Usefulness of carbon-11-labeled methionine positron-emission tomography for assessing the treatment response of primary central nervous system lymphoma

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CONFLICT OF INTEREST STATEMENT

All authors declare that they have no competing interests.

Abstract

Background: Primary central nervous system lymphoma (PCNSL) responds relatively quickly to chemotherapy or radiotherapy. However, determination of a complete response (CR) after treatment is often difficult because of extremely light residual contrast enhancement on magnetic resonance images due to the effects of microhemorrhages and scar tissue formation. These small enhancing lesions define an unconfirmed complete response (CRu). The aim of this study was to investigate the usefulness of carbon-11-labeled methionine (^{11}C-Met) positron-emission tomography (PET) for determining the treatment response of PCNSL.

Methods: Data for 36 patients who were treated for PCNSL between 2011 and 2015 and underwent MRI and ^{11}C-Met PET were reviewed. MRI findings were classified as CR, CRu, and tumor mass (TM; a composite of partial response, stable disease, and progressive disease). PET images were evaluated, standardized uptake values were quantified, and the tumor to normal tissue count ratio (TNR) was calculated. Receiver operating characteristic curves were generated to determine the optimal cut-off TNRs.

Results: The optimal TNRs for differentiating CR and CRu from TM were 1.83 (area under the curve [AUC], 0.951) and 1.80 (AUC, 0.932), respectively. The corresponding sensitivity and specificity values for the diagnosis of TM were 82.4% and 100%, respectively, in the CR group and 85.3% and 85%, respectively, in the CRu group.

Conclusions: A TNR of ≥1.80 can aid in the detection of active PCNSL using ^{11}C-Met PET. Thus, ^{11}C-Met-PET may be a useful tool for accurate evaluation of the treatment efficacy in PCNSL.

Mini-abstract

Carbon-11-labeled methionine positron-emission tomography can accurately assess the treatment response of primary central nervous system lymphoma, which is often difficult to assess using magnetic resonance images alone.

Key words: central nervous system, lymphoma, magnetic resonance imaging, methionine, positron-emission tomography

Abbreviations List

AUC: area under the curve, ^{11}C-Met PET: carbon-11-labeled methionine positron emission tomography, CR: complete response, CRu: unconfirmed complete response, CT: computed tomography, FDG: fluorodeoxyglucose, Gd-DTPA: gadolinium diethylenetriaminepenta-acetic acid, HD-MTX: high-dose methotrexate, IPCG: International Primary CNS Lymphoma Collaborative Group, MRI: magnetic resonance imaging, PCNSL: primary central nervous system lymphoma, PR: partial response, ROC: receiver operating characteristics, ROI: region of interest, SUV: standardized uptake value, SUV_{max}: maximum standardized uptake value, TM: tumor mass, TNR: tumor to normal tissue count ratio

Introduction

Primary central nervous system lymphoma (PCNSL) is the second most common malignant brain tumor (1). It responds relatively quickly to chemotherapy or radiotherapy, with complete disappearance of enhancing lesions being a frequent observation. However, recurrence is observed in several cases. Chemotherapy based on high-dose methotrexate (HD-MTX) has been widely used for the treatment of PCNSL, with an overall response rate of 30%–90%(2).

Magnetic resonance imaging (MRI) with gadolinium diethylenetriaminepenta-acetic acid (Gd-DTPA) is used for evaluating the effects of treatment for brain tumors. PCNSLs tend to be round or oval, although they can sometimes appear gyriform with modest surrounding edema. Multiple lesions occur in 11%–47% cases(3). When assessing PCNSLs, sufficient attention must be paid to subtle changes, such as light or extremely small areas of residual contrast enhancement due to the effects of tumor biopsy-associated microhemorrhages and scar tissue. These small changes complicate the determination of a complete response (CR) using MRI-based assessments; moreover, residual lesions from the influence of surgery or chemoradiotherapy cannot be differentiated. According to the Baseline Evaluation and Response Criteria of the International Primary CNS Lymphoma Collaborative Group (IPCG), in addition to CR, small enhancing lesions define an unconfirmed complete response (CRu), which is different from a partial response (PR)(4).

The possible usefulness of carbon-11-labeled methionine (^{11}C-Met) positron-emission tomography (PET) for the differentiation of CR, CRu, and PR has been mentioned in previous reports(4, 5). However, to our knowledge, no study has provided details about the role of ^{11}C-Met PET in the

confirmation of CR, CRu, and PR. The aim of the present study was to compare MRI and ^{11}C-Met PET findings for patients with PCNSL treated at our institution and investigate the usefulness of ^{11}C-Met PET for determining the treatment efficacy in these patients. Therefore, first, we examined the tumor to normal tissue count ratio (TNR) cut-off point between the tumor itself and the region in which the tumor had previously occupied prior to seemingly disappearing completely in response to chemotherapy and/or chemoradiotherapy. Second, we investigated the equality of CR and CRu.

Materials and Methods

Patient characteristics and timing of examinations

We retrospectively reviewed the medical records of patients with pathologically proven diffuse large B-cell lymphoma of the CNS, PCNSL, who had received treatment and undergone MRI and ^{11}C-Met PET examinations within a 1-week interval, at least once during treatment, between 2011 and 2015. Thirty-six patients (22 men and 14 women) aged 35–86 years (median, 66 years) were considered eligible. They had undergone a total of 69 imaging studies, which were performed at the time of disease onset, after initial chemotherapy, after initial chemoradiotherapy, before treatment for recurrence, or after chemotherapy or radiotherapy for recurrence (Table 1). Thus, the timing of the imaging studies varied among patients, and 50% patients underwent multiple ^{11}C-Met PET examinations.

Our treatment regimen for newly diagnosed PCNSL comprised 3–5 cycles of biweekly HD-MTX (3.5–5.5 g/m^2) chemotherapy, followed by whole brain radiotherapy (30–40 Gy) with or without local

boost therapy (10 Gy). The treatment regimen for recurrence involved HD-MTX rechallenge (biweekly, 3–5 cycles) with or without rituximab (375 mg/m^2). Five patients with recurrent PCNSL received only radiation therapy.

