Usefulness of ^{11}C-Methyl-L-and D-Methionine PET in Gliomas : with Special Attention to Recurrence

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Objective : This study concerns the usefulness of ^{11}C-methyl-L-and D-methionine(Met)-positron emission tomography(PET) for glioma grading and detection of recurrence in gliomas, compared with fluorine-18, 2-fluoro-deoxyglucose(FDG)-PET.
Methods : Eighty patients underwent Met-PET study for evaluation of glioma : 37 astrocytomas (WHO grade II, 3; III, 8; IV, 26), 27 oligodendrogliomas (WHO grade II, 16; III, 11), and 12 suspicious recurrent gliomas. All images were taken within 2 weeks before operation. For suspicious recurrent cases on magnetic resonance images, both FDG-PET and Met-PET were performed.
Results : In astrocytoma, Mean maximum standard uptake value(SUV) of region of interest(ROI) was not different between WHO grades (p=0.108), but ROI/normal contralateral tissue SUV (T/N) ratio was statistically different between WHO grades (p=0.002). T/N ratio was more closely related to visual scale than maximum SUV of ROI (p<0.001 and p=0.107 respectively). In oligodendroglioma, there was no statistical difference between WHO grades in view of maximum SUV and T/N ratio. For recurrent gliomas, sensitivity of FDG-PET and Met-PET was 25% and 100%, while specificity of FDG-PET and Met-PET were 100% and 80%, respectively.
Conclusion : Met-PET might be an appropriate tool for tumor grading in astrocytoma and be more sensitive for detection of recurrence in gliomas than FDG-PET.

KEY WORDS : Methionine · Glioma · PET · Recurrence.

Introduction

The fluorine-18, 2-fluoro-deoxyglucose(FDG)-positron emission tomography(PET) has been standard tracer for tumor detection, grading, and discrimination between radiation necrosis and tumor recurrence[1]. However, this tracer is sometimes not a good one, because of high physiological uptake in normal brain parenchyma and low uptake in some low-grade tumors[1]. Moreover FDG uptake is sometimes non-specific, such as uptake in inflammation and granulation tissue[10,21]. Methionine is essential natural amino acid and enters tumor cell via the L-amino acid transporter, to meet the demands of accelerated protein and RNA synthesis in tumors, and ^{11}C-methyl-L-and D-methionine(Met) is commonly used tracer for PET[22]. Owing to its low uptake in normal brain tissue, Met-PET has been shown to be a sensitive tracer in tumor detection and tumor delineation. Additionally, it has been used to differentiate benign from malignant lesions with high sensitivity and specificity[10]. The authors analyzed the results of Met-PET in gliomas with different WHO grades and compared the results of Met-PET with those of FDG-PET in suspicious recurrent gliomas, in order to evaluate its usefulness for glioma grading and detection of recurrence in gliomas.

Materials and Methods

From 1997 to 2003, 80 patients underwent Met-PET study for the evaluation of glioma : 37 astrocytomas (WHO grade II, 3; III, 8; IV, 26), 27 oligodendrogliomas (WHO grade II, 16; III, 11), and 12 suspicious recurrent gliomas. Mixed oli-goastrocytoma was excluded in this study. Mean age was 48 for astrocytoma, 37 for oligodendroglioma, and 40 years old

for suspicious recurrent glioma. All images were taken within 2 weeks before operation. If recurrent glioma was suspicious on magnetic resonance(MR) images, both FDG-PET and Met-PET were taken at the same time, except for two cases. All studies were performed with written consent from patients after full explanation of cost and benefit of the study. All tumors were pathologically proven by craniotomy or stereotactic biopsy except recurrent tumor. Hot area on FDG-PET/Met-PET or enhancing area on MR images was chosen as a target of stereotactic biopsy. For suspicious glioma, tumor recurrence was radiologically defined as steady growth of enhancing portion and increasement of mass effect despite steroid therapy if pathologically not proven[6].

Synthesis of F-18 FDG and C-11 Met

F-18 FDG was synthesized by the fluorination of 1,3,4,6-tetra-O-acetyl-2-trifluoromethanesulfonyl-mannose, with the produced F-18 in the presence of phase-transfer catalyst, and subsequent hydrolyzed with 1 N HCl. The synthesized F-18 FDG was neutralized with 1 N NaOH and filtered through 0.22 μm filters.

C-11 Met was synthesized by using a minor modification of a reported method[7]. C-11 CO_2 was produced by irradiating N_2 gas with 13 MeV protons accelerated in a cyclotron (Ebco Technologies, Canada). C-11 CO_2 was reduced to C-11 methanol using lithium aluminum hydride and subsequently converted to C-11 methyl iodide by adding of hydrogen iodide. C-11 methyl iodide was distilled into a vial containing L-homocysteine thiolactone solution in water/acetone. C-11 Met was synthesized by the S-methylation of L-homocysteine in the presence of potassium hydroxide as a base. After neutralizing with 1 N HCl, C-11 Met was filtered through 0.22 μm filters. Radiochemical purity of the prepared C-11 Met was confirmed to be higher then 95% by TLC/80% acetonitrile (Rf=0.2)

Positron Emission Tomography(PET) method

PET scanning was performed using and ECAT EXACT 47 scanner (Siemens-CTI, Knoxville, TN, USA). After fasting for at least 6 hours, PET images were acquired in the resting supine position, with eyes closed. For attenuation correction, transmission scanning with triple germanium-68 ring sources was performed for 7 min. A dose of 370-555 MBq of F-18 FDG, or 555-740 MBq of C-11 Met was injected intravenously. Regional emission images of the brain were obtained for 20 minutes, beginning 40 minutes after the F-18 FDG injection, and 10 minutes after the C-11 Met injection.

