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Utility of [^{18}F]fluciclovine PET/MRI for identifying the optimal biopsy target region, helping to avoid underdiagnosis in patients with glioblastoma: illustrative case

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BACKGROUND Glioblastoma (GBM) is known for its significant intratumoral heterogeneity, making biopsies susceptible to underdiagnosis if samples are taken from less malignant regions. [^{18}F]Fluciclovine, a novel PET tracer, has demonstrated high accumulation in glioma tissue, with minimal uptake in normal brain tissue.

OBSERVATIONS A 50-year-old woman presented with sensory aphasia. MRI revealed a FLAIR lesion extending from the left parietal to the medial temporal lobe. [^{18}F]Fluciclovine PET/MRI identified two areas of increased uptake, both FLAIR negative. Stereotactic biopsy was used to obtain samples from PET-positive (PET+) and FLAIR-positive (FLAIR+) lesions. Pathological analysis of the PET+ lesion revealed densely proliferating tumor cells with irregularly enlarged nuclei, while the FLAIR+ lesion exhibited sparsely proliferating cells. Molecular analysis showed that both lesions were IDH wildtype with *MGMT* promoter hypomethylation. Sanger sequencing identified a telomerase reverse transcriptase promoter −124 C>T mutation in the PET+ lesion but not in the FLAIR+ lesion. The integrated diagnosis, based primarily on the PET+ lesion, was GBM, IDH wildtype.

LESSONS This case highlights the importance of [^{18}F]fluciclovine PET/MRI in identifying high-cell-density regions, minimizing the risk of underdiagnosis in GBM. Further studies are necessary to evaluate its prognostic value in GBM management.

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KEYWORDS [^{18}F]fluciclovine; glioblastoma; PET; biopsy

Glioblastoma (GBM) is the most aggressive and common primary brain tumor in adults. According to the 2021 WHO classification of central nervous system tumors, GBM is defined as an IDH-wildtype diffuse astrocytic glioma in adults. It is characterized by histopathological features such as microvascular proliferation or necrosis or by molecular markers such as telomerase reverse transcriptase (*TERT*) promoter mutations, EGFR gene amplification, or +7/−10 chromosomal copy number changes.[1] Typically, GBM tissue is obtained through resection for both diagnostic and therapeutic purposes. However, in cases in which resection is not feasible, or if only a limited amount of tissue can be removed, or when a patient's condition prohibits general anesthesia, needle biopsy is used for diagnosis. A significant challenge with needle biopsy is GBM's intratumoral heterogeneity, as different regions of the tumor can have distinct molecular profiles.[2,3] This raises the risk of underdiagnosis if the biopsy sample is taken from a less malignant region.

[^{18}F]Fluciclovine (FACBC; Axumin, Nihon Medi-physics Co., Ltd.) is a novel synthetic amino acid PET tracer that crosses cell membranes via amino acid transporters (LAT1 and ASCT2),[4] which are overexpressed in many cancers.[5] Its accumulation reflects amino acid metabolism.[6] Studies have shown that this tracer significantly accumulates in glioma tissue while exhibiting minimal uptake in normal brain or inflammatory sites.[7] This leads to a higher tumor-to–normal tissue ratio compared with a conventional amino acid tracer,[11] C-methionine,[8] and results in a high positive predictive value.[9] In May 2024, Japan included FACBC in its insurance coverage for visualizing suspected

ABBREVIATIONS CBV = cerebral blood volume; FACBC = [^{18}F]fluciclovine; GBM = glioblastoma; MAF = mutant allele frequency; PCR = polymerase chain reaction.

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malignant gliomas to aid in determining the extent of tumor resection based on MRI findings.

We present the case of a patient with an IDH-wildtype GBM in which preoperative FACBC PET/MRI accurately identified a malignant lesion, helping to avoid underdiagnosis.

Illustrative Case

A 50-year-old woman presented to a previous hospital with sensory aphasia and symptoms of temporal lobe epilepsy. She had no significant medical history, was not on any medications, and had no notable family history. On examination, she displayed speech difficulties, gaze disturbances, staring episodes, and repetitive chewing movements. After hospital admission, she experienced generalized convulsions.

MRI revealed an extensive FLAIR lesion extending from the left parietal lobe to the medial temporal lobe (Fig. 1). The tumor appeared hypointense on T1-weighted images and hyperintense on T2-weighted images, with no enhancement on gadolinium-enhanced T1-weighted imaging. Suspected of having a glioma on imaging, this patient was referred to our hospital 6 days after experiencing a seizure. To assist in diagnosis, a needle biopsy was planned, and FACBC PET/MRI was performed to identify the target lesion. FACBC PET/MRI revealed two areas of increased uptake in the left temporal lobe, which were both FLAIR negative (FLAIR−). Perfusion MRI revealed no increase in cerebral blood volume (CBV) in either region. To ensure an accurate diagnosis, biopsies were planned for two independent regions: one from the FACBC PET/MRI+/FLAIR− lesion (PET+) and another from the FACBC PET/MRI−/FLAIR+ lesion (FLAIR+) (Fig. 2).

