Prognostic Value of Metabolic Tumor Volume on ^{11}C -Methionine PET in Predicting Progression-Free Survival in High-Grade Glioma

Min Young Yoo¹ · Jin Chul Paeng¹ · Gi Jeong Cheon^{1,2} · Dong Soo Lee^{1,3} · June-Key Chung^{1,2} · E. Edmund Kim^{3,4} · Keon Wook Kang^{1,2}

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Abstract

Purpose C-11 methionine (MET) PET is commonly used for diagnosing high-grade glioma (HGG). Recently, volumetric analysis has been widely applied to oncologic PET imaging. In this study, we investigated the prognostic value of metabolic tumor volume (MTV) on MET PET in HGG.

Methods A total of 30 patients with anaplastic astrocytoma ($n=12$) and glioblastoma multiforme ($n=18$) who underwent MET PET before treatment (surgery followed by chemoradiotherapy) were retrospectively enrolled. Maximal tumor-to-normal brain ratio (TNR_{max} , maximum tumor activity divided by mean of normal tissue) and MTV (volume of tumor tissue that shows uptake >1.3 -fold of mean uptake in normal tissue) were measured on MET PET. Adult patients were classified into two subgroups according to Radiation Therapy Oncology Group Recursive Partitioning Analysis (RTOG RPA) classification. Prognostic values of TNR_{max} , MTV and clinicopathologic factors were evaluated with regard to progression-free survival (PFS).

Results Median PFS of all patients was 7.9 months (range 1.0–53.8 months). In univariate analysis, MTV (cutoff 35 cm^3) was

a significant prognostic factor for PFS ($P=0.01$), whereas TNR_{max} (cutoff 3.3) and RTOG RPA class were not ($P=0.80$ and 0.61, respectively). Treatment of surgical resection exhibited a borderline significance ($P=0.06$). In multivariate analysis, MTV was the only independent prognostic factor for PFS ($P=0.03$).

Conclusion MTV on MET PET is a significant and independent prognostic factor for PFS in HGG patients, whereas TNR_{max} is not. Thus, performing volumetric analysis of MET PET is recommended in HGG for better prognostication.

Keywords C-11 methionine · PET · High-grade glioma · Prognosis · Volumetric analysis

Introduction

High-grade glioma (HGG) is a rapidly progressing brain malignancy originating from glial cells. The incidence of HGG is less than 5 per 100,000 people a year [1], which is approximately 1 % of all newly diagnosed cancers. Total resection can be a definite treatment for HGG [2], and chemo-radiotherapy using temozolomide is commonly used as an adjuvant treatment [3]. However, HGG is very infiltrative, and complete resection is unavailable in most cases. The majority of HGG recurs within 1 year after initial treatment, and overall survival from HGG is very poor, despite the standard treatment [1]. For prognostication of HGG, age, pathologic type, Karnofsky performance status (KPS) score and genetic mutation patterns have been suggested as prognostic factors [4, 5]. Additionally, the Radiation Therapy Oncology Group Recursive Partitioning Analysis (RTOG RPA) criteria have been suggested [6], in which pathologic type, KPS score and treatment options were included as prognostic factors.

✉ Jin Chul Paeng
paengjc@snu.ac.kr

¹ Department of Nuclear Medicine, Seoul National University Hospital, 101 Daehak-ro, Jongno-gu, Seoul 110-744, Korea

² Cancer Research Institute, Seoul National University College of Medicine, Seoul, Korea

³ Department of Molecular Medicine and Biopharmaceutical Sciences, Graduate School of Convergence Science and Technology, Seoul National University, Seoul, Korea

⁴ Department of Radiological Sciences, University of California, Irvine, CA, USA

C-11 methionine (MET) positron emission tomography (PET)/computed tomography (CT) is now widely used for detection, guidance of operation range, treatment efficacy monitoring and surveillance of recurrence in gliomas [7–9]. In a previous study, MET PET exhibited a sensitivity of 87 % and specificity of 89 % in detecting HGG, with a cutoff of 1.3 tumor-to-normal brain ratio (TNR) [10]. TNR values on MET PET have also exhibited correlations with pathologic types of glioma [11, 12]. Additionally, it has been reported in several studies that TNR on MET PET may be used for predicting prognosis of glioma [13, 14]. However, the prognostic value of TNR on MET PET still remains controversial.

