Maximum Lesion-To-Contralateral Normal Brain Tissue Ratio of ^{11}C -Methionine PET as a Prognostic Imaging Biomarker for Newly Diagnosed and Untreated Astrocytic Glioma

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Abstract

Purpose: This study aimed whether the uptake of amino tracer positron emission tomography (PET) can be used as an additional imaging biomarker to estimate the prognosis of glioma.

Methods: Participants comprised 56 adult patients with newly diagnosed and untreated World Health Organization (WHO) grade II–III astrocytic glioma who underwent surgical excision and were evaluated by 11C-methionine PET prior to the surgical excision at Osaka City University Hospital from July 2011 to March 2018. Clinical and imaging studies were retrospectively reviewed based on medical records at our institution.

Results: Preoperative Karnofsky Performance Status (KPS) only influenced progression-free survival (PFS) (hazard ratio [HR] 0.20; 95% confidence interval [CI] 0.10–0.41, $p < 0.0001$), whereas histology (anaplastic astrocytoma: HR 5.30, 95%CI 1.23–22.8, $p = 0.025$; glioblastoma: HR 11.52, 95%CI 2.27–58.47, $p = 0.0032$), preoperative KPS ≥ 80 (HR 0.23, 95%CI 0.09–0.62, $p = 0.004$), maximum lesion-to-contralateral normal brain tissue (LN max) ≥ 4.03 (HR 0.24, 95%CI 0.08–0.71, $p = 0.01$), and isocitrate dehydrogenase (*IDH*) status (HR 14.06, 95%CI 1.81–109.2, $p = 0.011$) were factors influencing overall survival (OS) in multivariate Cox regression. OS was shorter in patients with LN max ≥ 4.03 (29.3 months) than in patients with LN max < 4.03 (not reached; $p = 0.03$). OS differed significantly between patients with *IDH* mutant/LN max < 4.03 and patients with *IDH* mutant/LN max ≥ 4.03 .

Conclusions: LN max using 11C-methionine PET may be used in prognostic markers for newly identified and untreated WHO grade II–III astrocytic glioma.

Introduction

Gliomas are the second most common primary brain tumors according to the 2012–2016 Central Brain Tumor Registry of the United States¹. Approximately 48.3% of primary malignant brain tumors are glioblastomas, 16.7% are other astrocytomas, and 4.5% are oligodendrogliomas¹. Overall incidence rates for diffuse astrocytoma, anaplastic astrocytoma, and oligodendroglioma have been decreasing recently, but overall incidence rates for glioblastoma have remained stable².

Although magnetic resonance imaging (MRI) has been one of the basic and less-invasive imaging modalities used in the management of glioma, brain PET imaging has recently been recommended^{3,4}. We have previously reported a positive correlation between WHO grade and accumulation of 11C-methionine among astrocytomas, but that study did not analyze the relationship with prognosis⁵. Additional analysis was thus performed in the current study. Moreover, the clinical studies investigating the relationship between molecular analysis and uptake of amino acid PET in glioma patients are sparse, and detailed prognostic analyses of associations with molecular profiles and 11C-methionine PET uptake in glioma

patients have not been fully completed. This study aimed to evaluate the association between 11C-methionine uptakes, gene status, and prognosis in cases of newly diagnosed and untreated adult astrocytic glioma.

Methods

Patients

From July 2011 to March 2018, there were 66 adult patients and two patients under 18 years old with newly diagnosed and untreated WHO gradeⅡ-Ⅲ glioma who underwent surgical tumor resection and preoperative 11C-methionine PET examination, as previously reported⁵. From this previous cohort, we included adult astrocytic glioma patients with *IDH* mutated- *TERT* promoter wild-type, or those with *IDH* wild-type in the present study. Finally, a total of 56 patients with astrocytic tumor were included in the present cohort. The 56 patients were comprised of 36 male and 20 female patients, with a mean age of 54.0 years (range, 21–82 years). All 11C-methionine PET was performed within one month prior to tumor resection in glioblastoma patients and within six months in patients with lower-grade glioma. Pathological diagnosis was determined according to the 2016 WHO classification for central nervous system tumors⁶. This study was approved by the institutional review boards at the Graduate School of Medicine, Osaka City University (approval numbers: 2047 and 2020 – 115), and Osaka National Hospital (approval number: 0713). Written informed consent was obtained from all individual participants included in this study. This study was complied with all tenets of the Declaration of Helsinki.