All patients who underwent ^{11}C-Met PET provided written informed consent. This observational study was approved by the Institutional Review Board of the National Cancer Center.

Acquisition of MRI and ^{11}C-Met PET images

MRI was performed using a 1.5 T clinical scanner (MAGNETOM Avanto; Siemens Healthcare, Erlangen, Germany; maximum gradient strength, 45 mT/m; maximum slew rate, 200 mT/m/s). Our routine imaging protocol included axial T1-weighted imaging (WI), T2-WI, fluid attenuated inversion recovery imaging, and T1-WI with Gd-DTPA in at least two dimensions of axial and coronal sections. Based on the IPCG Baseline Evaluation and Response Criteria(4), the findings in the acquired images were categorized as CR, CRu, PR, stable disease, or progressive disease. CR was defined as when the lesions had disappeared completely. CRu was defined as when the lesions had almost disappeared but a light or extremely small lesion was visible, which had not increased in size on subsequent MRI taken at least one month later.

For ^{11}C-Met PET, ^{11}C-Met was synthesized by methylation with L-homocysteine thiolactone, followed by isolation of the final product by solid phase extraction(6), in the radiochemistry laboratory of our institute. The radiochemical purity of ^{11}C-Met ranged from 95% to 99%. Brain ^{11}C-Met PET/computed tomography (CT) was performed 10 min after intravenous administration of

^{11}C-Met (ca. 4 MBq/kg). Initially, a scout image was acquired under settings of 10 mA and 120 kV to determine the scanning field range from the vertex of the head to the neck of the patient. This was followed by cranial 16-slice helical CT for the targeted region. The acquired CT images were reconstructed as 512 × 512 matrix images (0.58 × 0.58 mm) with a 3.3-mm slice thickness. Subsequently, cranial three-dimensional PET images were acquired in two bed positions, with a 2-min acquisition time per bed position. The images covered the same field covered by the CT images, and they were reconstructed as 192 × 192 matrix images (3.65 × 3.65 mm) with a 3.3-mm slice thickness using a three-dimensional ordered subsets-expectation maximization algorithm. Evaluation of the PET images and quantification of standardized uptake values (SUVs) were performed using AW Volume Share 4.5 software (GE Healthcare, Milwaukee, WI, USA). Regions of interest (ROIs) were delineated on the PET/CT images, and the maximum SUV (SUV_{max}) in each ROI was determined. SUV was defined as the regional radioactivity divided by the injected radioactivity normalized for the body weight. ROIs were placed within the tumor and in the contralateral region of the brain (white matter). The tumor ROIs were defined as the areas of highest activity, while those on the contralateral side were used to calculate the tumor to normal tissue count ratio (TNR). Several target regions were assessed for SUV_{max} and TNR measurements, and the highest value was selected from each examination.

Evaluation of MRI and ^{11}C-Met PET findings

MRI and ^{11}C-Met PET were performed at the time of treatment initiation as part of the baseline

evaluation and at the end of each chemotherapy or radiotherapy cycle. At least three neurosurgical oncologists reviewed the post-treatment magnetic resonance images. The MRI findings were classified as per the five categories described above. Subsequently, PR, stable disease, and progressive disease, all of which are characterized by the presence of enhancing lesions, were combined into a single category termed tumor mass (TM). Based on the same concept, lesions with high intensity on MRI T1-WI with Gd-DTPA at the time of onset or recurrence were also included in the TM group. Thus, the MRI findings were eventually categorized as CR, CRu, and TM.

ROIs on the ^{11}C-Met PET images corresponded to the enhancing lesions evident on MRI performed during the same period. We delineated ROIs by referring to previous magnetic resonance images that showed lesions with marked enhancement, as well as the serial shrinkage of such lesions. If MRI showed multiple lesions, ROI was selected by reference to the largest area of enhancement. TNR was calculated by at least two authors. When two authors individually calculated TNR, the larger ratio was culled.

Statistical analysis

Receiver operating characteristics (ROC) curve analysis was used to determine the optimal cut-off TNRs according to the maximal Youden's index, which is the maximum value of J (J = sensitivity + specificity – 1)(7). The area under the curve (AUC) was calculated to determine the accuracy of the cut-off TNRs in identification of the treatment response. All statistical analyses were performed using JMP® version 11 (SAS Institute, Cary, NC, USA).

Results

TNR and SUV_{max} for the TM group

To assess the relationship between the tumor itself and TNR and SUV_{max}, we selected eight, 13, nine, and four patients with clear enhancing lesions on MRI at onset, at recurrence, after initial chemotherapy, and after chemoradiotherapy, respectively. These 34 cases were assigned to the TM group (Table 1). TNR and SUV_{max} at onset, at recurrence, after initial chemotherapy, and after chemoradiotherapy are presented in Table 2.

TNR and SUV_{max} for the CR and CRu groups

The imaging findings for seven and 13 patients were compatible with CR and CRu, respectively, after initial chemotherapy. We identified one case of CR after initial radiotherapy and three cases of CRu after initial chemoradiotherapy. After chemotherapy or radiotherapy for recurrence, seven and four cases exhibited CR and CRu, respectively. TNR and SUV_{max} data for all these patients are presented in Table 2.

ROC curves, cut-off values, and diagnostic accuracy

According to the ROC curve analyses, the optimal cut-off TNRs for differentiating TM from CR was 1.83 (AUC, 0.951; Fig. 1A), with sensitivity and specificity values of 82.4% and 100%, respectively. The optimal cut-off TNR for differentiating TM from CRu was 1.80 (AUC, 0.932; Fig. 1B), with

sensitivity and specificity values of 85.3% and 85%, respectively. If 1.83 was applied as the cut-off TNR for differentiating CRu from TM, the sensitivity and specificity for the diagnosis of TM were 82.3% and 85%, respectively.