In case of F-18 fluorodeoxyglucose (FDG) PET, volumetric analysis is widely used for evaluating the metabolic tumor burden in terms of treatment efficacy monitoring and prognostication [15, 16]. Volumetric analysis was also applied to MET PET in a study [17] where metabolic tumor volume (MTV) was measured in HGG by using TNR 1.3 as a cutoff for the isocontour tumor margin, and it was reported that MTV exhibited a significant correlation with the volume measured on contrast-enhanced magnetic resonance imaging (MRI) [17].

In the present study, we measured MTV on MET PET in HGG patients in addition to TNR, a metabolic index, and investigated their prognostic values for progression-free survival (PFS) in comparison with several clinicopathologic parameters.

Materials and Methods

Patients

From January 2008 to December 2013, HGG patients who underwent MET PET as an initial evaluation in our institution were retrospectively enrolled. In case MET PET was performed during or after treatment, the patient was excluded from the study. All patients underwent stereotactic biopsy and/or surgical resection, and diagnosis was confirmed by histopathological review of tumor tissues. After surgical treatment, patients received standard chemo-radiotherapy using temozolomide and irradiation of 45–61 Gy. As a clinical prognostic index, adult patients were classified by the RTOG RPA criteria [6]: low RTOG RPA class (class 1–3), and high RTOG RPA class groups (class 4–6).

The study design was approved by the Institutional Review Board of our institution, and written informed consents were waived.

Image Acquisition and Analysis

MET PET scans were performed at 1–32 days (median 7 days) before stereotactic biopsy or surgical resection. After 6-h fasting, MET (5.55 MBq/kg) was injected intravenously, and

the PET/CT scan was started 10 min after injection. Using hybrid PET/CT scanners (Biograph mCT40 and Biograph mCT64; Siemens Medical Solution, Erlangen, Germany), a low-dose CT scan (120 kVp, 50 mAs) was acquired for attenuation correction and lesion localization. Afterwards, brain PET images were acquired for 20 min for one bed position. CT images were reconstructed into 5-mm slice thickness, and PET images were reconstructed on 200×200 matrices using an iterative algorithm (iteration 2, subset 21).

MET PET/CT images were reviewed by two experienced nuclear medicine physicians and semiquantitatively analyzed using a vendor-supplied analyzing software package (Syngo.via, Siemens Medical Solutions, Erlangen, Germany). A spherical volume of interest (VOI) with 10-mm radius was manually drawn to include the maximal activity in the tumor. The same VOI was drawn in the unaffected contralateral cerebral parenchyma to measure activity of the normal brain (Fig. 1). TNR was calculated as the ratio between the uptake activities of tumor tissue and the normal brain, and maximum TNR (TNR_{max}) was deemed to be a marker for metabolic activity. For volumetric analysis, an isocontour VOI was automatically drawn around a tumor by using TNR 1.3 as a threshold, based on a previous report [17]. The volume of this VOI was defined as MTV and deemed to be a marker for metabolic tumor burden.

Follow-Up of Patients

Clinicopathologic data of all patients were obtained from review of medical records. Information on age, gender, KPS score, histopathological findings including MGMT methylation, tumor size (the longest diameter) measured on MRI and selected treatment options was obtained. During follow-up, brain MRI was performed periodically (every 2–3 months) and when abnormal neurologic symptoms or signs were presented. When tumor size was increased or any new lesion was detected on MRI, it was defined as tumor progression. PFS was defined as the time between the dates of initial MET PET and confirmation of tumor progression.