11C-methionine PET

An Eminence B PET scanner (Shimadzu, Kyoto, Japan) or Biograph-16 PET scanner (Siemens, Bon, Germany) was used for 11C-methionine PET, according to previously reported procedures^{5,7}. Mean and maximum lesion-to-contralateral normal brain tissue (L/N) ratios were determined by dividing the tumor standardized uptake value by the mean standardized uptake value of the normal contralateral region of the brain, as previously reported⁵.

Genetic Analysis

Genetic analysis was performed as previously described⁵. Genomic DNA was extracted from surgically resected tumor specimens using the DNeasy Blood & Tissue Kit (Qiagen, Valencia, CA, USA) or NucleoSpin Tissue (Machery-Nagel, Duren, Germany). Hotspot mutations of *IDH1/2* (codon 132 of *IDH1* and codon 172 of *IDH2*) and *TERT* promoter (termed C228 and C250) were examined using Sanger sequencing with a 3130xLGenetic Analyzer (Thermo Fisher Scientific, Waltham, MA, USA) and Big-Dye® Terminator v1.1 Cycle Sequencing Kit (Thermo Fisher Scientific, Waltham, MA, USA).

Survival Times

Progression-free survival (PFS) was defined as the time in months between evaluation with 11C-methionine PET and tumor progression according to the Response Assessment in Neuro-oncology

working group⁸. Overall survival was defined as the time in months between evaluation with 11C-methionine PET and death.

Statistical Analysis

Patients were subdivided into several groups on the basis of age (≥ 70 or < 70 years), preoperative KPS (≥ 80 or < 80), LN mean (≥ 2.46 or < 2.46), LN max (≥ 4.03 or < 4.03), and extent of resection (biopsy or partial removal, $< 90\%$; subtotal/gross total removal, $\geq 90\%$) for statistical analysis.

To compare the patients background characteristics of each group classified according to *IDH* status or LN max or both, we performed statistical analysis using Pearson's chi-square test. PFS and OS were analyzed using the Kaplan-Meier method. Survival date were evaluated using uni- and multivariate Cox regression analyses. The stepwise method was used to evaluate PFS and OS multivariate Cox regression analyses. Statistical significance was defined at the level of $p < 0.05$. All statistical analyses were conducted using EZR software (Saitama Medical Center, Jichi Medical University, Saitama, Japan)⁹.

Results

Patient Characteristics

Patient characteristics are summarized in Table 1. Majority of patients with *IDH* mutant astrocytoma showed lower-grade astrocytoma especially diffuse astrocytoma, whereas the majority of patients with *IDH* wild-type astrocytoma had high-grade glioma, especially glioblastoma ($p = 0.009$). Median LN mean and LN max were 2.46, and 4.03, respectively. Approximately 70% of patients with LN max ≥ 4.03 showed glioblastoma, whereas nearly 60% of patients with LN max < 4.03 showed diffuse astrocytoma ($p < 0.0001$). According to *IDH* status/LN max classification, 10 patients with diffuse astrocytoma, one patient with anaplastic astrocytoma, and one patient with glioblastoma were classified into the *IDH* mutant with LN max < 4.03 group. One patient with anaplastic astrocytoma, and two patients with glioblastoma were classified into the *IDH* mutant with LN max ≥ 4.03 group. Seven patients with diffuse astrocytoma, five patients with anaplastic astrocytoma, and four patients with glioblastoma were classified into the *IDH* wild-type with LN max < 4.03 group. Two patients with diffuse astrocytoma, five patients with anaplastic astrocytoma, and 18 patients with glioblastoma were classified into the *IDH* wild-type with LN max ≥ 4.03 group.