Representative case

Patient 1

A 64-year-old man visited a local physician with chief complaints of difficulty in speech and forgetfulness. MRI revealed clear enhancement in the splenium of the corpus callosum (Fig. 2A, B), and biopsy specimens showed a diffuse large B-cell lymphoma. ^{11}C-Met PET revealed clear uptake (TNR, 3.33; SUV_{max}, 6.0) at the same site (Fig. 2C). He received HD-MTX chemotherapy and whole brain radiotherapy (40 Gy), and post-treatment MRI showed marked shrinkage of the tumor. However, residual enhancement was observed in the core of the tumor (Fig. 2D, E). ^{11}C-Met PET showed a TNR and an SUV_{max} of 1.31 and 1.7, respectively (Fig. 2F). Based on these findings, we determined the treatment response as CRu and observed the patient through regular follow-up visits. MRI performed at 2 months after treatment completion revealed residual enhancing areas, although they appeared to be shrinking (Fig. 2G). No contrast enhancement was observed at 3 and 5 months after treatment (Fig. 2H, I).

Discussion

According to the IPCG criteria, CRu is defined by the presence of small but persistent enhancing abnormalities, which are associated with surgical intervention, focal microhemorrhages, or chemotherapeutic effects, on magnetic resonance images(4). Therefore, the assessment of CRu using MRI is occasionally difficult. However, no other effective assessment tool has been validated. In the present study, ^{11}C-Met PET could clearly distinguish CR from TM, and the SUV_{max} and TNR for the CR region were similar to those for the CRu region. These findings suggest that a combination of ^{11}C-Met PET and MRI allows for more accurate assessment of CRu than does MRI alone.

One of the most common and inevitable side effects of chemoradiotherapy is leukoencephalopathy due to concomitant use of MTX and whole brain radiotherapy. The accompanying neurological symptoms and cognitive dysfunction are serious problems for patients with PCNSL; the reported frequency is 20%–30%(8, 9). Various treatment protocols, such as high-dose chemotherapy without the use of whole brain radiotherapy, have been proposed for the prevention of leukoencephalopathy; therefore, the accuracy of therapeutic response assessments after initial chemotherapy is extremely important. Although chemotherapy achieves high response rates in cases of PCNSL, assessment of the treatment response is difficult in some patients for the following reasons: disappearance of lesions because lesions may disappear in response to corticosteroid administration only, presence of enhancing lesions on MRI both in residual lesions and in invasive surgery, and occasional enhancement of hemorrhages and infarcts by contrast media. Küker *et al*. were the first to point out these problems(5). They proposed revised PCNSL response criteria, which stated that CR should be assumed if complete resolution of enhancing lesions is observed or, in the absence of edema, a

residual, nodular, enhancing lesion measuring <5 mm persists in the region of biopsy, microhemorrhages, or infection or in cases where the initial mass measured >5 cm in diameter(5). IPCG-based criteria for the assessment of CRu were developed from their report, but such novel response criteria are sometimes difficult to apply with the use of MRI alone. Both IPCG and Küker *et al*. mentioned that this problem could be resolved by the use of PET for the qualitative assessment of tumor activity that cannot be determined by MRI(5). With the use of ^{11}C-Met PET, differentiation between PR and CRu will become objective.

Several previous studies have reported the utility of PET examination for the diagnosis of brain tumors and the differentiation of recurrence from radionecrosis(10-17). PET with fluorodeoxyglucose (FDG) is the most widely used and well-reported method(11). However, because FDG preferentially accumulates in both tumor tissue and normal brain tissue, distinction between these tissues becomes difficult(15). Malignant cells frequently display a high demand for and utilization of amino acids, whereas amino acid transport in normal brain tissue is low. Therefore, the contrast between tumor tissue and normal brain tissue is generally better appreciated on ^{11}C-Met PET than on FDG PET(11, 15). Despite this, ^{11}C-Met PET is not commonly used because the half-life of ^{11}C-Met is short (20 min), which limits its use to research facilities that have a cyclotron(10).

^{11}C-Met uptake in PET reflects the malignancy of a glioma, and TNR is reported to be significantly higher for high-grade (2.15 ± 0.77) gliomas than for low-grade (1.56 ± 0.74) gliomas(16). Furthermore, the utility of ^{11}C-Met PET for the differentiation of malignant gliomas, metastatic brain tumors, and radionecrosis has been reported, with mean TNRs of 1.58–1.87 for recurrent tumors and

1.3–1.41 for necrotic tissue. Furthermore, a correlation between TNR determined by ^{11}C-Met PET and the prognosis has been reported in patients with gliomas(16).

In an assessment of PCNSLs using FDG-PET, Yamaguchi *et al*. reported an optimal cut-off TNR of 2.0(18). However, there are few reports on the use of ^{11}C-Met PET for the assessment of PCNSLs(10, 12-14). Kawase *et al*. reported the differences between FDG PET and ^{11}C-Met PET for PCNSLs; SUV in ^{11}C-Met PET was lower than that in FDG PET, with a mean TNR of 2.99 (1.46–5.14). Moreover, ^{11}C-Met PET allowed superior differentiation of PCNSL(12).

Ahn et al have reported the prognostic significance of interim ^{11}C-Met PET /CT in PCNSL(19). They described that higher IELSG risk scores were associated with higher median values for interim metabolic tumor volume and TNR, as well as poor outcomes, and concluded that response assessments based on interim ^{11}C-Met PET /CT could predict the therapeutic outcome of PCNSL. Although we did not assess the prognostic significance of interim ^{11}C-Met PET /CT, their results are interesting and impressive. Furthermore, they indicated that according to the ROC analysis, the optimal cut-off value for the interim TNR was 1.67 with an AUC of 0.804 (sensitivity, 71.4%; specificity, 83.3%; $P < 0.001$). We are unaware of the methodology they used to evaluate cut-off value by using ROC; their reported AUC of 0.804 was lower than the AUC reported in the present study. If their ROC analysis methodology was similar to the one in our study evaluate the cut-off value, we would expect the cut-off value to be similar to ours.