Image analysis

PET images were visually interpreted by two experienced nuclear physicians. Visual scale was classified as : -1 as low, 0 as iso,

1 as moderately high and 2 as intensely high. On PET images, a Region Of Interest(ROI) was drawn manually around the hypermetabolic area or corresponding lesion detected on MR images, if there was no visual lesion. A ROI was also defined in the contralateral hemisphere to obtain tumor to normal brain uptake ratios (T/N ratio). Maximal Standard Uptake Value (SUV) of ROI and SUV ratio of ROI/normal contralateral tissue (T/N ratio) was used for quantification of Met-PET.

Statistical analysis

Kruskal-Wallis test was used for comparison of multiple groups and Mann-Whitney test and student's t-test was used for comparison of two groups. All the statistical analyses were performed with commercially available software (SPSS®, version 10.0, SPSS Inc., Chicago, IL).

Results

Astrocytoma

Mean maximum SUVs of ROI were 1.73 for WHO grade II astrocytoma, 3.47 for grade III astrocytoma and 3.68 for grade IV astrocytoma (Table 1). This figure was not different between groups (p=0.108, Kruskal-Wallis test). T/N ratios were 1.12 for WHO grade II astrocytoma, 1.83 for WHO grade III astrocytoma and 2.73 for WHO grade IV astrocytoma (Table 1). There was statistically significant difference between groups (p=0.002, Kruskal-Wallis test). There was a significant difference between WHO grade III and IV tumor (p=0.012, Mann-Whitney's U t-test). However, there was no significant difference in T/N ratio between WHO grade II and III tumor (p=0.13, Mann-Whitney's U t-test). T/N ratio was more closely related to visual scale than maximum SUV of ROI (p<0.001 and p=0.107 respectively, Kruskal-Wallis test). There was statistically significant difference in T/N ratio between visual scale 0 versus 1 and 1 versus 2 (p= 0.028 and p<0.001 respectively, Mann-Whitney's U test). Thus, T/N ratio rather than SUV of ROI was more correlated with visual grade (Fig. 1).

Table 1. Summary of result

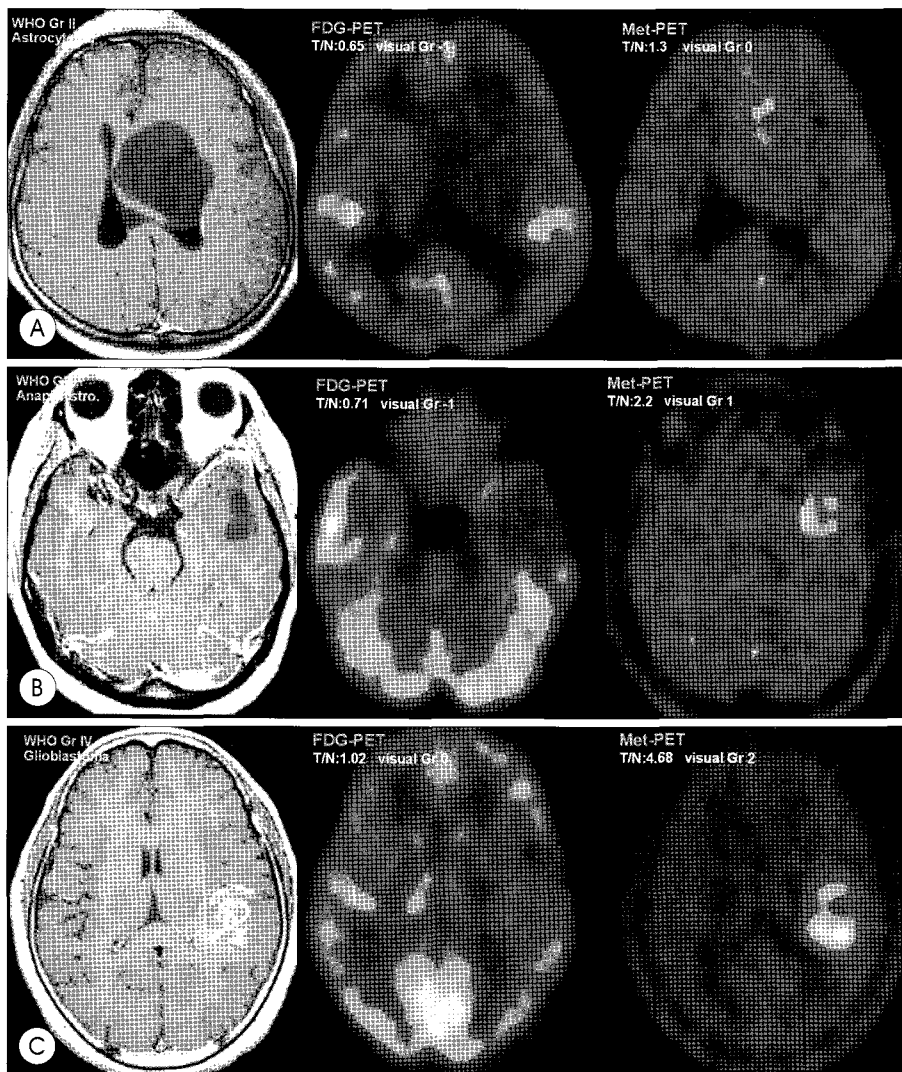| Diagnosis	No of case	Mean age	Mean SUV	Mean T/N ratio
Astrocytoma				
WHO Grade II	3	27	1.73±0.19	1.12±0.18
WHO Grade III	8	46	3.47±2.49	1.83±0.64
WHO Grade IV	26	51	3.68±2.08	2.73±0.89
Oligodendroglioma				
WHO Grade II	16	36	3.00±2.40	1.79±0.81
WHO Grade III	11	39	3.07±1.34	1.77±1.04
Meningioma				
WHO Grade I	3	51	9.05	3.07
WHO Grade III	1	67	4.94	3.84
Lymphoma	7	51	3.8	2.02