Statistical Analysis

All data are expressed as mean±SD. Comparison of values between two subgroups was performed using Student's *t*-test. Kaplan-Meier survival analysis was used for survival curve plotting. Additionally, log-rank test and Cox proportional hazard regression analysis were used to evaluate the efficacy of prognostic factors, in univariate and multivariate analyses, respectively. For survival analysis, optimal cutoff values for TNR_{max} and MTV were determined from iterative pilot analyses. In brief, the median value was used as the first cutoff

Fig. 1 Volumetric analysis method on MET PET. A tumor lesion was identified on transaxial (a) and coronal (b) images of MRI (arrowhead). On transaxial (c) and coronal (d) images of MET PET, spherical VOIs of 10-mm radius were drawn in the tumor area of maximal uptake (white circle) and contralateral brain parenchyma (black circle) to calculate TNR_{max} . For MTV measurement, a larger spherical VOI (purple circle) was drawn to include the whole tumor (arrow), and an isocontour VOI was automatically drawn by using $TNR_{1.3}$ as the cutoff

value for a survival analysis. Afterward, the next values to the tested cutoff values were used as the cutoff values for survival analysis, and the *P*-values were compared between the cutoff values. This process was repeated, and the cutoff values for the lowest *P*-values were selected as the optimal cutoff values.

Statistical analysis was performed using a commercial statistics software package (SPSS Statistics 21.0 for Windows, IBM Corp., NY, USA). *P*-values less than 0.05 were regarded as significant.

Results

Patients

A total of 30 patients (21 males and 9 females) were included in the final analysis. Among them, 12 had anaplastic astrocytoma and 18 glioblastoma multiforme. The patients were followed up for 1.0–53.8 months; tumor progression was observed in 26 patients at 7.6 ± 5.7 months (range; 1.0–24.0 months) during follow-up. In four patients, there was no tumor progression, and median PFS in overall patients was 7.9 months. Patient characteristics are summarized in Table 1. Thirteen patients received only chemo-radiotherapy with temozolomide after stereotactic biopsy, and 17 patients underwent near-total or total resection of the tumor. Among them, 14 patients received postoperative adjuvant chemo-

radiotherapy, and 3 patients received postoperative radiotherapy only because of poor general condition.

Table 1 Patient characteristics

Characteristics	Values
Number	30
Age (years)	35 ± 4 (2–70)
Sex (M:F)	21:9
Histopathology (n)	
Anaplastic astrocytoma	12 (40 %)
Glioblastoma multiforme	18 (60 %)
KPS score	
<70	12 (40 %)
≥ 70	18 (60 %)
RTOG RPA criteria	
Not classified (children)	12 (40 %)
Low (class 1–3)	7 (23 %)
High (class 4–6)	11 (37 %)
Treatment	
CCRT only	13 (43 %)
Total resection with following RT	3 (10 %)
Total resection with following CCRT	14 (47 %)

KPS Karnofsky performance status, *RTOG RPA* Radiation Therapy Oncology Group recursive partitioning analysis, *CCRT* concurrent chemo-radiotherapy, *RT* radiotherapy

Table 2 MET PET results and patient outcome according to RTOG RPA criteria

Characteristics	Children	All adults	RTOG RPA criteria		
			Low	High	<i>P</i>
<i>n</i>	12	18	7	11	
TNR _{max}	3.2±1.3	3.8±0.3	2.9±0.9	4.4±1.3	0.02
MTV (cm ³)	40.6±72.7	40.2±32.8	36.7±43.5	42.4±26.2	0.71
PFS (Mo)	9.3±8.8	13.1±15.4	15.6±17.4	11.5±14.7	0.60

TNR_{max} maximum tumor-to-normal ratio, MTV metabolic MET uptake volume, PFS progression-free survival

Image Findings

In all patients, TNR_{max} and MTV were successfully measured. In overall patients, TNR_{max} was 3.6±1.4 (range 1.8–6.9), and MTV was 39.1±51.4 cm³ (range 0.02–265.7 cm³). When patients were classified by RTOG RPA criteria, there was a significant difference in TNR_{max} between low and high RTOG RPA class groups (*P*=0.02), whereas no significant difference existed in MTV (*P*=0.71, Table 2).