In the present study, the efficacy of treatment for PCNSL was determined based on TNR and SUV_{max} derived from ^{11}C-Met PET in addition to MRI findings. However, SUV_{max} differs depending on the

tumor site, and some patients exhibit a high ratio despite a low SUV_{max}. Therefore, TNR may be more useful. This is particularly true in cases of recurrence, considering that SUV_{max} did not differ between CR and CRu before treatment (Supplementary Figure 2). We also compared values obtained after initial treatment with those obtained before treatment for recurrence and found a significant difference in patients with CR after initial treatment, whereas TNR was low in all cases (<1.80). Furthermore, TNRs were similar for patients with CR and those with small residual enhancing lesions indicating CRu, with no significant differences between the two groups. These findings suggest that CRu in cases where CR confirmation based on MRI findings was difficult is equivalent to an objectively determined CR. Because treatment completion can be determined, such patients may proceed to the follow-up phase. In three representative cases involving small enhancing lesions after treatment completion in the present study (Fig. 2 and Supplementary Figures 1 and 2), CRu was determined based on MRI findings. All three patients exhibited a TNR of <1.80, and the enhancing lesions disappeared after 3–5 months. This indicates the benefit of ^{11}C-Met-PET for determining the efficacy of treatment for PCNSLs.

Our ROC curve analyses showed that the optimal cut-off TNRs for differentiating TM from CR and CRu were 1.83 and 1.80, respectively, with corresponding AUCs of 0.951 and 0.932. The categories used to summarize the accuracy according to the AUC value are as follows: excellent (0.9–1), good (0.8–0.9), fair (0.7–0.8), poor (0.6–0.7), and fail (0.5–0.6)(7). Accordingly, tests with an AUC of ≥0.85 are generally considered accurate, and the cut-off TNR of 1.80 (AUC = 0.932) may be highly reliable and accurate for the differentiation of CRu from TM. This is the first report to demonstrate

optimal cut-off values of ^{11}C-Met PET for the evaluation of TM in patients with PCNSL.

Although we believe ^{11}C-Met PET scan to be reliable, García-Garzon et al pointed out a false negative case when comparing the use of ^{11}C-Met PET with ^{18}FDG PET(20). In that case, the MRI lesion corresponded with an inconclusive metabolic pattern of intense ^{18}F-FDG uptake and no significant ^{11}C-Met uptake. Thus, we must take into consideration that false negatives could occur in rare cases; it is necessary to pay attention to the chance of regrowth and ensure close follow-up is performed where CRu is achieved.

Conclusions

In conclusion, our findings suggest that ^{11}C-Met PET is a useful tool for determining the treatment response in patients with PCNSLs, with a TNR of ≥1.80 serving as an optimal measure for differentiation between CRu and progressive disease. To the best of our knowledge, this is the first study to demonstrate optimal ^{11}C-Met PET values for the evaluation of the treatment response in patients with PCNSLs.

References

1. Brain Tumor Registry of Japan (2005-2008). Neurologia medico-chirurgica. 2017;57(Suppl 1):9-102.
2. Omuro AM, Abrey LE. Chemotherapy for primary central nervous system lymphoma. Neurosurg Focus. 2006;21(5):E12.
3. Go JL, Lee SC, Kim PE. Imaging of primary central nervous system lymphoma. Neurosurg Focus. 2006;21(5):E4.
4. Abrey LE, Batchelor TT, Ferreri AJ et al. Report of an international workshop to standardize baseline evaluation and response criteria for primary CNS lymphoma. J Clin Oncol. 2005;23(22):5034-43.
5. Kuker W, Nagele T, Thiel E, Weller M, Herrlinger U. Primary central nervous system lymphomas (PCNSL): MRI response criteria revised. Neurology. 2005;65(7):1129-31.
6. Langstrom B, Antoni G, Gullberg P et al. Synthesis of L- and D-[methyl-11C]methionine. J Nucl Med. 1987;28(6):1037-40.
7. Akobeng AK. Understanding diagnostic tests 3: Receiver operating characteristic curves. Acta Paediatr. 2007;96(5):644-7.
8. Abrey LE, DeAngelis LM, Yahalom J. Long-term survival in primary CNS lymphoma. J Clin Oncol. 1998;16(3):859-63.
9. Omuro AM, Ben-Porat LS, Panageas KS et al. Delayed neurotoxicity in primary central nervous system lymphoma. Arch Neurol. 2005;62(10):1595-600.
10. Jang SJ, Lee KH, Lee JY et al. (11)C-methionine PET/CT and MRI of primary central nervous system diffuse large B-cell lymphoma before and after high-dose methotrexate. Clinical nuclear medicine. 2012;37(10):e241-4.
11. Kawai N, Miyake K, Yamamoto Y, Nishiyama Y, Tamiya T. 18F-FDG PET in the diagnosis and treatment of primary central nervous system lymphoma. Biomed Res Int. 2013;2013:247152.
12. Kawase Y, Yamamoto Y, Kameyama R, Kawai N, Kudomi N, Nishiyama Y. Comparison of 11C-methionine PET and 18F-FDG PET in patients with primary central nervous system lymphoma. Mol Imaging Biol. 2011;13(6):1284-9.
13. Ogawa T, Kanno I, Hatazawa J et al. Methionine PET for follow-up of radiation therapy of primary lymphoma of the brain. Radiographics. 1994;14(1):101-10.
14. Sawataishi J, Mineura K, Sasajima T, Kowada M, Sugawara A, Shishido F. Effects of radiotherapy determined by 11C-methyl-L-methionine positron emission tomography in patients with primary cerebral malignant lymphoma. Neuroradiology. 1992;34(6):517-9.
15. Schaller B. Usefulness of positron emission tomography in diagnosis and treatment follow-up of brain tumors. Neurobiol Dis. 2004;15(3):437-48.
16. Singhal T, Narayanan TK, Jacobs MP, Bal C, Mantil JC. 11C-methionine PET for grading and prognostication in gliomas: a comparison study with 18F-FDG PET and contrast enhancement on MRI. J Nucl Med. 2012;53(11):1709-15.
17. Yamaguchi S, Hirata K, Kaneko S et al. Combined use of 18 F-FDG PET and corticosteroid for diagnosis of deep-seated primary central nervous system lymphoma without histopathological confirmation.

