Maximum 11C-methionine PET uptake as a prognostic imaging biomarker for newly diagnosed and untreated astrocytic glioma

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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. Participants comprised 56 adult patients with newly diagnosed and untreated World Health Organization (WHO) grade II–IV 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. Preoperative Karnofsky Performance Status (KPS) only influenced progression-free survival (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. LN max using 11C-methionine PET may be used in prognostic markers for newly identified and untreated WHO grade II–IV astrocytic glioma.

Abbreviations

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
MGMT  O6-methylguanine-DNA methyltransferase

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Gliomas are the second most common primary brain tumors according to the 2012–2016 Central Brain Tumor Registry of the United States. Approximately 48.3% of primary malignant brain tumors are glioblastomas, 16.7% are other astrocytomas, and 4.5% are oligodendrogiomas.

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. 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 prognosis. 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, 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 grade II–IV glioma who underwent surgical tumor resection and preoperative 11C-methionine PET examination, as previously reported. 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 tumors. 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). Genetic analyses were performed after obtaining written consent. 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. 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 reported.

Genetic analysis. Genetic analysis was performed as previously described. 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 3130xL Genetic Analyzer (Thermo Fisher Scientific, Waltham, MA, USA) and Big-Dye Terminator v1.1 Cycle Sequencing Kit (Thermo Fisher Scientific, Waltham, MA, USA). The methylation status of O6-methylguanine-DNA methyltransferase (MGMT) promoter was analyzed using quantitative methylation-specific PCR after bisulfite modification of tumor genomic DNA, as previously reported.

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 group. 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 removal, ≥90% or gross total removal, ≥95%) 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 data were evaluated using univariate and multivariate Cox regression analyses. Prognostic factors with a p < 0.05 in the univariate analysis were included in the multivariate analysis. 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).

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).

Consent to participate. Patient informed consents were waived due to the retrospective nature of the study.
### Results

#### Patient characteristics.

Patient characteristics are summarized in Table 1. Ten patients were classified into IDH mutant diffuse astrocytoma, 2 patients with IDH mutant anaplastic astrocytoma, 3 patients with IDH mutant glioblastoma, 9 patients with IDH wild-type diffuse astrocytoma, 10 patients with IDH wild-type ana-

| Pathology | Value | DA | AA | GBM | P value |
|-----------|-------|----|----|-----|---------|
| Sex       |       |    |    |     | 0.202   |
| Female    | 20    | 6  | 7  | 7   |         |
| Male      | 36    | 13 | 5  | 18  |         |
| Age(years), median (IQR) | 59 (40–70) | | | | 0.021 |
| ≥70       | 15    | 1  | 4  | 10  |         |
| <70       | 41    | 18 | 8  | 15  |         |
| Contrast Enhancement in MRI |       |    |    |     | < 0.0001 |
| Yes       | 42    | 6  | 11 | 25  |         |
| No        | 14    | 13 | 1  | 0   |         |
| KPS, median (IQR) | 80 (60–100) | | | | < 0.0001 |
| ≥80       | 35    | 19 | 8  | 8   |         |
| <80       | 21    | 0  | 4  | 17  |         |
| LN mean, median (IQR) | 2.46 (1.68–3.04) | | | | < 0.0001 |
| ≥2.46     | 28    | 2  | 7  | 19  |         |
| <2.46     | 28    | 17 | 5  | 6   |         |
| LN max, median (IQR) | 4.03 (2.56–4.89) | | | | < 0.0001 |
| ≥4.03     | 28    | 2  | 6  | 20  |         |
| <4.03     | 28    | 17 | 6  | 5   |         |
| IDH status |       |    |    |     | 0.00897 |
| Mutant    | 15    | 10 | 2  | 3   |         |
| Wild-type | 41    | 9  | 10 | 22  |         |
| TERT promoter status |       |    |    |     | 0.0133  |
| Mutant    | 19    | 2  | 4  | 13  |         |
| Wild-type | 37    | 17 | 8  | 12  |         |
| MGMT      |       |    |    |     | 0.693   |
| Met       | 30    | 11 | 5  | 14  |         |
| Un-Met    | 26    | 8  | 7  | 11  |         |
| Treatment |       |    |    |     | 0.00962 |
| Biopsy    | 6     | 2  | 4  | 0   |         |
| PR        | 17    | 6  | 5  | 6   |         |
| STR, GTR  | 33    | 11 | 3  | 19  |         |
| Adjuvant Therapy |       |    |    |     | < 0.0001 |
| None      | 18    | 16 | 1  | 1   |         |
| CRT       | 33    | 2  | 9  | 22  |         |
| RT Only   | 2     | 1  | 1  | 0   |         |
| Chemo Only| 3     | 0  | 1  | 2   |         |
| IDH status/LN max |       |    |    |     | < 0.0001 |
| Mutant/< 4.03 | 12 | 10 | 1  | 1   |         |
| Mutant/≥ 4.03 | 3  | 0  | 1  | 2   |         |
| Wild-type/< 4.03 | 16 | 7  | 5  | 4   |         |
| Wild-type/≥ 4.03 | 25 | 2  | 5  | 18  |         |