Survival Analysis

In the iterative pilot analyses, 3.3 and 35 cm³ were selected as the optimal cutoff values for TNR_{max} and MTV in prognosis prediction. In univariate analyses of overall patients, MTV was a significant prognostic factor for PFS (*P*=0.01, Fig. 2a), whereas TNR_{max} was not significant (*P*=0.80, Fig. 2b). RTOG RPA class was also not a significant prognostic factor (*P*=0.61, Fig. 2c). In contrast, history of resection exhibited a borderline significance, although it was negative (*P*=0.06). None of the other tested clinicopathologic parameters of age, gender, histopathology, tumor size, KPS score, and MGMT methylation was significant in predicting PFS (Table 3).

Among the tested parameters, multivariate analysis was performed for five parameters: four most significant parameters (MTV, treatment, histopathology and KPS score) and one clinical prognostic index (RTOG RPA class). In the multivariate analysis, MTV was selected as the only independent prognostic factor for PFS, and the hazard ratio of high MTV was 2.55 (range 1.09–5.98, Table 3). Representative cases are shown in Fig. 3.

Discussion

The aim of the present study was to investigate prognostic value of metabolic and volumetric indices on MET PET in HGG compared to other clinicopathologic parameters. As a result, MTV was demonstrated to be the only significant and independent prognostic factor for PFS in HGG.

MET PET has been reported to be effective in HGG in terms of lesion detection, margin delineation and differentiation from treatment-induced necrosis. In most such studies, TNR was utilized as a quantitative index for metabolic activity [10, 19, 20]. Several studies have reported that there is a correlation between aggressiveness of glioma and TNR [21, 22], and TNR also exhibited correlations with prognosis in several studies [13, 14]. However, the prognostic value of TNR on MET PET still remains controversial.

Volumetric analysis of FDG PET has been performed in treatment efficacy monitoring and prognostication of diverse cancers [23, 24]. Because MTV reflects the overall tumor burden, it has been reported to have a higher prognostic value than the maximal standardized uptake value (SUV). Based on these results, volumetric analysis was also applied to MET PET in glioma patients in several studies [17, 18, 25], some of which reported that MTV has a higher prognostic value for overall survival than TNR [18, 25]. In

Fig. 2 Survival curves according to the tested prognostic factors. MTV (a) was a significant prognostic factor for PFS, whereas TNR_{max} (b) and RTOG RPA classification (c) were not

Table 3 Results of survival analysis

Variables	Univariate analysis		Multivariate analysis	
	Hazard ratio (95%CI)	P	Hazard ratio (95%CI)	P
Age				
<20	1.00			
≥20	1.10 (0.50–2.44)	0.80	–	–
Sex				
Male	1.00			
Female	1.46 (0.62–3.43)	0.38	–	–
Histopathology				
AA	1.00		1.00	
GBM	1.93 (0.85–4.4)	0.10	1.75 (0.74–4.10)	0.19
Tumor size on MRI				
≥35 cm	1.76 (0.86–3.9)	0.15		
<35 cm	1.00			
MGMT methylation				
Negative	1.00			
Positive	1.17 (0.50–2.76)	0.71	–	–
RTOG RPA class*				
Low	1.00			
High	1.31 (0.47–3.66)	0.61	–	–
Treatment				
Not resected	1.45 (0.86–3.1)	0.06	1.62 (0.71–3.66)	0.24
Resected	1.00		1.00	
TNR _{max}				
<3.3	1.00			
≥3.3	1.10 (0.51–2.39)	0.80	–	–
MTV (cm ³)				
<35 cm ³	1.00		1.00	
≥35 cm ³	2.11 (1.12–4.73)	0.01	2.55 (1.09–5.98)	0.03
KPS score				
<70	1.62 (0.74–3.57)	0.23	–	–
≥70	1.00			

AA anaplastic astrocytoma, GBM glioblastoma multiforme, MGMT O-6-methylguanine-DNA methyl-transferase, RTOG RPA Radiation Therapy Oncology Group Recursive Partitioning Analysis, TNR_{max} maximum tumor-to-normal brain ratio, MTV metabolic tumor volume, KPS Karnofsky performance

the present study, we analyzed the prognostic value of MTV regarding PFS in HGG patients who were treated according to the standard treatment protocol and demonstrated a similar prognostic value of MTV.

