices using the TrueX algorithm plus time-of-flight (TOF) reconstruction (UltraHD PET). The images were analyzed using a dedicated workstation and analysis software (Syngo.via, Siemens Medical Solutions, Knoxville, TN, USA).

2.3. ^{18}F-FDG PET/CT image analysis

All of the following ^{18}F-FDG PET/CT parameters were acquired by defining a volume of interest (VOI) at the workstation by two nuclear medicine physicians blinded to the study. Standardized uptake value (SUV) was calculated initially, using the following equation: SUV = (tissue radioactivity [Bq]/tissue weight [g])/(injected activity [Bq]/body weight [g]). Maximum pixel uptake (maxSUV) and peak pixel uptake (peakSUV) of brain tumor were measured at base (-base) and delayed (-delay) scan. Mean pixel uptake (meanSUV) of contralateral white matter was measured as background,[16] and tumor-to-background ratio (TBR; brain tumor uptake divided by background uptake) was calculated (maxTBR-base, peakTBR-base, maxTBR-delay, and peakTBR-delay, respectively). The ratio between base and delay scan ([delay uptake–base uptake]/[delay uptake]) of maxSUV and peak SUV were also evaluated and named as maxSUV ratio and peakSUV ratio, respectively.[17] The largest diameter of the brain tumor was measured as tumor size (cm) in transaxial fusion PET/CT images.

2.4. Intraoperative 5-ALA-induced fluorescence and its evaluation

All of the included patients received 5-ALA (20 mg/kg body weight; Gliolan, medac, Wedel, Germany) for fluorescence-guided brain tumor resection. The 5-ALA solution was prepared by dissolving a vial of 5-ALA (1:5 g) in 50 ml of water. The 5-ALA solution was administered orally 3 h before induction of anesthesia. Surgery was performed by using a neurosurgical microscope (NC 4 OPMI Neuro FL or Pentero surgical microscope, Zeiss, Oberkochen). The microscope enabled switching from conventional white light to violet-blue excitation light to visualize tumor fluorescence. Before resection of the brain tumor, manual white balance was done to normalize the fluorescence signal intensity. Immediately after exposure of the lesions, the brain tumors were examined under the fluorescence mode of the microscope. The presence of 5-ALA fluorescence was visually graded on a scale of three after white (grade I as no or mild intensity, grade II as moderate intensity, and grade III as strong intensity) by two neurosurgeons blinded to the study (Fig. 1).[18] Tumor resection was performed as completely as possible and thought to be safely feasible by the surgeon.

2.5. Evaluation of pathologic parameter

All tissue samples were histologically classified according to the WHO classification of tumors of the central nervous system.[19] Additional immunohistochemistry (IHC) study was performed with antibodies against proliferation-associated antigen Ki-67 (clone: MIB-1, primary antibody dilution: 1:200; Dako) following standard protocols. IHC results of the Ki-67 index were quantified using semiquantitative staining scores according to cell and vascular density.[20,21]