Table 1. Patient characteristics and histology based on the revised WHO 2016 classification IQR interquartile range, MRI magnetic resonance imaging, KPS Karnofsky performance status, LN lesion-to-contralateral normal brain tissue, IDH isocitrate dehydrogenase, TERT telomerase reverse transcriptase, MGMT O6-methylguanine-DNA-methyltransferase, CRT chemoradiotherapy, RT radiation therapy, Chemo chemotherapy, PR partial resection, STR subtotal resection, GTR gross total resection, DA diffuse astrocytoma, AA anaplastic astrocytoma, GBM glioblastoma. P values in bold font are statistically significant.

Consent for publication. All authors have approved the manuscript and agree with publication.
plastic astrocytoma, and 22 patients with IDH wild-type glioblastoma. Median LN mean was 2.46 (interquartile range, 1.68–3.04), and median LN max was 4.03 (interquartile range, 2.56–4.89).

Univariate 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, adjuvant therapy, and IDH status influenced OS (Table 2, Fig. 1). In multivariate Cox regression analysis, preoperative KPS only influenced PFS (HR 0.20, 95% CI

|                          | PFS                              | OS                               |
|--------------------------|----------------------------------|----------------------------------|
|                          | Time (month)         | 95% CI | P value | Time (month) | 95% CI | P value |
|                          |         |         |         |         |         |         |
| Sex                      |         |         |         |         |         |         |
| Female                   | 10.5    | 5.0–45.8| 0.15    | 83.3     | 12.6- Not Reached | 0.52    |
| Male                     | 8.3     | 4.3–11.4|         | 35.9     | 20.5–56.6 |         |
| Age                      |         |         | <0.0001 |         | <0.0001 |         |
| ≥70                      | 3.6     | 1.0–6.1 | <0.0001 | 12.8     | 5.7–29.3 | <0.0001 |
| <70                      | 9.7     | 8.3–36.4|         | 83.3     | 30.1- Not Reached |         |
| Enhancement in MRI       | 0.03    |         | 0.002   |         |         |         |
| Yes                      | 8.3     | 4.7–9.7 |         | 27.1     | 13.3–39.8 |         |
| No                       | 37.2    | 5.3–70.9| Not Reached | 52.3- Not Reached |         |         |
| KPS                      |         |         | <0.0001 |         |         | <0.0001 |
| ≥80                      | 12.5    | 9.2–45.8|         | 83.3     | 39.8- Not Reached |         |
| <80                      | 4.7     | 2.8–8.3 |         | 12.6     | 7.4–27.1 |         |
| LN mean                  |         |         | 0.1     |         | 0.008   |         |
| ≥2.46                    | 6.1     | 3.5–9.7 |         | 26.1     | 10.4–35.9 |         |
| <2.46                    | 11.8    | 7.4–37.2| Not Reached | 30.1- Not Reached |         |         |
| LN max                   |         |         | 0.19    |         | 0.03    |         |
| ≥4.03                    | 7.3     | 3.6–10.5|         | 29.3     | 12.8–39.8 |         |
| <4.03                    | 11.3    | 5.3–37.2| Not Reached | 20.5- Not Reached |         |         |
| Histology                |         |         | 0.0003  |         | <0.0001 |         |
| DA                       | 37.2    | 9.5–70.9| Not Reached | 52.3- Not Reached |         |         |
| AA                       | 9.6     | 5.3–11.8| 27.1     | 11.7- Not Reached |         |         |
| GBM                      | 4.7     | 2.9–8.3 | 20.5     | 7.7–30.1 |         |         |
| IDH status               |         |         | 0.013   |         | <0.0001 |         |
| Mutant                   | 45.8    | 9.2–70.9| Not Reached | Not Reached- Not Reached |         |         |
| Wild-type                | 7.4     | 4.3–9.7 | 26.1     | 12.8–39.8 |         |         |
| TERT promoter status     |         |         | 0.019   |         | 0.054   |         |
| Mutant                   | 5.4     | 2.8–9.7 | 13.3     | 7.4–56.6 |         |         |
| Wild-type                | 10.5    | 7.4–37.2| 52.3     | 26.1- Not Reached |         |         |
| MGMT                     |         | 0.77    |         | 0.81    |         |         |
| Met                      | 9.7     | 3.0–17.4| 52.3     | 12.8- Not Reached |         |         |
| Un-Met                   | 8.9     | 5.4–11.3| 27.1     | 18.3- Not Reached |         |         |
| Adjuvant Therapy         |         | 0.0651  | 0.0002  |         |         |         |
| None                     | 37.2    | 9.2–70.9| Not Reached | Not Reached- Not Reached |         |         |
| CRT                      | 7.4     | 4.7–9.6 | 26.1     | 12.8–30.0 |         |         |
| RT Only                  | 9.2     | 0.9-Not Reached | 32.4    | 12.6- Not Reached |         |         |
| Chemo Only               | 1.6     | 1.0-Not Reached | 7.4    | 5.7- Not Reached |         |         |
| Treatment                |         | 0.09    |         | 0.14    |         |         |
| Biopsy                   | 5.3     | 0.9- Not Reached | Not Reached | 12.6- Not Reached |         |         |
| PR                       | 7.4     | 3.0–12.5| 18.3     | 6.2- Not Reached |         |         |
| STR, GTR                 | 9.5     | 7.4–12.5| 48.9     | 29.3- Not Reached |         |         |