Acta Neurochir (Wien). 2015;157(2):187-94.

18. Yamaguchi S, Hirata K, Kobayashi H et al. The diagnostic role of (18)F-FDG PET for primary central nervous system lymphoma. Ann Nucl Med. 2014;28(7):603-9.

19. Ahn SY, Kwon SY, Jung SH et al. Prognostic Significance of Interim 11C-Methionine PET/CT in Primary Central Nervous System Lymphoma. Clinical nuclear medicine. 2018;43(8):e259-e64.

20. Garcia-Garzon JR, Villasboas-Rosciolesi D, Baquero M, Bassa P, Soler M, Riera E. A False-Negative Case of Primary Central Nervous System Lymphoma on 11C-Methionine PET and Intense 18F-FDG Uptake. Clinical nuclear medicine. 2016;41(8):664-5.

Figure legends

Figure 1. Findings of receiver operating characteristics (ROC) curve analysis for the tumor to normal tissue count ratio (TNR) determined by carbon-11-labeled positron-emission tomography for patients with primary central nervous system lymphomas

(A) Complete response versus tumor mass groups

(B) Unconfirmed complete response versus tumor mass groups

Figure 2.

Magnetic resonance imaging (MRI) and carbon-11-labeled methionine positron-emission tomography (^{11}C-Met PET) images for a 64-year-old man with a primary central nervous system lymphoma

(A, B) Pretreatment MRI without (A) and with (B) gadolinium diethylenetriaminepenta-acetic acid (Gd-DTPA)

The images show a lesion with marked enhancement in the corpus callosum and extending into both frontal lobes.

(C) ^{11}C-Met PET/computed tomography (CT) demonstrates increased tracer uptake in the same lesion.

(D–F) After completion of chemoradiotherapy, MRI without (D) and with (E) Gd-DTPA shows tiny areas of enhancement in the tumor cavity (inferiorly), while ^{11}C-Met PET/CT (F) demonstrates no tracer uptake.

(G, H) Two months after initial treatment, MRI without (G) and with (H) Gd-DTPA shows a small amount of residual enhancement.

(I) Five months after the induction phase, MRI with Gd-DTPA shows complete disappearance of contrast enhancement.

Supplementary Figure 1.

Patient 2

Magnetic resonance imaging (MRI) and carbon-11-labeled methionine positron-emission tomography (^{11}C-Met PET) images for a 68-year-old man with a primary central nervous system lymphoma

The patient presented with disorientation and right-sided hemiparesis.

(A) MRI indicates a brain tumor in the left basal ganglia.

Biopsy revealed diffuse large B-cell lymphoma.

(B) ^{11}C-Met PET (B) reveals clear uptake (tumor to normal tissue count ratio [TNR], 8.29; maximum standardized uptake value [SUV_{max}], 11.6).

(C, D) MRI performed after high-dose methotrexate chemotherapy and whole-brain radiotherapy (40 Gy) reveals slight, pale contrast enhancement.

(E) ^{11}C-Met PET image (SUV_{max}, 2.8; TNR, 1.75) obtained after treatment

On the basis of the imaging findings, an unconfirmed complete response (CRu) was determined for this patient.

MRI performed at 2 months after treatment completion showed tiny areas of residual enhancement that appeared to be shrinking.

(F) Contrast enhancement is no longer observed on MRI performed at 3 months after treatment.

Supplementary Figure 2.

Patient 3

Magnetic resonance imaging (MRI) and carbon-11-labeled methionine positron-emission tomography (^{11}C-Met PET) images for a 66-year-old man with a primary central nervous system lymphoma

The patient underwent chemotherapy with high-dose methotrexate (HD-MTX), followed by radiotherapy (40 Gy) 3 years back. He initially had multiple lesions located in the hypothalamus, cerebellum, and corpus callosum.

(A) MRI performed at 3 years after the achievement of a complete response (CR) shows an enhancing lesion in the left caudate head (A); this was diagnosed as PCNSL recurrence.

(B) ^{11}C-Met PET image (tumor to normal tissue count ratio [TNR], 2.89; maximum standardized uptake value [SUV_{max}], 2.6) obtained before treatment

Five cycles of chemotherapy (rituximab and HD-MTX) were administered.

(C, D) Slight residual contrast enhancement can be seen on MRI performed after treatment.

(E) ^{11}C-Met PET image (SUV_{max}, 7.8; TNR, 1.39) obtained after treatment

An unconfirmed complete response (CRu) was determined for this patient, and he was routinely monitored.

(F) Contrast enhancement has considerably reduced on MRI performed at 4 months after treatment completion.