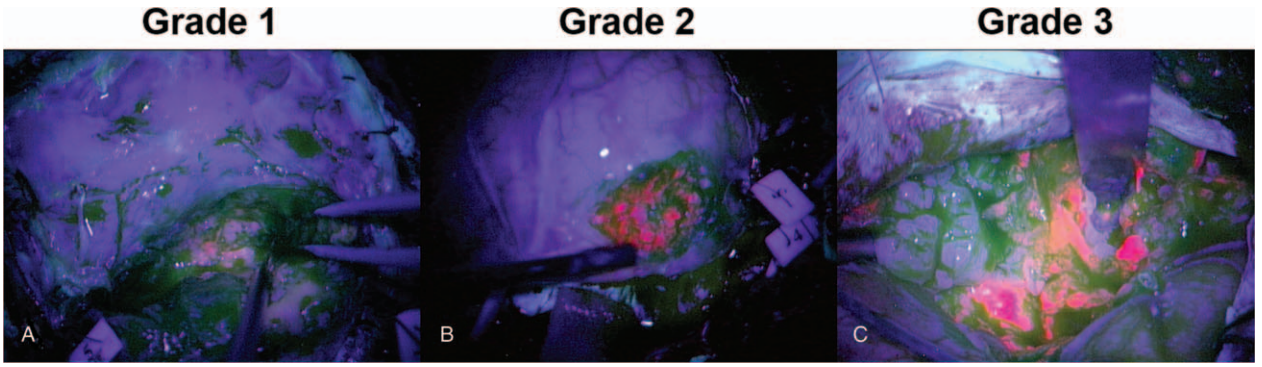

Figure 1. Grade of intraoperative 5-aminolevulinic acid (5-ALA) fluorescence. Fluorescence intensity of 5-ALA was graded on a scale of three; grade I as no or mild intensity (A), grade II as moderate intensity (B), and grade III as strong intensity (C).

Table 1

Baseline characteristics of the patients.

Characteristics	Values
Number of patients	31
Gender	male:female = 19:12
Age (years)	60.6 ± 11.2 (range = 38.0–80.0)
Tumor size (cm)	4.8 ± 1.8 (range = 1.3–9.0)
Tumor side	right:left = 20:11
Tumor location	
Frontal lobe	8 (25.8%)
Parietal lobe	6 (19.4%)
Temporal lobe	10 (32.3%)
Basal ganglia & thalamus	5 (16.1%)
Cerebellum	2 (6.4%)
Tumor pathology	
Anaplastic astrocytoma	4 (12.9%)
Anaplastic oligodendroglioma	2 (6.5%)
Anaplastic oligoastrocytoma	1 (3.2%)
Glioblastoma	23 (74.2%)
Giant cell glioblastoma	1 (3.2%)
WHO grade	
Grade III	7 (22.6%)
Grade IV	24 (77.4%)
Ki-67 index (%)	25.7 ± 15.6 (range = 6.0–70.0)

2.6. Statistical analysis

Direct comparison between parameters obtained from base and delayed ^{18}F-FDG PET/CT scans was done by paired t-test, and evaluation of ^{18}F-FDG PET/CT parameters according to grade of 5-ALA was done by Mann-Whitney U test. Comparison of ^{18}F-FDG PET/CT parameters and grade of 5-ALA according to Ki-67 index was performed using Pearson's correlation coefficient. A *P*-value less than .05 was considered significant. All statistical analyses were performed using SPSS software (Version 18.0; SPSS Inc., Chicago, IL, USA) and MedCalc (Version 12.2; MedCalc Inc., Mariakerke, Belgium).

3. Results

3.1. Patients

Thirty-one patients with pathologically proven high-grade glioma were included in this study (male:female = 19:12, mean age = 60.6 ± 11.2 years). Mean tumor size was 4.8 ± 1.8 cm (range = 1.3–9.0 cm) and main tumor locations were frontal lobe in eight patients, parietal lobe in six patients, temporal lobe in 10 patients, basal ganglia/thalamus in five patients, and cerebellum in two patients. WHO grade of brain tumor was grade III in seven patients: Anaplastic astrocytoma (4), anaplastic oligodendroglioma (2), and anaplastic oligoastrocytoma (1); and grade IV in 24 patients: Glioblastoma (23), and giant cell glioblastoma (1). The mean Ki-67 index of the tumors was 25.7% ± 15.6% (range = 6.0–70.0%) (Table 1).

3.2. Results of dual-time point ^{18}F-FDG PET/CT and 5-ALA-induced fluorescence

All of the brain tumors showed discernible ^{18}F-FDG uptake in both base and delayed PET/CT (Fig. 2). Delayed parameters