Uni- and Multivariate Analyses for PFS and OS

In univariate analysis, age, enhancement on MRI, preoperative KPS, histology, *IDH* status, and *TERT* promoter status influenced PFS, whereas age, enhancement on MRI, preoperative KPS, LN mean, LN max, histology, and *IDH* status influenced OS (Table 2, Fig. 1). In multivariate Cox regression analysis, preoperative KPS only influenced PFS (HR 0.20, 95%CI 0.1–0.41, $p < 0.0001$), whereas histology (anaplastic astrocytoma: HR 5.3, 95%CI 1.23–22.8, $p = 0.025$; glioblastoma: HR 11.52, 95%CI 2.27–58.47, $p = .0032$), preoperative KPS ≥ 80 (HR 0.23, 95%CI 0.09–0.62, $p = 0.004$), LN max ≥ 4.03 (HR 0.24, 95%CI

0.08–0.71, $p = 0.01$), and *IDH* status (HR 14.06, 95%CI 1.81–109.2, $p = 0.011$) were influential factors on OS (Table 3).

Median PFS in patients with diffuse astrocytoma, anaplastic astrocytoma, and glioblastoma were 37.2 months, 9.6 months, and 4.7 months, respectively ($p = 0.0003$, Table 2). Median OS was more favorable in patients with preoperative KPS ≥ 80 (83.3 months) than in patients with preoperative KPS < 80 (12.6 months, $p < 0.0001$; Table 2, Fig. 2a). Median OS was more favorable in patients with diffuse astrocytoma, anaplastic astrocytoma, and glioblastoma were not applicable, 27.1 months, and 20.5 months, respectively ($p < 0.0001$, Table 2, Fig. 2b). Median OS was more favorable in patients with *IDH* mutation than that in patients with *IDH* wild-type (not reached vs. 26.1 months, respectively, $p < 0.0001$, Fig. 2c). Furthermore, OS appeared shorter in patients with LN max ≥ 4.03 (29.3 months) than in patients with LN max < 4.03 (not reached, $p = 0.03$; Fig. 2d).

OS in Patients Classified According to the *IDH* Status/LN max (Fig. 3)

Median OSs in patients with *IDH* mutant/LN max < 4.03 , *IDH* mutant/LN max ≥ 4.03 , *IDH* wild-type/LN max < 4.03 , and *IDH* wild-type/LN max ≥ 4.03 were not applicable (95%CI, NA-NA), 30.1 (95%CI, 30.1-NA), 20.5 (95%CI, 7.4–52.3) and 27.1 (95%CI, 12.6–39.8) months, respectively ($p = 0.001$). A significant difference in OS was seen between patients with *IDH* mutant/LN max < 4.03 and those with *IDH* mutant/LN max ≥ 4.03 ($p = 0.034$), although no significant difference in OS was seen between patients with *IDH* mutant/LN max ≥ 4.03 and those with *IDH* wild-type/LN max < 4.03 ($p = 0.40$), or between patients with *IDH* wild-type/LN max < 4.03 and those with *IDH* wild-type/LN max ≥ 4.03 ($p = 0.84$).

Discussion

The revised WHO 2016 classification of the central nervous system tumor requires the pathological diagnosis with molecular analysis to reach a diagnosis of glioma⁶. This molecular information has been said to correlate with prognosis, whereas there is still a matter of debate whether imaging biomarkers help estimation of prognosis. Although MRI remains the gold standard for diagnosing glioma, its role in estimating prognosis is limited¹⁰. On the other hand, 11C-methionine PET using amino tracer might be useful to detect the tumor, predict the grade or genetic status or both^{5,11–14}, and distinguish tumor recurrence from radiation necrosis^{15–17} in glioma patients. However, relatively few reports have investigated the relationship between the uptake of amino tracer using PET and prognosis in glioma. Moreover, reports investigating prognosis of glioma patients in association with molecular analysis and PET in glioma have been limited^{18–22}. Thus, our goal in the present study was to determine whether 11C-methionine PET can be used as an additional imaging biomarker of prognosis.