Fig. 1. ^{11}C−methyl−L−and D−methionine(Met)−positron emission tomography(PET) and fluorine−18, 2−fluoro−deoxyglucose(FDG)−PET findings according to grade of astrocytoma in the aspect of tumor to normal brain uptake ratio (T/N ratio), visual Met−PET and FDG−PET grade. A : Grade II astrocytoma. B : Grade III astrocytoma. C : Grade IV astrocytoma.

Oligodendroglioma

Mean maximum SUVs of ROI were 3.00 for WHO grade II oligodendroglioma and 3.07 for WHO grade III oligodendroglioma. Mean T/N ratios were 1.79 for WHO grade II oligodendroglioma and 1.77 for WHO grade III oligodendroglioma. With Mann-Whitney test, there was no significant difference in mean maximum SUV and T/N ratio between WHO grade II and III oligodendroglioma.

Astrocytoma versus oligodendroglioma

Mean maximum SUV of ROI in oligodendroglioma was similar with that of WHO grade III and IV glioma (Table 1). However, there were no statistical significant differences between astrocytoma and oligodendroglioma in maximum SUV of ROI and T/N ratio, when comparing in same WHO grade (Mann-Whi-

tney's U test). Apparently, SUV of ROI and T/N ratio was much larger in oligodendroglioma than astrocytoma in WHO grade II, probably due to small number.

Recurrent glioma

There were twelve cases of suspicious recurrent gliomas. FDG-PET was recommended first except two and Met-PET was done for all these twelve cases. As mentioned in the material and method, growing of enhancing portion on follow-up image was considered recurrence and stationary or regressing enhancing lesion was considered as radiation necrosis. Visual grade of Met-PET was low in two cases, moderately high in 4 cases and intensely high in 6 cases (Table 2). Metabolic defect lesion on FDG-PET was 8 cases and the result of Met-PET for these eight cases was like this : recurrent glioma was 8 cases and radiation necrosis was 4 cases. Rationale for diagnosis was as follows : growth of lesion was showed in 8 cases. Three cases also showed seeding and one case was pathologically proven. Two lesions showed stationary enhancement for 4 years follow-up and one cases showed regression of enhancing lesion. Study of Met-PET and FDG-PET were performed for one patient due to new appearing lesion without enhancement of previous site of glioma operation (Table 2).

Sensitivity of Met-PET was 100% (8/8) and specificity was 80% (8/10). Sensitivity of FDG-PET was 25% (2/8) and specificity was 25% (2/8).

Case illustration
Case 1

A 60-year old man was transferred to emergency room complaining of altered mentality. On brain computed tomography(CT), intracranial hemorrhage at right parietal lobe was identified. Hemorrhage was mixed with contrast-enhancing solid portion, which was suspicious of bleeding from brain tumor. Emergent craniotomy and hematoma evacuation was done. Brain was very edematous and solid abnormal lesion was indistinguishable because hematoma was mixed with swollen brain parenchyme. Pathologic

report was glioblastoma. His mentality was normally recovered after operation. He was transferred and received chemotherapy with ACNU (nimustine) and CDDP (cisplatin), followed by radiation therapy with 5940Gy for partial brain. On 1-year