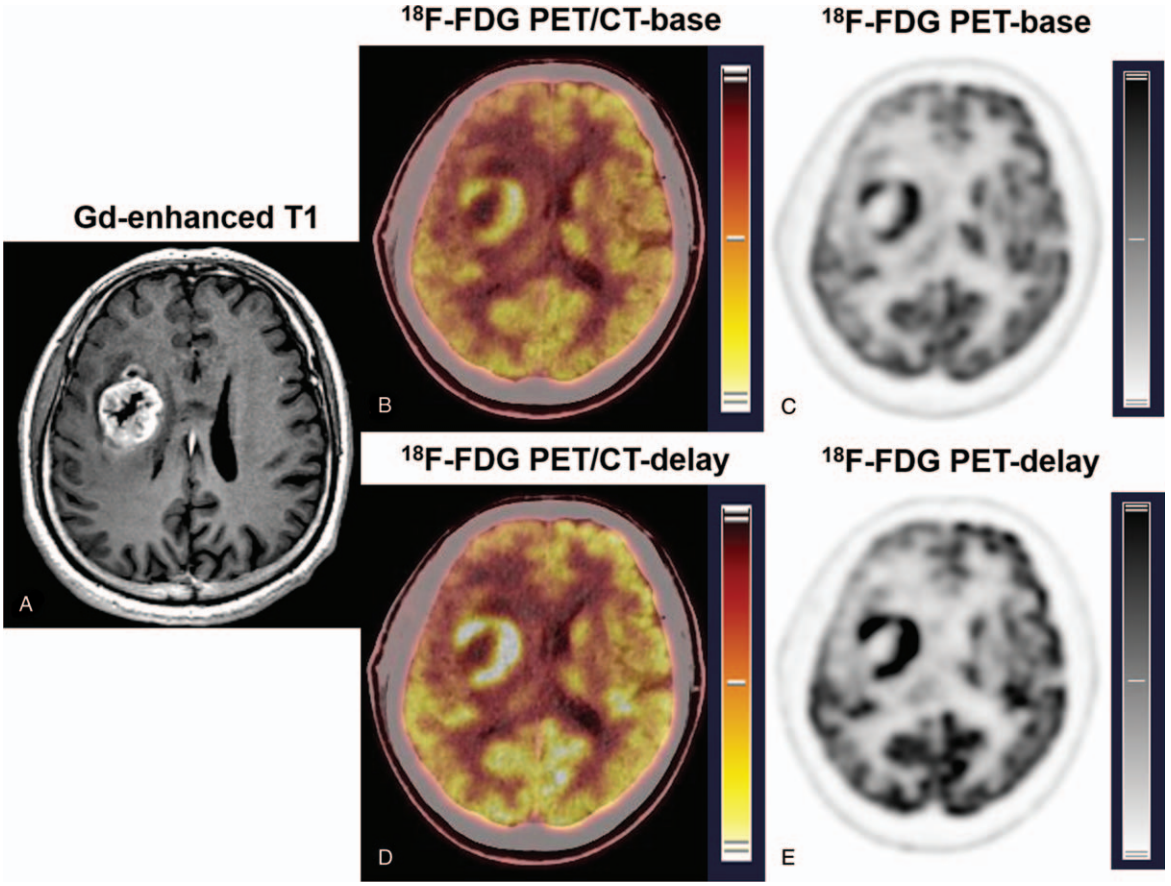

Figure 2. Representative ^{18}F-FDG PET/CT base and delayed scan images. A 65-year-old man underwent dual-time point ^{18}F-FDG PET/CT due to a 4.7 cm-sized enhancing brain tumor in the right basal ganglia (A). Base (B & C; maxTBR-base = 6.12, peakTBR-base = 4.60) and delayed (D & E; maxTBR-delay = 9.64, peakTBR-delay = 7.18) parameters demonstrated intense uptake in the brain tumor. The brain tumor was found to be glioblastoma, and the Ki-67 index was high (70%).