In this study, MTV on MET PET was identified as the only significant and independent prognostic factor for PFS in HGG patients. However, other clinicopathologic factors including age, sex, pathologic type, RTOG RPA classification and KPS score were not significant prognostic factors, although RTOG RPA classification has been reported to be a significant prognostic factor in several

previous studies [6, 18]. It is speculated that the result may be the small case number of our study, which was not enough for high statistical power. TNR_{max} was also not a significant factor for prognosis, whereas treatment option exhibited a borderline significance. However, it should be noted that MTV was a significant factor in both univariate and multivariate analyses, despite probable low statistical power. Further studies with larger case numbers are warranted regarding the prognostic value of volumetric analysis on MET PET.

When TNR_{max}, MTV and PFS were compared between the high and low RTOG RPA class groups, there was a significant difference only in TNR_{max} between the two groups. Because pathologic type, KPS score and age are included in the RTOG RPA criteria, this appears to be in accordance with previous reports that TNR reflects the pathologic type of glioma [11, 12]. MTV and RTOG RPA class did not exhibit a significant correlation with each other probably because the RTOG RPA criteria do not include tumor size or burden; moreover, MTV is considerably different from anatomical tumor burden.

In the present study, we performed volumetric analysis using an isocontour VOI as performed in previous volumetric analysis studies on FDG PET. We adopted TNR 1.3 as a threshold for isocontour, whereas a certain value of SUV or a certain percentage of maximal SUV is used on FDG PET. In case of MET PET, SUV is not a reliable index for amino acid metabolism of glioma because of a large interindividual variation of neutral amino acids in plasma [20, 26]. These amino acids are not distinguished from MET by the amino acid transporter, which results in a variation in overall amino acid uptake. Thus, TNR has been adopted in many studies on MET PET, and TNR 1.3 was reported to be effective in differentiating HGG with high diagnostic performance [10]. TNR 1.3 was also adopted in previous volumetric analysis studies on MET PET [17, 18]; thus, we adopt this cutoff value in the present study. However, further studies are required to determine an optimal method for volumetric analysis on MET PET.

This study has several limitations. First of all, the case number is relatively small, although the prognostic value of MTV was statistically significant. Further studies with larger case numbers are required to confirm the prognostic values of metabolic and volumetric indices on MET PET. Second, our study included relatively many pediatric patients, which may have been a bias factor because several studies have reported a slightly better prognosis of HGG in younger patients [4, 27, 28]. The difference in prognosis was reported to depend on the clinicopathologic factors, genetic mutation profiles and location of tumors, most of which were statistically controlled in our study. However, it should be noted that the MTV value would have a different implication between adult and pediatric patients

Fig. 3 Images of representative cases. On MRI (**a, b**) and MET PET (**c, d**), a 23-year-old male patient with glioblastoma multiforme presented a relatively low TNR_{max} (2.8) but a high MTV (38.2 cm^3), and the PFS was 7.7 months after initial treatment. In another 41-year-old male patient

with glioblastoma multiforme (**e–f**), MTV was low (9.8 cm^3), whereas TNR_{max} was relatively high (4.7). The patient exhibited PFS of 50.6 months

because of the difference in the brain size. Finally, this study had a retrospective design, and some data could not be obtained. Particularly, overall survival data were not available in this study because of considerable missing data.

Conclusion

In conclusion, MTV on MET PET is a significant and independent prognostic factor for PFS in HGG patients, whereas TNR_{max} is not. Thus, volumetric analysis of MET PET needs to be performed in HGG for better prognostication.

Compliance with Ethical Standards

Conflict of Interest Min Young Yoo, Jin Chul Paeng, Gi Jeong Cheon, Dong Soo Lee, June-Key Chung, E. Edmund Kim and Keon Wook Kang declare that they have no conflict of interest.

Ethical Statement All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study design was approved by the Institutional Review Board of Seoul National University Hospital (1504-046-663). The manuscript has not been published before, is not under consideration for publication anywhere else and has been approved by all coauthors.

Informed Consent Written informed consents were waived by the Institutional Review Board of Seoul National University Hospital.