In the present study, we excluded patients with oligodendroglioma, or those with *IDH* mutated- *TERT* promoter mutated, or both because oligodendroglioma is considered to show better prognosis than astrocytoma and is often accompanied by both *IDH* and *TERT* promoter mutations. Although *TERT*

promoter mutation is often seen in oligodendroglioma and primary glioblastoma, prognoses differ markedly between oligodendroglioma and glioblastoma^{23,24}. An argument has also been made regarding the association between uptake of 11C-methionine and oligodendroglioma^{14,25–28}. We have previously reported a positive correlation between WHO grade and the accumulation of 11C-methionine among astrocytomas, and a statistically higher uptake of 11C-methionine in oligodendroglioma than in diffuse astrocytoma⁵. Median survival rates in patients with diffuse astrocytoma, anaplastic astrocytoma, and glioblastoma in this study were 37.2 months, 9.6 months, and 4.7 months for PFS, and not reached, 27.1 months, and 20.5 months for OS, respectively. Reuss et al. reported that 139 of 152 patients with diffuse astrocytoma diagnosed according to the WHO 2007 classification of the central nervous system tumors showed *IDH* mutant diffuse astrocytoma, whereas more than half of patients with diffuse astrocytoma were *IDH* wild-type in our cohort²⁹. Minniti et al. reported that *IDH* mutant anaplastic astrocytoma was found in 56% of their anaplastic astrocytoma patients. OS in patients with *IDH* wild-type was 2.8 years³⁰. The relatively shorter PFS and OS of patients with diffuse astrocytoma and anaplastic astrocytoma in the current study were probably attributable to the fact that the present cohort included more patients with *IDH* wild-type astrocytoma than the previous study. On the other hand, Wakabayashi et al. reported that the median OS in patients with glioblastoma who received Stupp's regimen was 20.3 months³¹, similar to our result in the current study.

Brain PET imaging has recently been recommended for use in addition to MRI in the management of glioma^{3,4}. Takano et al. reported that PFS was worse with LN max ≥ 2.0 than with LN max < 2.0 using 11C-methionine PET among patients with untreated, lower-grade, non-enhancing gliomas³². Discrimination of high-grade glioma from low-grade glioma is usually difficult using MRI alone prior to tumor resection in patients with non-enhancing, lower-grade glioma, so we considered whether 11C-methionine PET can be used to predict the prognosis of glioma. However, we could not find significant differences in PFS between astrocytoma patients with LN max ≥ 4.03 and LN max < 4.03 or between those with LN mean ≥ 2.46 and LN mean < 2.46 in the current study.

Recently, some reports have investigated the relationship between prognosis from molecular analysis and uptake of PET using 18F-fluoro-ethyl-tyrosine (18F-FET) PET^{18–20,33} and 3,4-dihydroxy-6-18F-fluoro-ethyl-L-phenylalanine (18F-FDOPA) PET³⁴. Galldiks et al. in a study of photopenic *IDH* mutant gliomas reported that glioma with 18F-FET accumulation below the level of background healthy brain showed unfavorable outcomes, and thus should be treated more actively¹⁹. The utility of dynamic 18F-FET PET has also been reported²⁰. Suchorska et al. reported that longer minimal time-to-peak analysis using 18F-FET PET was associated with a favorable prognosis in *IDH* mutant astrocytomas²⁰. A time-to-peak analysis ≥ 25 min was associated with longer PFS and OS in patients with *IDH* wild-type high-grade astrocytoma according to Bauer et al³³. Kunz et al. reported homogeneous decreases in intratumoral uptake of 18F-FET over time as a factor associated with poor prognosis in non-enhancing glioma¹⁸. Using continuous measures of 18F-FDOPA PET, Patel et al. reported LN max and age as prognostic factors for OS in WHO grade IV gliomas, and that *IDH* or MGMT status did not correlate with uptake of 18F-FDOPA. In this study, we