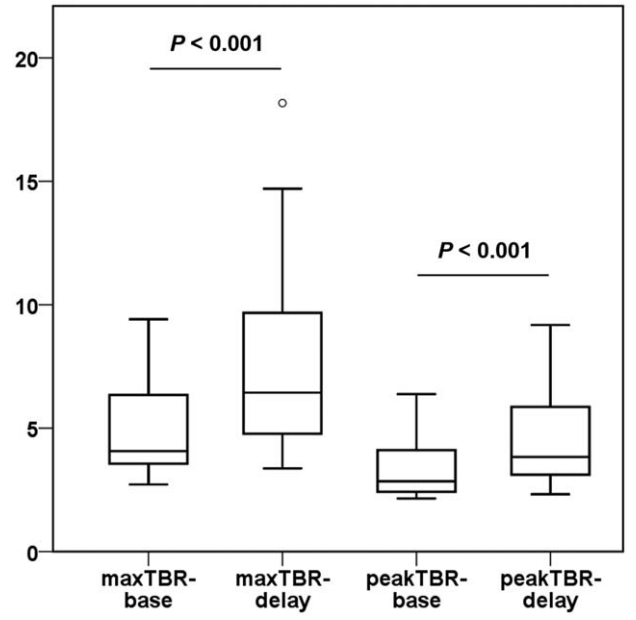

Figure 3. Comparison of dual-time point ^{18}F-FDG PET/CT parameters. MaxTBR-base (4.9 ± 1.9) and maxTBR-delay (7.4 ± 3.6) showed significance ($P < .001$), and peakTBR-base (3.3 ± 1.1) and peakTBR-delay (4.5 ± 1.8) also demonstrated significance ($P < .001$).

(maxTBR-delay = 7.4 ± 3.6, peakTBR-delay = 4.5 ± 1.8) showed significantly higher values than base parameters (maxTBR-base = 4.9 ± 1.9, peakTBR-base = 3.3 ± 1.1) (all $P < .001$, Fig. 3). The fluorescence intensity of 5-ALA was grade I in 13 patients, grade II in nine patients and grade III in nine patients.

3.3. Comparison between dual-time point ^{18}F-FDG PET/CT and 5-ALA fluorescence

Base, delay, and ratio parameters of ^{18}F-FDG PET/CT were compared according to grade of 5-ALA. Among those parameters, only maxTBR-delay showed significance ($P = .030$), and maxTBR-delay gradually decreased as the fluorescence intensity increased (Table 2). Post hoc analysis of maxTBR-delay showed significance between 5-ALA grade I versus II ($P = .025$) and 5-ALA grade I versus III ($P = .030$).

3.4. Correlation of ^{18}F-FDG PET/CT and 5-ALA fluorescence with Ki-67 index

Base, delay, and ratio parameters of ^{18}F-FDG PET/CT and grade of 5-ALA were correlated with Ki-67 index in each case. MaxTBR-delay and peakTBR-delay showed significant positive correlation ($P = .011$ and .009, respectively; Fig. 4). However, other ^{18}F-FDG PET/CT parameters and grade of 5-ALA did not demonstrate significant results (Table 3).

4. Discussion

In summary, ^{18}F-FDG PET/CT parameters of delayed scan showed significantly higher uptake values than base scan, and maxTBR-delay was associated with intraoperative 5-ALA fluorescence. Also, maxTBR-delay and peakTBR-delay demonstrated positive correlation with brain tumor Ki-67 index, while 5-ALA fluorescence did not. To our knowledge, ours is the first study to evaluate the relationship among dual-time point ^{18}F-FDG PET/CT, intraoperative 5-ALA fluorescence, and a pathologic parameter (Ki-67 index).

Intraoperative 5-ALA-induced fluorescence has been known to be a sensitive and specific tool for visualizing residual contrast-enhancing tumor during surgery for high-grade gliomas.[22] However, the influence on patient survival of intraoperative use of 5-ALA is relatively small.[6,23] In our study, 5-ALA fluorescence was helpful to identify the lesion in all of the patients; however, no association was found to the Ki-67 index, which is a tumor proliferation marker known to reflect prognosis.[24,25] The accumulation of 5-ALA requires metabolic conversion into fluorescing protoporphyrin IX in glioma cells.[5] However, because the mechanisms governing 5-ALA uptake and conversion into fluorescent porphyrin IX are not well understood, the relationship between 5-ALA uptake and FDG uptake is of special interest.