Table 2. Prognostic factors for PFS, and OS in the univariate analyses. P values in bold font are statistically significant. MRI magnetic resonance imaging, KPS Karnofsky performance status, LN lesion-to-contralateral normal brain tissue, DA diffuse astrocytoma, AA anaplastic astrocytoma, GBM glioblastoma, IDH isocitrate dehydrogenase, TERT telomerase reverse transcriptase, MGMT O6-methylguanine-DNA-methyltransferase, Met methylation, CRT chemoradiotherapy, RT radiation therapy, Chemo chemotherapy, PR partial resection, STR subtotal resection, GTR gross total resection, PFS progression-free survival, CI confidence interval, NA not applicable, OS overall survival.
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, \( p = 0.0032 \)), 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 not reached for patients with diffuse astrocytoma, 27.1 months for those with anaplastic astrocytoma, and 20.5 months for those with glioblastoma (\( p < 0.0001 \), 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, Table 2).

Median OS was not reached for patients with IDH mutant/LN max < 4.03, 30.1 (95% CI, 30.1–Not reached) months for those with IDH mutant/LN max ≥ 4.03, 20.5 (95% CI, 7.4–52.3) months for those with IDH wild-type/LN max < 4.03, and 27.1 (95% CI, 12.6–39.8) months for those with IDH wild-type/LN max ≥ 4.03, 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 glioma\(^5\). 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 limited\(^10\). 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\(^4,7,11–13\), and distinguish tumor recurrence from radiation necrosis\(^14–16\) in glioma patients, although 11C-methionine PET can only be used in limited institutions that have a cyclotron since 11C-methionine has a short half-life about 20 min. 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\(^17–21\). 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\(^22,23\). An argument has also been made regarding the association between uptake of 11C-methionine and oligodendroglioma\(^4,24–27\). 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 astrocytoma\(^4\). In the current study, median PFS was 37.2 months for patients...
Table 3. Prognostic factors for PFS, and OS in the multivariate analyses. KPS, Karnofsky performance status; LN, lesion-to-contralateral normal brain tissue; DA, diffuse astrocytoma; AA, anaplastic astrocytoma; GBM, glioblastoma; IDH, isocitrate dehydrogenase; TERT, telomerase reverse transcriptase; MGMT, O^6^-methylguanine-DNA-methyltransferase; Met, methylation; CRT, chemoradiotherapy; RT, radiation therapy; Chemo, chemotherapy; PR, partial resection; STR, subtotal resection; GTR, gross total resection; PFS, progression-free survival; OS, overall survival. *P* values in bold font are statistically significant.