concluded that patients with LN max ≥ 4.03 displayed unfavorable OS compared to patients with LN max < 4.03 among patients with WHO grade 2-3 astrocytoma. We also concluded that patients with LN max ≥ 4.03 showed unfavorable OS compared those with LN max < 4.03 among patients with WHO grade 2-3 *IDH* mutant astrocytoma, although no significant difference in OS was evident between *IDH* wild-type WHO grade 2-3 astrocytoma with LN max ≥ 4.03 and those with LN max < 4.03 . Thus, no other molecular imaging markers might be needed to estimate prognosis in *IDH* wild-type astrocytoma.

Some limitations need to be considered for the current study. First, the relatively small cohort of the current study might have influenced statistical analyses. For example, *TERT* promoter status did not influence OS in our cohort, although Arita et al. reported the usefulness of *TERT* promoter status in addition to the *IDH* status³⁵. Further study with a larger cohort is thus needed to assess the correlation between prognosis and molecular/imaging biomarkers with amino-tracer PET in patients with astrocytoma. Second, we did not take volumetric analyses into consideration in the current study, although some reports have suggested that metabolic tumor volume did not correlate with survival outcomes^{18,20,33,34,36}.

Conclusion

LN max using 11C-methionine PET offers a marker for estimating OS in patients with grade 2-3 astrocytoma. LN max can also be used as a prognostic imaging biomarker to estimate OS in addition to *IDH* status in *IDH*-mutated astrocytoma.

Abbreviations And Acronyms

PET: positron emission tomography; WHO: World Health Organization; KPS: Karnofsky Performance Status; PFS: progression-free survival; HR: hazard ratio; CI: confidence interval; TERT: telomerase reverse transcriptase; LN: lesion-to-contralateral normal brain tissue; IDH: isocitrate dehydrogenase; OS: overall survival; MRI: magnetic resonance imaging; 18F-FET: 18F-fluoro-ethyl-tyrosine; 18F-FDOPA: 3,4-dihydroxy-6-18F-fluoro-ethyl-L-phenylalanine

Declarations

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Author contributions

K.N.: Conceptualization, Investigation, Writing-original draft. T.U.: Investigation, Supervision. T.K.: Writing-original draft. Y.T.: Investigation, Supervision. K.I.: Investigation, Supervision. N.T.: Conceptualization, Investigation, Supervision. Y.T.: Writing-original draft. A.N.: Writing-original draft. H.U.: Writing-original draft. S.K.: Writing-original draft. T.S.: Writing-original draft. K.O.: Supervision. Y.K.: Investigation, Resources, Supervision. T.G.: Supervision.

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Availability of date and materials.

The data in the current study are available from the corresponding author on reasonable request.

Conflicts of interest

No funds were received in support of this work. No benefits in any form have been or will be received from any commercial party related directly or indirectly to the subject of this manuscript.

Consent to participate

Patient informed consents were waived due to the retrospective nature of the study.

Consent for publication

All authors have approved the manuscript and agree with publication.

Ethical approval

This study was approved by the institutional review boards at the Graduate School of Medicine, Osaka City University (approval numbers: 2047 and 2020-115), and Osaka National Hospital (approval number: 0713).

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Figures

Figure 1

Kaplan-Meier plot of PFS in relation to preoperative KPS.

Figure 2

Kaplan-Meier plot of OS in relation to preoperative KPS (A), histology (B), IDH status (C), and LN max (D).

Figure 3

Kaplan-Meier plot of the OS in relation to the IDH status/LN max classification. A significant difference in OS existed between patients with IDH mutant/LN max<4.03 and those with IDH mutant/LN max ≥4.03 (p=0.034), although no significant difference in OS was evident between patients with IDH mutant/LN max ≥4.03 and those with IDH wild-type/LN max<4.03 (p=0.40), or between patients with IDH wild-type/LN max<4.03 and those with IDH wild-type/LN max≥4.03 (p=0.84).

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