It has been demonstrated that the use of ^{18}F-FDG PET/CT scan can detect high-grade brain tumor,[26] differentiate tumor recurrence,[27] predict prognosis,[28,29] and has been studied to discern the type of brain tumor.[30] Despite the usefulness of ^{18}F-FDG PET/CT, ^{18}F-FDG PET/CT has limitation for accurate assessment of brain tumor as the radiotracer has high physiologic uptake in normal gray matter.[31,32] To overcome this limitation, there have been several attempts to enhance the detection rate of brain tumors with dual-time point ^{18}F-FDG PET/CT.[9,10,33,34] According to previous studies, tumor tissue shows gradual accumulation of ^{18}F-FDG, suggesting that the contrast between tumor and normal background on delayed PET/CT could be higher than that on base PET/CT.[35,36] In our study, as in previous studies, delay parameters revealed significantly higher values than base parameters. Therefore, the delayed PET/CT could characterize high- grade tumor better than base PET/CT. Also, only parameters obtained from delayed PET/CT (maxTBR-delay) demonstrated a significant association with 5-ALA fluorescence.

Table 2

Comparison of ^{18}F-FDG PET/CT parameters according to grade of 5-ALA.

Parameters	5-ALA grade I ($n = 13$)	5-ALA grade II ($n = 9$)	5-ALA grade III ($n = 9$)	*P*-value
Tumor size (cm)	5.0 ± 2.1	4.5 ± 1.9	4.8 ± 1.1	0.909
MaxTBR-base	5.9 ± 2.3	3.9 ± 1.2	4.4 ± 1.1	0.083
PeakTBR-base	3.7 ± 1.2	2.9 ± 0.9	3.0 ± 0.7	0.412
MaxTBR-delay	9.7 ± 4.2	5.9 ± 2.3	5.7 ± 1.6	0.030*
PeakTBR-delay	5.4 ± 2.0	4.0 ± 1.7	3.7 ± 0.7	0.091
MaxTBR-ratio	0.36 ± 0.14	0.31 ± 0.81	0.20 ± 0.16	0.065
PeakTBR-ratio	0.30 ± 0.13	0.25 ± 0.10	0.17 ± 0.14	0.561

5-ALA = 5-aminolevulinic acid, CT = computed tomography, FDG = fluorodeoxyglucose, maxTBR = maximum tumor-to-background ratio, peakTBR = peak tumor-to-background ratio, PET = positron emission tomography.

* Statistically significant ($P < .05$).