| Factor                  | PFS HR (95% CI) | P value | OS HR (95% CI) | P value |
|-------------------------|-----------------|---------|----------------|---------|
| Sex                     |                 |         |                |         |
| Female                  |                 |         |                |         |
| Male                    |                 |         |                |         |
| Age                     |                 |         |                |         |
| ≥ 70                    | Excluded by factor selection with step-wise method |         | Excluded by factor selection with step-wise method |         |
| < 70                    |                 |         |                |         |
| Enhancement             |                 |         |                |         |
| Yes                     | Excluded by factor selection with step-wise method |         | Excluded by factor selection with step-wise method |         |
| No                      |                 |         |                |         |
| KPS                     |                 |         |                |         |
| ≥ 80                    | 0.20 (0.1–0.41) | < 0.0001 | 0.23 (0.09–0.62) | 0.004   |
| < 80                    | Reference       |         | Reference      |         |
| LN mean                 |                 |         |                |         |
| ≥ 2.46                  | Excluded by factor selection with step-wise method |         |                |         |
| < 2.46                  |                 |         |                |         |
| LN max                  |                 |         |                |         |
| ≥ 4.03                  | Reference       |         |                |         |
| < 4.03                  | 0.24 (0.08–0.71) | 0.01    |                |         |
| Histology               |                 |         |                |         |
| DA                      |                 |         |                |         |
| AA                      | Excluded by factor selection with step-wise method |         | Reference      |         |
| GBM                     |                 |         |                |         |
| IDH status              |                 |         |                |         |
| Mutant                  | Excluded by factor selection with step-wise method |         | Reference      |         |
| Wild-type               | 14.06 (1.81–109.2) | 0.011   |                |         |
| TERT promoter           |                 |         |                |         |
| Mutant                  | Excluded by factor selection with step-wise method |         |                |         |
| Wild-type               |                 |         |                |         |
| MGMT                    |                 |         |                |         |
| Met                     |                 |         |                |         |
| Un–Met                  |                 |         |                |         |
| Adjuvant therapy        |                 |         |                |         |
| None                    | Excluded by factor selection with step-wise method |         |                |         |
| CRT                     |                 |         |                |         |
| RT only                 |                 |         |                |         |
| Chemo only              |                 |         |                |         |
| Treatment               |                 |         |                |         |
| Biopsy                  |                 |         |                |         |
| PR                      |                 |         |                |         |
| STR, GTR                |                 |         |                |         |

with diffuse astrocytoma, 9.6 months for those with anaplastic astrocytoma, and 4.7 months for those with glioblastoma, respectively. Median OS was not reached for patients with diffuse astrocytoma, 27.1 months for those with anaplastic astrocytoma, and 20.5 months for those with glioblastoma, 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 cohort. 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 years. 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 months, 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. 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 gliomas. 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 and 3,4-dihydroxy-6-18F-fluoro-ethyl-L-phenylalanine (18F-FDOPA) PET. Galldiks et al. in a study of photopenic IDH mutant gliomas reported that gliomas with 18F-FET accumulation below the level of background healthy brain showed unfavorable outcomes, and thus should be treated more actively. The utility of dynamic 18F-FET PET has also been reported. Suchorska et al. reported that longer minimal time-to-peak analysis using 18F-FET PET was associated with a favorable prognosis in IDH mutant astrocytomas. 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 al. Kunz et al. reported homogeneous decreases in intratumoral uptake of 18F-FET over time as a factor associated with poor prognosis in non-enhancing glioma. Using continuous measures of 18F-FDOPA PET, Patel et al. reported LN max and age as prognostic factors for OS in WHO grade I–IV gliomas, and that IDH or MGMT status did not correlate with

Figure 2. Kaplan–Meier plot of OS in relation to preoperative KPS (A), histology (B), IDH status (C), and LN max (D).
uptake of 18F-FDOPA. In this study, we concluded that patients with LN max ≥ 4.03 displayed unfavorable OS compared to patients with WHO grade II-IV astrocytoma. We also concluded that patients with LN max ≥ 4.03 showed unfavorable OS compared to those with LN max < 4.03 among patients with WHO grade II-IV IDH mutant astrocytoma, although no significant difference in OS was evident between IDH wild-type WHO grade II-IV astrocytoma with LN max ≥ 4.03 and those with LN max < 4.03. Thus, another 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 status. 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.

Conclusion

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

Data availability

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

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