Prior to surgery, the patient was conscious, alert, and exhibited no neurological symptoms. We administered 5-aminolevulinic acid to improve tumor visualization. A stereotactic needle biopsy was performed to obtain samples from both lesions. Under blue light, the PET+ lesion showed bright red fluorescence, indicating densely proliferating tumor tissue with high cell density,[10] whereas the FLAIR+ lesion showed no fluorescence.

Postoperative MRI confirmed successful biopsies from both target areas (Fig. 2). The patient experienced no neurological deficits postsurgery and was discharged 5 days later with a Karnofsky Performance Status of 90.

Pathological analysis of the PET+ lesion revealed densely proliferating tumor cells with irregularly enlarged nuclei, ranging from short spindle-shaped to epithelioid forms, in a solid and infiltrative pattern. More than 10 mitotic figures were observed in the small sample, although there was no evidence of necrosis, microvascular proliferation, eosinophilic granular bodies, or Rosenthal fibers. In contrast, the FLAIR+ lesion showed tumor cells with similarly irregularly enlarged nuclei and cytoplasmic processes, but these cells were proliferating more sparsely (Fig. 3).

Molecular analysis was conducted to further characterize and compare the two lesions. Sanger sequencing revealed that both the PET+ and FLAIR+ lesions were *IDH1* R132H wildtype and *IDH2* R172H

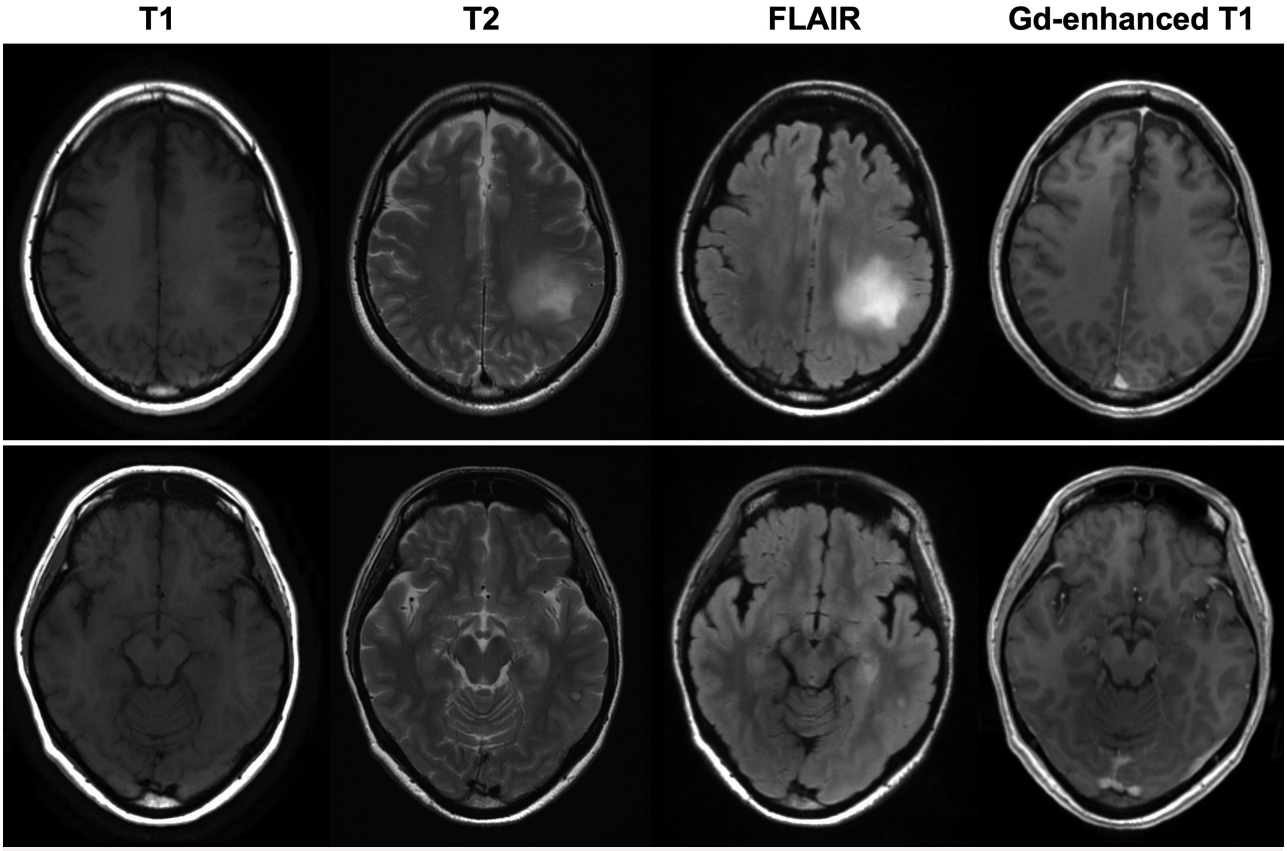

FIG. 1. Preoperative axial T1- and T2-weighted, FLAIR, and Gd-enhanced T1-weighted images at the centrum ovale level (**upper**) and midbrain level (**lower**).