Table 2. Summary of suspicious recurrent gliomas

No.	Visual– FDG[1]	Visual– Met[2]	Diagnosis	Rationale[3]
1	Low	Intensely high	Recurrence	Growth and seeding
2	Low	Intensely high	Recurrence	Growth
3	Low	Moderately high	Recurrence	Growth and seeding
4	Low	Moderately high	Recurrence	Growth
5	Low	Moderately high	Recurrence	Growth and seeding
6	Intense	Intensely high	Recurrence	Growth (pathologically proven)
7	Moderate	Moderately high	Recurrence	Growth
8	NA[4]	Intensely high	Recurrence	Growth
9	Low	Moderately high	Radiation necrosis	Regression (pathologically proven)
10	Low	Low	Radiation necrosis	Non-enhancing new lesion
11	Low	Low	Radiation necrosis	Stationary
12	NA	Intensely high	Radiation necrosis	Regression

Abbreviations, 1) Visual FDG–PET grade, 2) Visual Met–PET grade, 3) Rationale for diagnosis, 4) Not available

follow-up MR images, abnormally enhancing lesion adjacent to previous operated lesion was identified. As radiation necrosis and tumor recurrence was not definite, MR images, and Met-PET were examined, 2 months later. Size of enhancing portion on MR images increased, and hyper-metabolism at the same area on Met-PET was confirmed. On 4-month follow-up MR images, enhancing portion more increased (Fig. 2). Although biopsy was not performed due to neurological deterioration and decrease in general condition, continuous increase in size preferred recurrence to radiation necrosis. He was eventually expired due to progression of brain lesion.

Case 2

A 46 years old woman complained of progressive headache. On MR images, 6 × 4.5cm sized cystic and solid mass at left frontal lobe was identified. On FDG-PET, metabolism increased just along capsule. Craniotomy and subtotal resection of mass was performed. On biopsy, anaplastic oligodendroglioma was reported. Radiation therapy (partial brain, 6120Gy) was preceded by chemotherapy (procarbazine and vincristine). On 3-month and 10- month follow-up MR images, there was no evidence of disease. Nodular enhancement at left frontal lobe was identified on 15-month MR images. On Met-PET, metabolism at that site increased, too. 24-month follow-up MR images showed increased size of enhancing lesion although FDG-PET did not demonstrate metabolism change. Re-operation was done, but biopsy result was 'radiation necrosis only.' On 36-month follow-up MR images, size of enhancing lesion at left frontal lobe decreased and so did surrounding edema markedly (Fig. 3). Her Karnofsky performance status was 90.
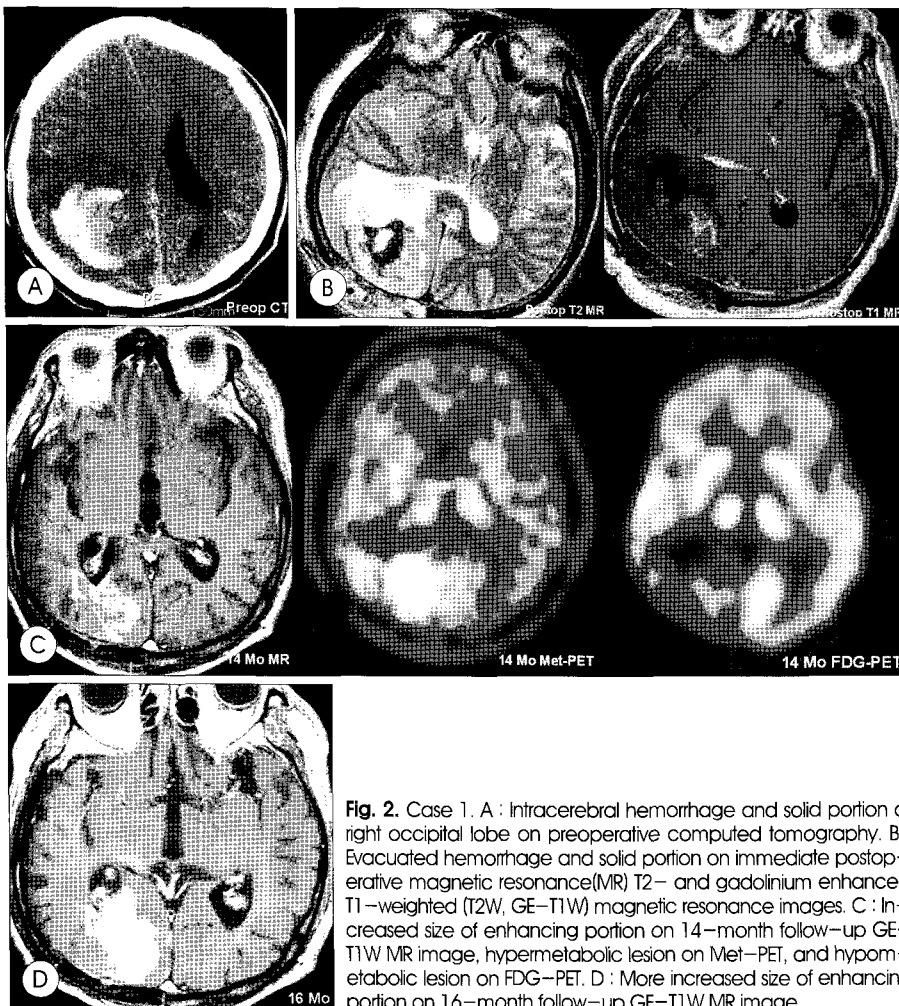
Discussion

Fig. 2. Case 1. A : Intracerebral hemorrhage and solid portion at right occipital lobe on preoperative computed tomography. B : Evacuated hemorrhage and solid portion on immediate postoperative magnetic resonance(MR) T2– and gadolinium enhanced T1–weighted (T2W, GE–T1W) magnetic resonance images. C : Increased size of enhancing portion on 14–month follow-up GE–T1W MR image, hypermetabolic lesion on Met–PET, and hypometabolic lesion on FDG–PET. D : More increased size of enhancing portion on 16–month follow–up GE–T1W MR image.