References

1. Stupp R, Brada M, van den Bent MJ, Tonn JC, Pentheroudakis G, Group EGW. High-grade glioma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2014;25 Suppl 3:iii93–101.
2. Lacroix M, Abi-Said D, Fourney DR, Gokaslan ZL, Shi W, DeMonte F, et al. A multivariate analysis of 416 patients with glioblastoma multiforme: prognosis, extent of resection, and survival. *J Neurosurg*. 2001;95:190–8.
3. Hart MG, Garside R, Rogers G, Stein K, Grant R. Temozolomide for high grade glioma. *Cochrane Database Syst Rev*. 2013;4, CD007415. doi:10.1002/14651858.CD007415.pub2.
4. Lamborn KR, Chang SM, Prados MD. Prognostic factors for survival of patients with glioblastoma: recursive partitioning analysis. *Neuro Oncol*. 2004;6:227–35.
5. Weller M, Felsberg J, Hartmann C, Berger H, Steinbach JP, Schramm J, et al. Molecular predictors of progression-free and overall survival in patients with newly diagnosed glioblastoma: a prospective translational study of the German Glioma Network. *J Clin Oncol*. 2009;27:5743–50.
6. Paravati AJ, Heron DE, Landsittel D, Flickinger JC, Mintz A, Chen YF, et al. Radiotherapy and temozolomide for newly diagnosed glioblastoma and anaplastic astrocytoma: validation of Radiation Therapy Oncology Group-Recursive Partitioning Analysis in the IMRT and temozolomide era. *J Neurooncol*. 2011;104:339–49.
7. Galldiks N, Kracht LW, Berthold F, Miletic H, Klein JC, Herholz K, et al. [^{11}C]-L-methionine positron emission tomography in the management of children and young adults with brain tumors. *J Neurooncol*. 2010;96:231–9.
8. Grosu AL, Weber WA, Riedel E, Jeremic B, Nieder C, Franz M, et al. L-(methyl- ^{11}C) methionine positron emission tomography for target delineation in resected high-grade gliomas before radiotherapy. *Int J Radiat Oncol Biol Phys*. 2005;63:64–74. doi:10.1016/j.ijrobp.2005.01.045.
9. Pirotte BJ, Levivier M, Goldman S, Massager N, Wikler D, Dewitte O, et al. Positron emission tomography-guided volumetric resection