Table 1. Patient population

		Population
Male : Female		22 : 14
Age		35-86 (median 66)
Timing of image acquisition		Pt No. (Exam No.)
Newly-diagnosed	At onset	8 (8)
	Post-chemotherapy	27 (29)
	Post-irradiation	8 (8)
Recurrent	At recurrence	10 (13)
	Post-treatment	5 (11)

Abbreviations: Pt No. = number of patient; Exam No. = number of examination

Table 2. A relationship between MRI findings and TNR and SUVmax

	TM	CR	CRu
	n TNR range (mean), SUVmax range (mean)	n TNR range (mean), SUVmax range (mean)	n TNR range (mean),SUVmax range (mean)
All examinations	n=34 1.45-8.05 (3.30), 1.43-11.59 (4.41)	n=15 1.06-1.80 (1.46), 1.22-7.11 (2.45)	n=20 1.14-2.40 (1.51), 1.22-7.80 (2.29)
Newly-diagnosed PCNSL			
At onset	n=8 1.95-8.05 (4.09), 2.92-11.59 (6.28)	-	-
Post-chemotherapy	n=9 1.54-7.23 (3.56), 1.74-7.11 (4.00)	n=7 1.06-1.80 (1.40), 1.39-2.60 (1.93)	n=13 1.14-2.40 (1.48), 1.22-3.00 (2.02)
Post-chemoradiation	n=4 1.45-2.46 (2.00), 2.28-5.24 (3.23)	n=1 1.71, 1.88	n=3 1.29-1.73 (1.47), 1.39-2.82 (2.11)
Recurrent PCNSL			
Pre-treatment	n=13 1.80-4.57 (3.03), 1.43-8.32 (3.91)	-	-
Post-treatment	none	n=7 1.11-1.72 (1.48), 1.22-7.11 (3.04)	n=4 1.40-2.13 (1.61), 1.52-7.80 (3.33)

Abbreviations: PCNSL = primary central nervous system lymphoma; TM = tumor mass; CR = complete response; CRu = unconfirmed CR; TNR = tumor versus normal tissue count ration; SUVmax = maximum standardized uptake value; n = number

Figure 1A

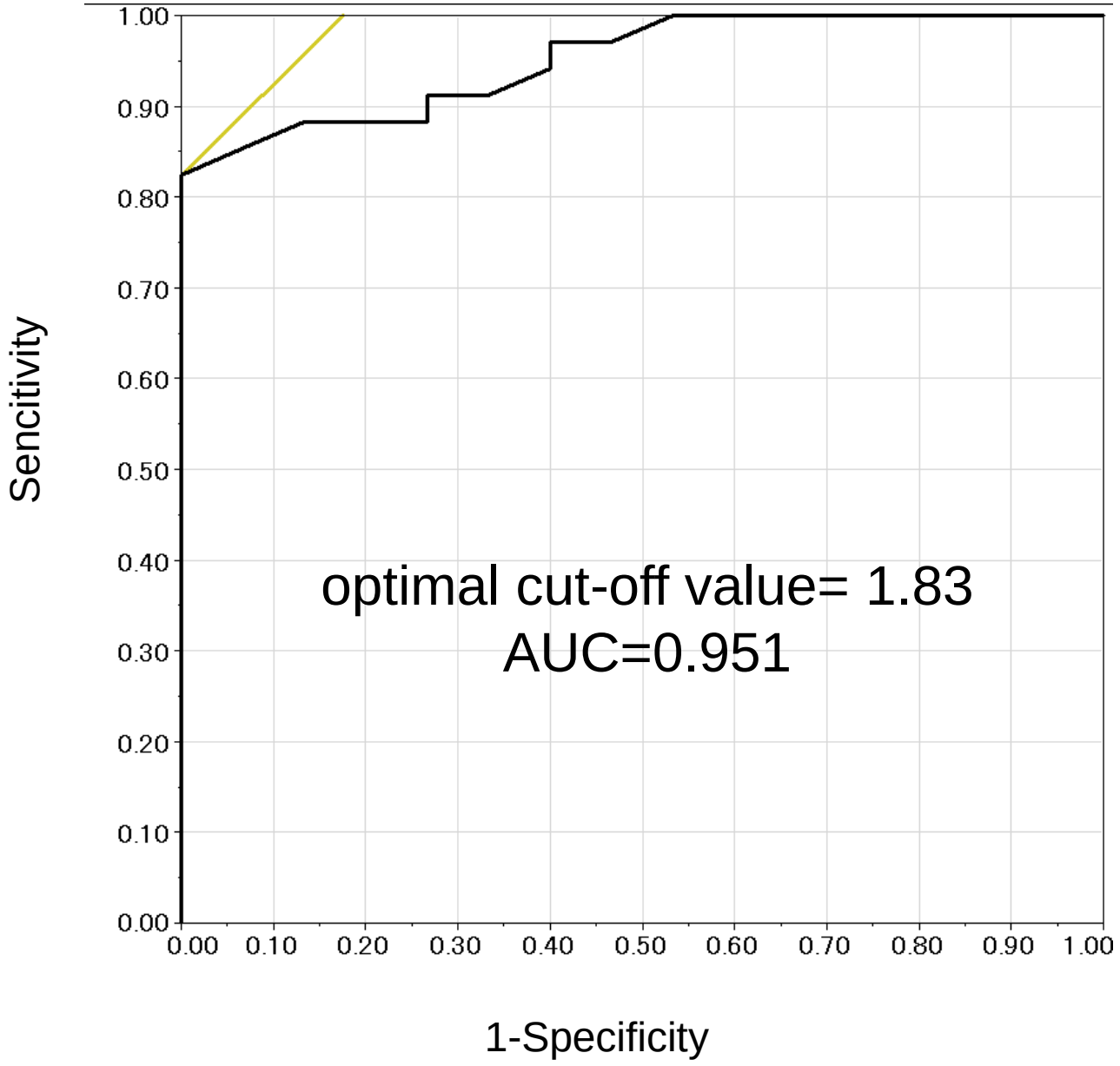

Sencitivity
1.00
0.90
0.80
0.70
0.60
0.50
0.40
0.30
0.20
0.10
0.00
0.00 0.10 0.20 0.30 0.40 0.50 0.60 0.70 0.80 0.90 1.00
optimal cut-off value= 1.83
AUC=0.951
1-Specificity