FDG-PET can detect hypermetabolic lesion and the fluorine-18 2-fluoro-deoxyglucose positron emission tomography (^{18}F-FDG-PET) has been the standard tracer for tumor detection, staging, and discrimination between radiation necrosis and tumor recurrence[1]. However, this tracer is sometimes not a good one, because of high phy-
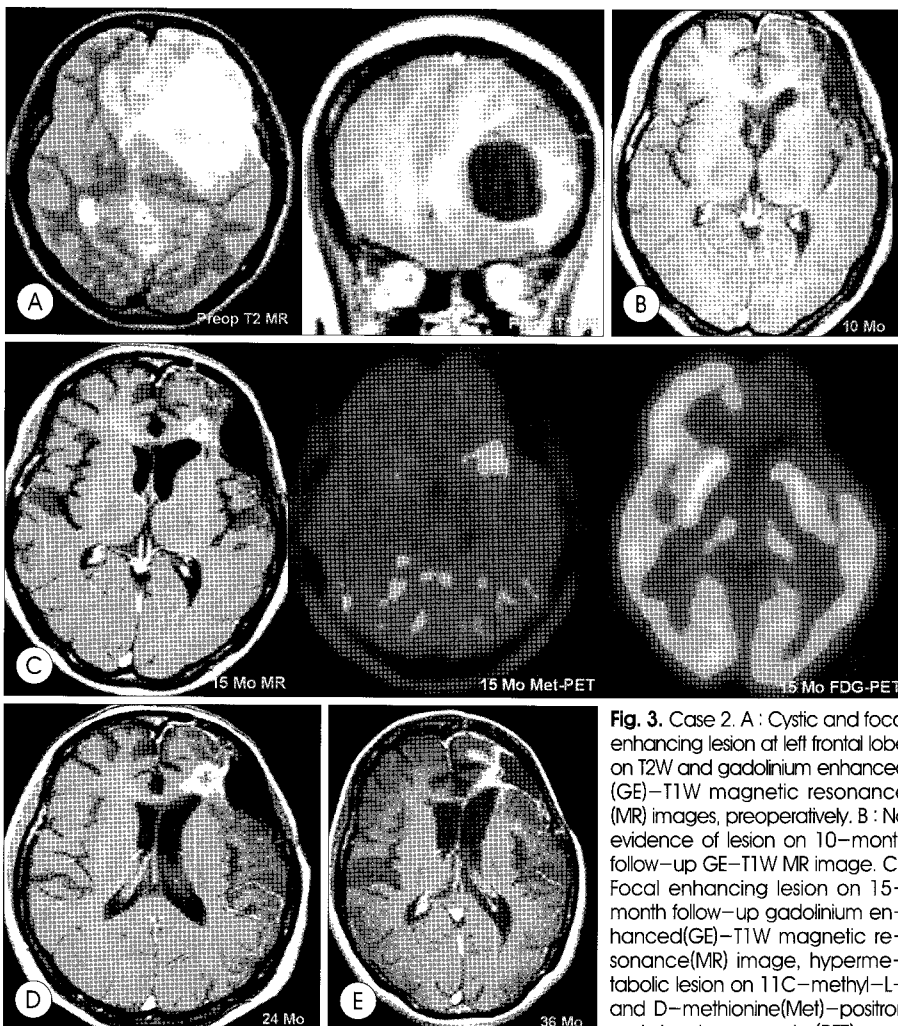
Fig. 3. Case 2. A : Cystic and focal enhancing lesion at left frontal lobe on T2W and gadolinium enhanced (GE)–T1W magnetic resonance (MR) images, preoperatively. B : No evidence of lesion on 10–month follow–up GE–T1W MR image. C : Focal enhancing lesion on 15–month follow–up gadolinium enhanced(GE)–T1W magnetic resonance(MR) image, hyperme–tabolic lesion on 11C–methyl–L– and D–methionine(Met)–positron emission tomography(PET), and hypometabolic lesion on fluorine–18, 2–fluoro–deoxyglucose(FDG)–PET. D : Increased size of enhancing lesion on 24–month follow–up GE–T1W MR image. E : Decreased size of enhancing lesion on 36–month follow–up GE–T1W MR image.

and to differentiate benign from malignant lesions with high sensitivity and specificity[10]. Great advantage of Met over PET is its potential for the imaging of low grade glioma[2].