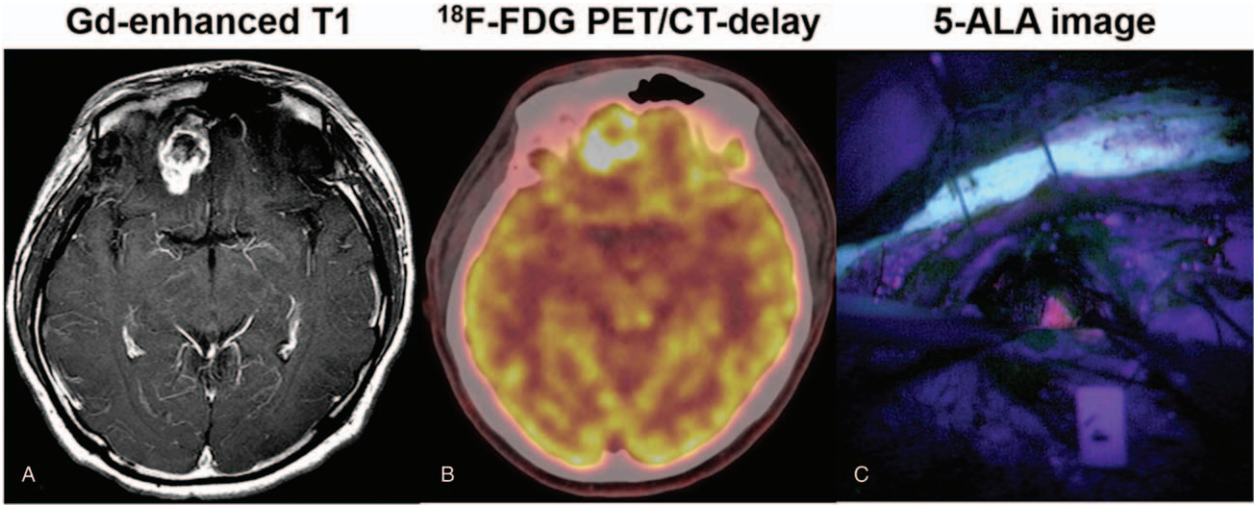

Figure 4. Complementary role between ^{18}F-FDG PET/CT delayed parameters and grade of 5-ALA. A 42-year-old man underwent dual-time point ^{18}F-FDG PET/CT due to a 3.5 cm-sized enhancing brain tumor in the right frontal lobe (A). Delay parameters (B; maxTBR-delay = 6.35, peakTBR-delay = 9.91) demonstrated intense uptake in the brain tumor; however, 5-ALA fluorescence showed mild intensity (grade I). The brain tumor was found to be glioblastoma, and Ki-67 index was high (45%).

Ki-67 index, also known as proliferation activity or proliferation fraction, is a powerful prognostic indicator in a variety of cancers. High Ki-67 index is associated with worse disease-free survival and/or overall survival in brain tumor.[24,37] Also, there is strong correlation between the grade of malignancy and Ki-67 index in glial neoplasms.[38] Furthermore, Ki-67 index is affordable and easily assessed on paraffin-embedded tumor. For these reasons, we used the Ki-67 index for the high-grade gliomas we assessed. In our study, Ki-67 index was significantly correlated with delay PET/CT parameters (maxTBR-delay and peakTBR-delay), but it was not associated with base and ratio PET/CT parameters. This means that maxTBR-delay and peakTBR-delay could reflect the tumor proliferation activity and could possibly predict the prognosis.

Our study has some limitations. First, this is a retrospective study and the number of included patients was relatively small. Second, the mechanism of the association between delayed ^{18}F-FDG PET/CT uptake and 5-ALA fluorescence was not studied. Last, prognosis (disease-free survival and/or overall survival) of the patients was not evaluated due to the small number of follow-up patients and short follow-up period. A larger-scale, prospective study investigating mechanism and prognosis is required to confirm our results.

Table 3

Correlation between ^{18}F-FDG PET/CT parameters and grade of 5-ALA with Ki-67 index.

Parameters correlated with Ki-67 index	Pearson's correlation coefficient	*P*-value
Tumor size	−0.086	0.647
MaxTBR-base	0.260	0.158
PeakTBR-base	0.287	0.118
MaxTBR-delay	0.452	0.011*
PeakTBR-delay	0.464	0.009*
MaxTBR-ratio	0.205	0.269
PeakTBR-ratio	0.174	0.349
5-ALA fluorescence	0.064	0.730

5-ALA = 5-aminolevulinic acid, CT = computed tomography, FDG = fluorodeoxyglucose, maxTBR = maximum tumor-to-background ratio, peakTBR = peak tumor-to-background ratio, PET = positron emission tomography.
* Statistically significant ($P < .05$).

5. Conclusions

In conclusion, we found complementary roles for ^{18}F-FDG PET/CT delayed scan and intraoperative 5-ALA fluorescence in the evaluation and treatment of high-grade gliomas. ^{18}F-FDG PET/CT delayed scan could reflect the proliferation status of the brain tumor as well as detect most of the lesions, and 5-ALA fluorescence could guide exact localization and resection of the brain tumor. Our study suggests that both ^{18}F-FDG PET/CT delayed scan and 5-ALA fluorescence should be performed for accurate characterization and surgery in high-grade glioma.

Author contributions

Conceptualization: Yong-il Kim, Su Jin Jang.
Data curation: Kyung Gi Cho.
Formal analysis: Yong-il Kim.
Methodology: Yong-il Kim, Su Jin Jang.
Resources: Kyung Gi Cho.
Supervision: Su Jin Jang.
Writing – original draft: Yong-il Kim.
Writing – review & editing: Kyung Gi Cho, Su Jin Jang.
Su Jin Jang orcid: 0000-0001-6103-6830.

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