Figure 1B

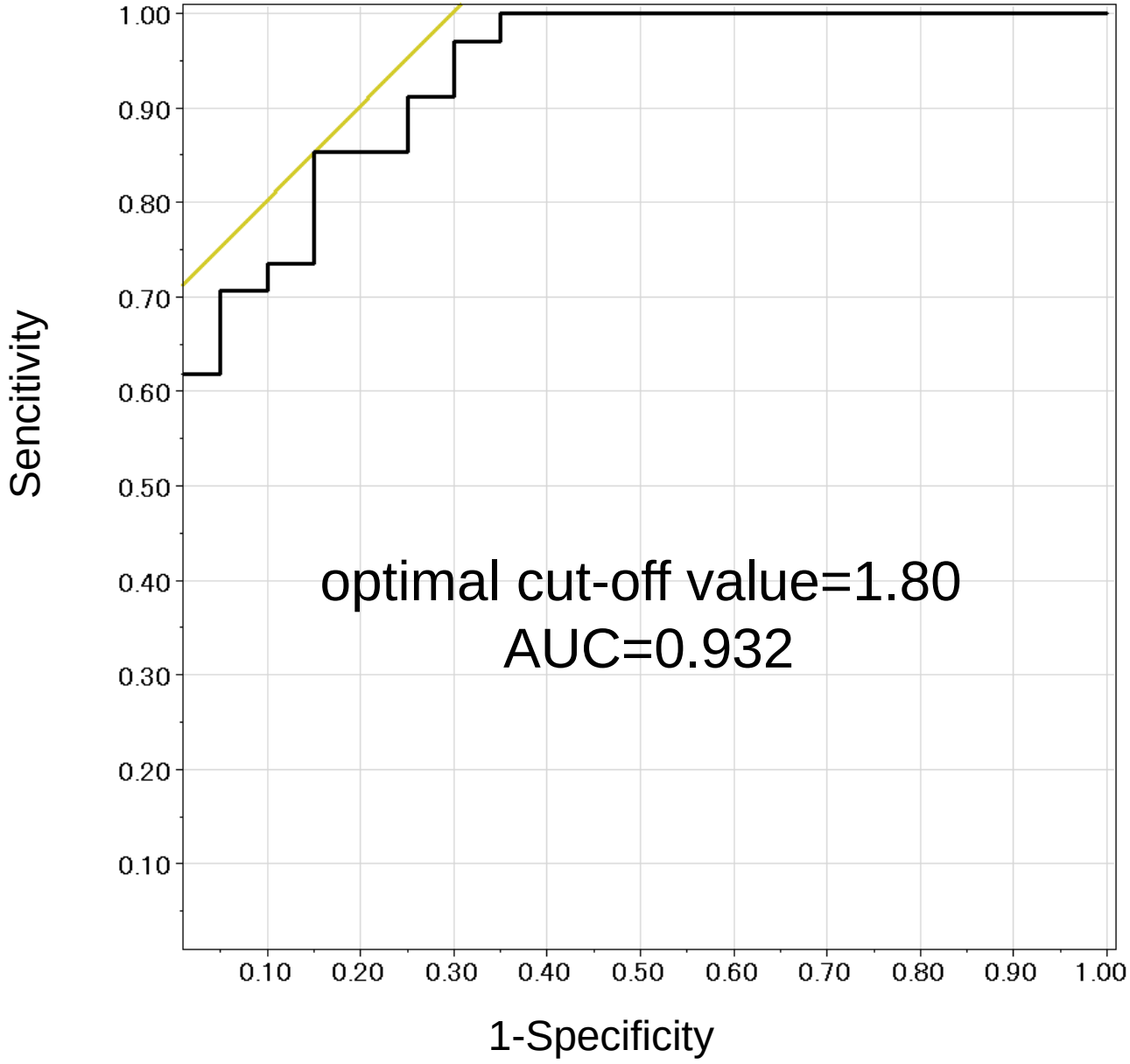
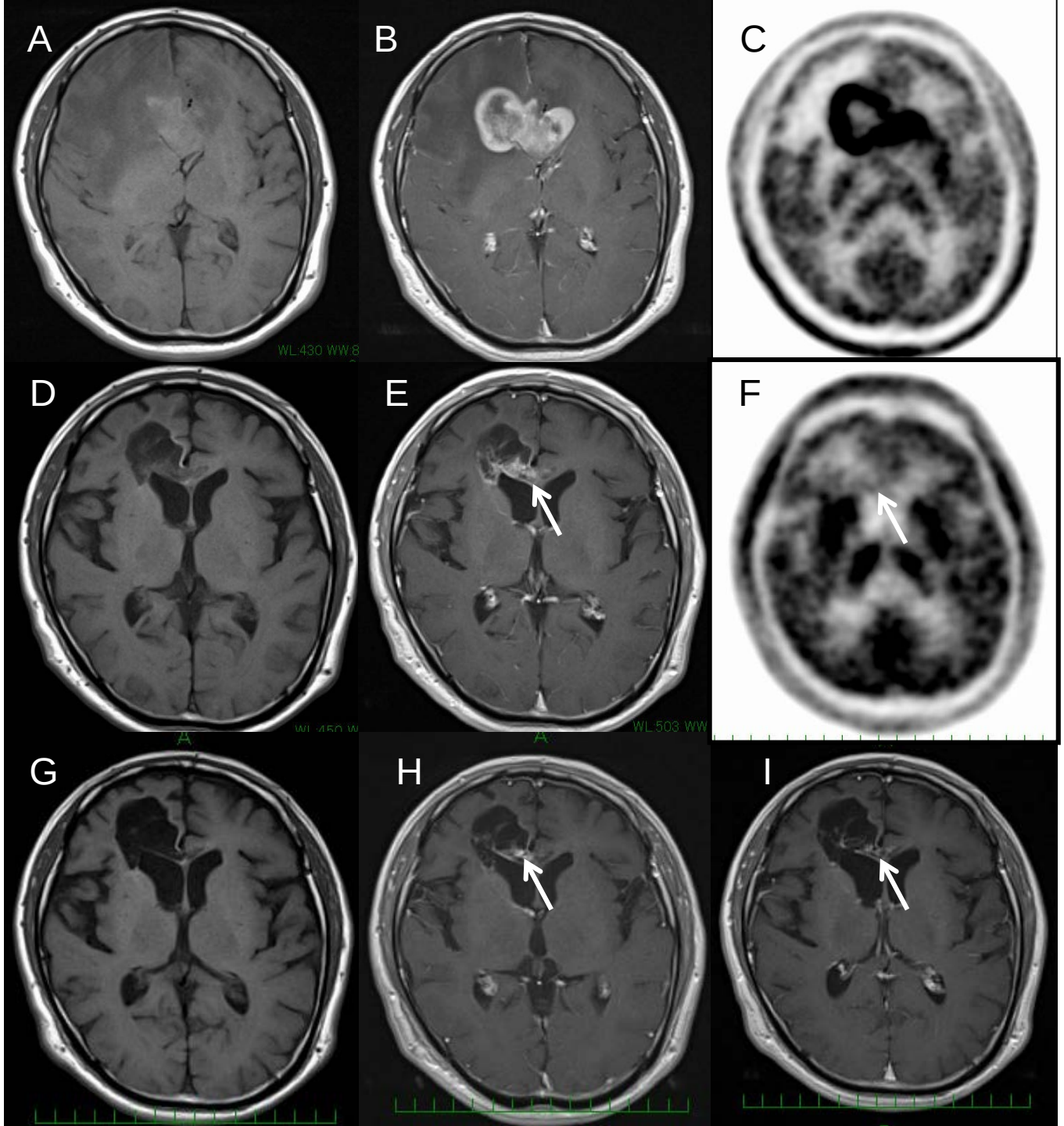
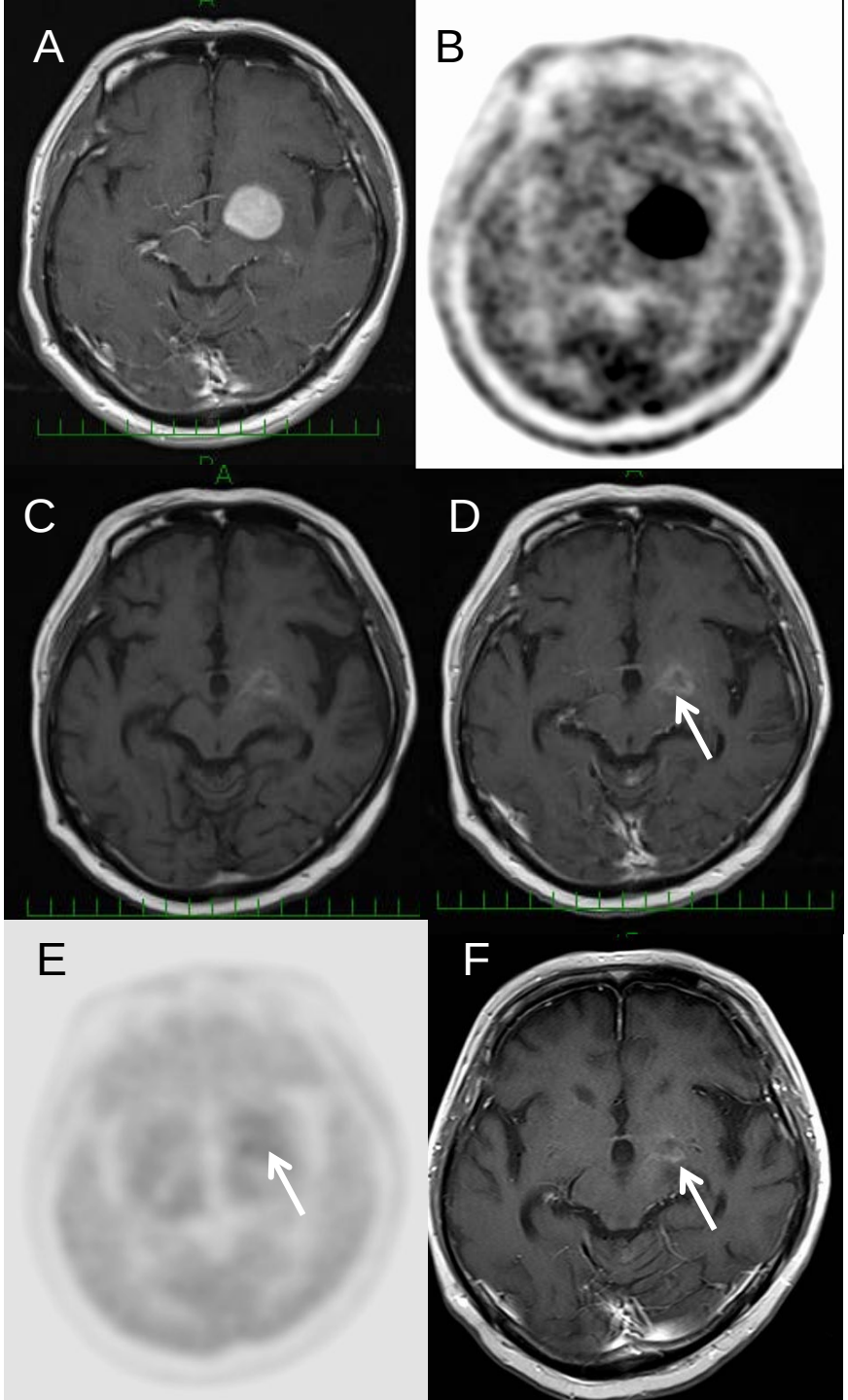

Sencitivity
1.00
0.90
0.80
0.70
0.60
0.50
0.40
0.30
0.20
0.10
optimal cut-off value=1.80
AUC=0.932
0.10
0.20
0.30
0.40
0.50
0.60
0.70
0.80
0.90
1.00
1-Specificity

Figure 2



Supplementary Figure 1.



Supplementary Figure 2.