Met uptake is increased in high-grade glioma and known to be able to differentiate histologic grade of tumor[2,3,14,20,21]. In the authors' cases, Met-PET could differentiate astrocytoma according to histologic grade between WHO grade III versus IV and this was statistically significant. Thus, Met-PET is potentially useful method to discriminate the histologic grade of gliomas[2,14,20,21]. However, this had been only applicable to astrocytoma and not applicable to oligodendroglioma in our series. Histological discrimination is not usually possible with FDG-PET[20].

Luts et al. showed higher uptake in oligodendroglioma than same grade astrocytoma[8,20]. Uptake of methionine in low-grade oligodendroglioma was comparable to that of grade III or IV astrocytoma[3,8,14,20]. In our cases, although statistical significance was not obtained due to small number of cases, the result also showed similar result as showed in Table 1. Although accurate mechanism of this phenomenon had not been explained, vascularity suggested as a cause[8,14]. Increased neovascularization in oligodendroglioma is comparable to glioblastoma even in low-grade oligodendroglioma and they founded positive correlation between microvessel count and methionine uptake. So, methionine could suggest microvessel count and this could be applied anti-angiogenesis therapy[10]. Methionine uptake was very increased in meningioma and this might be also explained by vascularity.

Early detection of recurrent glioma is difficult with images, especially in irradiated patients. MR image and computed tomography cannot easily differentiate between radiation necrosis and tumor recurrence[14]. In this circumstance, FDG-PET is usually recommended[8]. However, there might be false positive or negative as showed in our cases. There are many reports that suggest the superior role of Met-PET for detection of recurrent tumor and discrimination of radiation necrosis and tumor rec-

siological uptake in normal brain parenchyma. This character compromises recognition of the growth of slowly growing tumors, as is often the case with low-grade tumor. But, Amino acid as a marker for viable brain tumor tissue is more sensitive and specific than FDG, in PET as well as in single-photon emission tomography[1,14]. They are known to be superior in detecting brain tumor recurrence. At present, methionine is most popular amino acid[1]. Methionine is essential natural amino acid and enters tumor cell via the L-amino acid transporter, to meet the demands of accelerated protein and RNA synthesis in tumors[22]. Methionine uptake is mainly dependent on a specific carrier mechanism rather than on passive diffusion in areas with a disturbed blood-brain barrier and increased amino acid uptake is not a direct measure of protein synthesis but rather seems to be due to increased transport medicated by type L amino acid carriers[1,3,10,20]. Owing to its low uptake in normal brain, Met-PET has been shown to be a sensitive tracer in tumor detection and tumor delineation

urrence[1,3,5,9]. As showed in the authors' cases, low uptake lesion on FDG-PET was not always able to differentiate tumor recurrences and these low metabolic lesions on FDG-PET were mostly true recurrences. On the contrary, Met-PET showed 100% sensitivity and 80% specificity. With this data, the authors suggest Met-PET might be more appropriate method for differentiating between radiation necrosis and tumor recurrence.

However, the major drawback of ^{11}C-Met is its short half time (20 min), so this tracer is unavailable without cyclotron. Thus, Met-PET imaging remote from a cyclotron is impossible[1].

Interpreting Met-PET result needs caution. Although, Met uptake is mainly dependent on a specific transport mechanism, passive diffusion might play some role[1]. There can be uptake such as in brain abscess, cerebral infarction, hemorrhage or demyelinating disease due to disrupted blood-brain barrier[1,3,12]. Although, Met-PET can differentiate radiation necrosis and tumor recurrence, there are reports showing uptake in radiation necrosis as showed in our case[2,12,19]. Moreover, negative methionine uptake not always excluded a tumor[2,12,13]. Negative Met uptake is also observed in 4~13% of low-grade gliomas[2,13]. Although high accumulation of methionine in brain gliomas is usually associated with malignancy grade, this is applicable only when analyzed in single tumor histology[13]. Moreover, Met-PET only shows increased transport mechanism and cannot show protein synthesis and increased metabolism that can be showed with FDG-PET. So, combination use of Met-PET and FDG-PET might be helpful for evaluation of brain tumors.

Analyzing of Met-PET needs quantification and T/N ratio rather than mean Maximum SUV was more correlated with visual grade, in the authors' study. Many data should be collected to show the cut off value of T/N ratio.

But, there is problem in our study. The recurrence is mostly clinical diagnosis rather than histological diagnosis. So study with exact histological diagnosis for other clinically diagnosed recurrent tumor or radiation necrosis may be needed. However, doctor cannot get all histological diagnosis for discrimination between radiation necrosis and tumor recurrence. Thus, clinical diagnosis may be the only method, and supporting study that shows more than anatomical features is necessary. In this respect, Met-PET might be more appropriate study than FDG-PET, as showed in the author's study.

Conclusion

D iscrimination between radiation necrosis and tumor recurrence is usually difficult without histological diagnosis. Although FDG-PET is frequently used for discrimination, negative FDG-PET not always excluded recurrence. Met-PET showed increased uptake even in false negative FDG-PET results in true recurrence. Thus, Met-PET might be as good tool

for tumor grading as FDG-PET and more appropriate tool for discrimination between radiation necrosis and tumor recurrence. And combination use of Met-PET and FDG-PET may be more helpful for evaluation of brain tumors.