- of supratentorial high-grade gliomas: a survival analysis in 66 consecutive patients. *Neurosurgery*. 2009;64:471–81.
10. Kracht LW, Miletic H, Busch S, Jacobs AH, Voges J, Hoevels M, et al. Delineation of brain tumor extent with [^{11}C]L-methionine positron emission tomography: local comparison with stereotactic histopathology. *Clin Cancer Res*. 2004;10:7163–70.
 11. Kato T, Shinoda J, Nakayama N, Miwa K, Okumura A, Yano H, et al. Metabolic assessment of gliomas using [^{11}C]methionine, [^{18}F]fluorodeoxyglucose, and [^{11}C]choline positron-emission tomography. *AJNR Am J Neuroradiol*. 2008;29:1176–82.
 12. Singhal T, Narayanan TK, Jain V, Mukherjee J, Mantil J. [^{11}C]L-methionine positron emission tomography in the clinical management of cerebral gliomas. *Mol Imaging Biol*. 2008;10:1–18.
 13. De Witte O, Goldberg I, Wikler D, Rorive S, Damhaut P, Monclus M, et al. Positron emission tomography with injection of methionine as a prognostic factor in glioma. *J Neurosurg*. 2001;95:746–50.
 14. Kim S, Chung J-K, Im S-H, Jeong JM, Lee DS, Kim DG, et al. [^{11}C]methionine PET as a prognostic marker in patients with glioma: comparison with [^{18}F]FDG PET. *Eur J Nuc Med Mol Imaging*. 2005;32:52–9.
 15. Im HJ, Pak K, Cheon GJ, Kang KW, Kim SJ, Kim IJ, et al. Prognostic value of volumetric parameters of [^{18}F]FDG PET in non-small-cell lung cancer: a meta-analysis. *Eur J Nucl Med Mol Imaging*. 2015;42:241–51.
 16. Kim YI, Cheon GJ, Paeng JC, Cho JY, Kwak C, Kang KW, et al. Usefulness of MRI-assisted metabolic volumetric parameters provided by simultaneous F-fluorocholine PET/MRI for primary prostate cancer characterization. *Eur J Nucl Med Mol Imaging*. 2015. doi:10.1007/s00259-015-3026-5.
 17. Galldiks N, Ullrich R, Schroeter M, Fink GR, Jacobs AH, Kracht LW. Volumetry of [^{11}C]methionine PET uptake and MRI contrast enhancement in patients with recurrent glioblastoma multiforme. *Eur J Nucl Med Mol Imaging*. 2010;37:84–92.
 18. Galldiks N, Dunkl V, Kracht LW, Vollmar S, Jacobs AH, Fink GR, et al. Volumetry of [^{11}C]methionine positron emission tomographic uptake as a prognostic marker before treatment of patients with malignant glioma. *Mol Imaging*. 2012;11:516–27.
 19. Borbely K, Nyary I, Toth M, Ericson K, Gulyas B. Optimization of semi-quantification in metabolic PET studies with [^{18}F]fluorodeoxyglucose and [^{11}C]methionine in the determination of malignancy of gliomas. *J Neurol Sci*. 2006;246:85–94.
 20. Shishido H, Kawai N, Miyake K, Yamamoto Y, Nishiyama Y, Tamiya T. Diagnostic value of [^{11}C]methionine (MET) and [^{18}F]fluorothymidine (FLT) positron emission tomography in recurrent high-grade gliomas; differentiation from treatment-induced tissue necrosis. *Cancers (Basel)*. 2012;4:244–56.
 21. Kaschten B, Stevenaert A, Sadzot B, Deprez M, Degueldre C, Del Fiore G, et al. Preoperative evaluation of 54 gliomas by PET with fluorine-18-fluorodeoxyglucose and/or carbon-11-methionine. *J Nucl Med*. 1998;39:778–85.
 22. Ceyssens S, Van Laere K, de Groot T, Goffin J, Bormans G, Mortelmans L. [^{11}C]methionine PET, histopathology, and survival in primary brain tumors and recurrence. *AJNR Am J Neuroradiol*. 2006;27:1432–7.
 23. Kim YI, Kim SK, Paeng JC, Lee HY. Comparison of F-18-FDG PET/CT findings between pancreatic solid pseudopapillary tumor and pancreatic ductal adenocarcinoma. *Eur J Radiol*. 2014;83: 231–5.
 24. Im HJ, Kim YK, Kim YI, Lee JJ, Lee WW, Kim SE. Usefulness of combined metabolic-volumetric indices of [^{18}F]FDG PET/CT for the early prediction of neoadjuvant chemotherapy outcomes in breast cancer. *Nucl Med Mol Imaging*. 2013;47:36–43.
 25. Kobayashi K, Hirata K, Yamaguchi S, Manabe O, Terasaka S, Kobayashi H, et al. Prognostic value of volume-based measurements on C-methionine PET in glioma patients. *Eur J Nucl Med Mol Imaging*. 2015. doi:10.1007/s00259-015-3046-1.
 26. Okubo S, Zhen HN, Kawai N, Nishiyama Y, Haba R, Tamiya T. Correlation of l-methyl-C-11-methionine (MET) uptake with l-type amino acid transporter 1 in human gliomas. *J Neurooncol*. 2010;99: 217–25.
 27. Laws ER, Parney IF, Huang W, Anderson F, Morris AM, Asher A, et al. Survival following surgery and prognostic factors for recently diagnosed malignant glioma: data from the Glioma Outcomes Project. *J Neurosurg*. 2003;99:467–73.
 28. Antonelli M, Buttarelli FR, Arcella A, Nobusawa S, Donofrio V, Oghaki H, et al. Prognostic significance of histological grading, p53 status, YKL-40 expression, and IDH1 mutations in pediatric high-grade gliomas. *J Neurooncol*. 2010;99:209–15.