References

1. Becherer A, Karanikas G, Szabo M, Zettinig G, Asenbaum S, Marosi C, et al : a comparison between [18F]fluorodopa and [11C]methionine. Eur J Nucl Med Mol Imaging 30 : 1561-1567, 2003
2. Braun V, Dempf S, Weller R, Reske SN, Schachenmayr W, Richter HP : Cranial neuronavigation with direct integration of (11)C methionine positron emission tomography (PET) data -- results of a pilot study in 32 surgical cases. Acta Neurochir (Wien) 144 : 777-782, 2002
3. Chung JK, Kim YK, Kim SK, Lee YJ, Paek S, Yeo JS, et al : Usefulness of 11C-methionine PET in the evaluation of brain lesions that are hypo- or isometabolic on 18F-FDG PET. Eur J Nucl Med Mol Imaging 29 : 176-182, 2002
4. 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 95 : 746-750, 2001
5. Derlon JM, Bourdet C, Bustany P, Chatel M, Theron J, Darcel F, et al : [11C]L-methionine uptake in gliomas. Neurosurgery 25 : 720-728, 1989
6. Hein PA, Eskey CJ, Dunn JF, Hug EB : Diffusion-weighted imaging in the follow-up of treated high-grade gliomas : tumor recurrence versus radiation injury. Am J Neuroradiol 25 : 201-209, 2004
7. Ishwate K, Ido T, Vaalburg W : Increased amount of D-enantiomer dependent on alkaline concentration in the synthesis of L-methyl-11C-methionine. Appl Radiat Isot 39 : 310-314, 1988
8. Jung HW, Paek SH, Kim DG : Differentiation of cerebral radiation necrosis from tumor recurrence in patients with malignant gliomas using 18F-FDG positron emission tomography. J Korean Neurosurg Soc 26 : 165-172, 1997
9. 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 39 : 778-785, 1998
10. Kracht LW, Friese M, Herholz K, Schroeder R, Bauer B, Jacobs A, et al : Methyl-[11C]- l-methionine uptake as measured by positron emission tomography correlates to microvessel density in patients with glioma. Eur J Nucl Med Mol Imaging 30 : 868-873, 2003
11. Kubota R, Yamada S, Kubota K, Ishiwata K, Tamahashi N, Ido T : intratumoral distribution of fluorodeoxyglucose in vivo : high accumulation in macrophage and granulation tissue studies by microautoradiography. J Nucl Med 33 : 1972-1980, 1992
12. Madakasira PV, Simkins R, Narayanan T, Dunigan K, Poelstra RJ, Mantil J : Cortical dysplasia localized by [11C]methionine positron emission tomography : case report. Am J Neuroradiol 23 : 844-846, 2002
13. Maehara T, Nariai T, Arai N, Kawai K, Shimizu H, Ishii K, et al : Usefulness of [11C]methionine PET in the diagnosis of dysembryoplastic neuroepithelial tumor with temporal lobe epilepsy. Epilepsia 45 : 41-45, 2004
14. Nuutinen J, Sonninen P, Lehikoinen P, Sutinen E, Valavaara R, Eronen E, et al : Radiotherapy treatment planning and long-term follow-up with [(11)C]methionine PET in patients with low-grade astrocytoma. Int J Radiat Oncol Biol Phys 48 : 43-52, 2000
15. Ogawa T, Inugami A, Hatazawa J, Kanno I, Murakami M, Yasui N, et al : Clinical positron emission tomography for brain tumors : comparison of fludeoxyglucose F 18 and L-methyl-11C-methionine. Am J Neuroradiol 17 : 345-353, 1996
16. Rau FC, Weber WA, Wester HJ, Herz M, Becker I, Kruger A, et al : O-(2-[(18)F]Fluoroethyl)- L-tyrosine (FET) : a tracer for differentiation of tumour from inflammation in murine lymph nodes. Eur J Nucl Med Mol Imaging 29 : 1039-1046, 2002
17. Ribom D, Eriksson A, Hartman M, Engler H, Nilsson A, Langstrom B, et al : Positron emission tomography (11)C-methionine and survival in patients with low-grade gliomas. Cancer 92 : 1541-1549, 2001

18. Ribom D, Engler H, Blomquist E, Smits A : Potential significance of (11)C-methionine PET as a marker for the radiosensitivity of low-grade gliomas. Eur J Nucl Med Mol Imaging 29 : 632-640, 2002
19. Sasaki M, Ichiya Y, Kuwabara Y, Yoshida T, Inoue T, Morioka T, et al : Hyperperfusion and hypermetabolism in brain radiation necrosis with epileptic activity. J Nucl Med 37 : 1174-1176, 1996
20. Sasaki M, Kuwabara Y, Yoshida T, Nakagawa M, Fukumura T, Mihara F, et al : A comparative study of thallium-201 SPET, carbon-11 methionine PET and fluorine-18 fluorodeoxyglucose PET for the differentiation of astrocytic tumours. Eur J Nucl Med 25 : 1261-1269, 1998
21. Sato N, Suzuki M, Kuwata N, Kuroda K, Wada T, Beppu T, et al : Evaluation of the malignancy of glioma using 11C-methionine positron emission tomography and proliferating cell nuclear antigen staining. Neurosurg Rev 22 : 210-214, 1999
22. Schober O, Duden C, Meyer GJ, Muller JA, Hundeshagen H : Non selective transport of 11C-methyl-L-and D-methionine into a malignant glioma. Eur J Nucl Med 13 : 103-105, 1987
23. Strauss LG, Conti PS : The applications of PET in clinical oncology. J Nucl Med 32 : 623-628, 1991

Commentary

In this clinical study, the authors evaluate the value of Met-PET(^{11}C-methyl-L and D-methionine) for the grading of glioma and differentiation of tumor recurrences from necrosis, compared with that of FDG-PET. PET imaging is used to assess the rates of biologic processes, in vivo, throughout the brain and body by using nonomolar concentrations of radio-acitvely labeled biologic probes. Applications of PET studies of brain tumors range from diagnosis and grading of gliomas to postsurgical assessment of gliomas and metastatic tumors. Several radiolabelled compounds are used in PET studies for protein synthesis such as [^{11}C-mehtyl]-L-methionine, L-1-[^{11}C] leucine, L-1-[^{11}C] valine,and L-1-[^{11}C] tyrosine. The main mechanism of[^{11}C]MET uptake is probably increased transport via the L-transporter system located in the endothelial cell membrane. [^{11}C]MET-PET offers a direct measure of amino acid transport and an indirect measure of microvessel density[1]. Owing to its low uptake in normal brain,[^{11}C]MET has been shown to be a sensitive tracer in tumor detection and tumor delineation, and to differentiate benign from malignant lesions with high sensitivity and specificity. Autoradiographic findings demonstrated that the level of increased [^{11}C]MET uptake correlates with the number of tumor cells, whereas no significant[^{11}C]MET uptake occurs in chronic inflammatory or radiogenic lesions. However, [^{11}C]MET uptake may be increased in acute inflammatory lesions and acute ischemic stroke with reperfusion[2]. To date, MET PET has been shown to be useful in various clinical situations : in guiding stereotactic biopsies, in differentiating between low-grade tumors and non-tumor lesions and as a prognostic marker.

Even though the patient sample in this study is small, we need more clarification on the following somewhat interesting results. First, the authors demonstrated that T/N ratio was significantly different between WHO III and IV but not between WHO II

and III. The uptake of carbon-11 methionine measured by PET has been correlated with the proliferative activity of gliomas in vivo and in vitro and has shown prognostic value in low-grade gliomas[3].

Why the MET-uptake was not different between low and high grade astrocytomas? Second, even though the author noted that there were no significant differences between astrocytoma and oligodendroglioma in maximum SUV of ROI and T/N ratio, Chan et al. found the contradictory results that highest microvessel counts in grade III oligodendrogliomas, these even higher than the counts in grade IV glioblastomas. The fact that WHO grade II oligodendrogliomas demonstrate high microvessel counts and high[^{11}C]MET uptake comparable to malignant astrocytomas[4]. Oligodendrogliomas have a significantly higher uptake of ^{11}C-methionine tracer than do lower grade astrocytomas, and that observation may be related to cell density and turnover in each of these tumors.

The authors also described that value of MET-PET in differentiating tumor recurrence from radiation necrosis. compared with that of FDG-PET. But only two out of 12 patients were confirmed pathologically. We must take into consideration that large numbers of recurrent tumors contained not only tumors but also radiation necrosis portions after adjuvant therapy using various types of radiation therapy and chemotherapy. There will be many areas for the clinical application of MET-PET. In the future, we have to clarify not only whether the uptake of MET may be a marker of the radiosensitivity of low-grade gliomas but also to apply MET-PET to select potential responders to anti-angiogenetic therapy. .

We understand that the information from this study might contribute the value of MET-PET not only for the grading of gliomas but also for the differentiation radiation necrosis from tumor recurrences.

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References

1. Kracht LW, Friese M, Herholz K, Schroeder R, Bauer B, Jacobs A, et al : Methyl-[^{11}C]-L-methionine uptake as measured by positron emission tomography correlates to microvessel density in patients with glioma. Eur J Nuc Med Mol Imaging 30 : 868-873, 2003
2. Kubota R, Kubota K, Yamada S, Tada M, Takahashi T, Iwata R, et al : Methionine uptake by tumor tissue : a microautographic comparison with FDG. J Nuc Med 36 : 484-492, 1995
3. Ribom D, Engler H, Blomquist E, Smits A : Potential significance of ^{11}C-methionine PET as a marker for the radiosensitivity of low-grade gliomas. Eur J Nuc Med 29 : 632-638, 2002
4. Chan AS, Leung SY, Wong MP, Yuen ST, Cheung N, Fan YW, et al : Expression of vascular endothelial growth factor and its receptors in the anaplastic progression of astrocytoma, oligodendroglioma, and ependymoma. Am J Surg Pathol 22 : 816-826, 1998