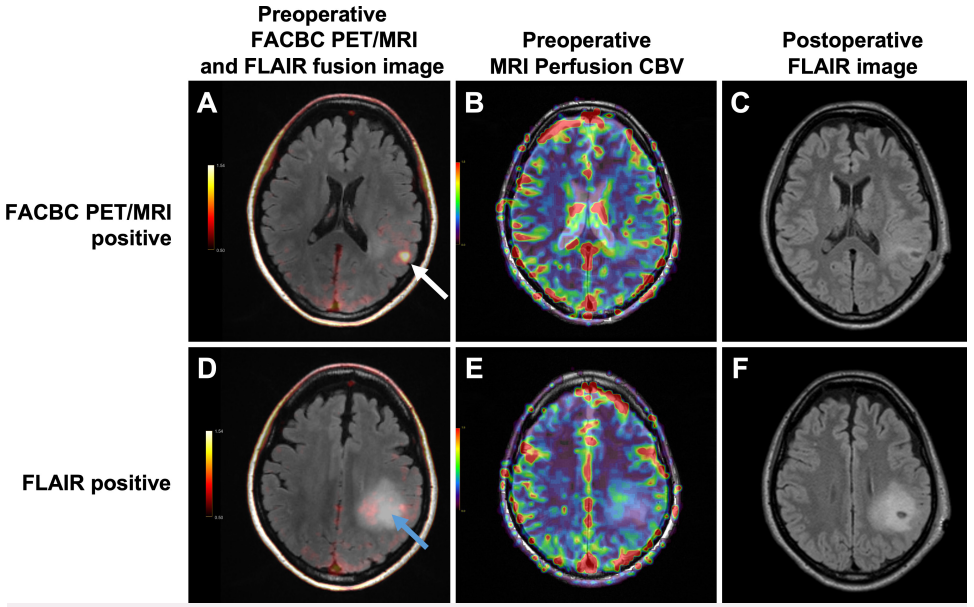

FIG. 2. Preoperative (**A, B, D, and E**) and postoperative (**C and F**) images. Representative images of the FACBC PET/MRI+ lesion (A–C). Representative images of the FLAIR+ lesion (D–F). *White* and *blue arrows* indicate the FACBC PET/MRI+ and FLAIR+ target lesions, respectively.

wildtype and showed *MGMT* promoter hypomethylation. However, the PET+ lesion harbored a *TERT* promoter −124 C>T mutation, whereas the FLAIR+ lesion did not (Fig. 4). Because of the high guanine and cytosine composition of the *TERT* promoter region, which makes it difficult to amplify by polymerase chain reaction (PCR), and the inability of Sanger sequencing to detect mutations when the mutant allele frequency (MAF) is below 15%–20%,[11] digital PCR was used to further validate the results. Digital PCR confirmed the *TERT* promoter −124 C>T mutation, with a low MAF of 14.2% in the FLAIR+ lesion versus 41.2% in the PET+ lesion. Based primarily on the PET+ lesion, the integrated diagnosis, following the 2021 WHO classification of central nervous system tumors, was determined to be GBM, IDH wildtype.

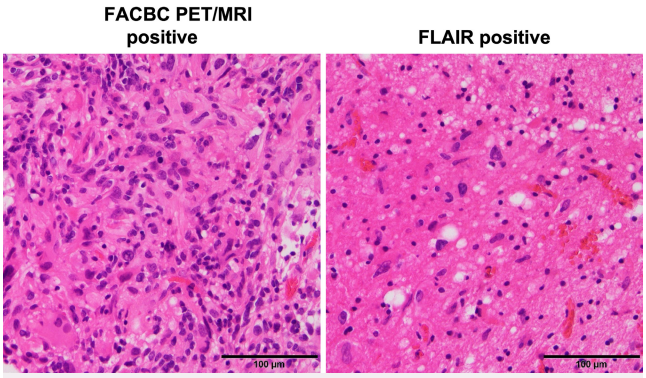

FIG. 3. Representative histopathological images stained with H&E. FACBC PET/MRI+ lesion (**left**) shows densely proliferating tumor cells with irregularly enlarged nuclei, ranging from short spindle-shaped to epithelioid forms, in a solid and infiltrative pattern. More than 10 mitotic figures were observed in the small sample, although there was no evidence of necrosis, microvascular proliferation, eosinophilic granular bodies, or Rosenthal fibers. The FLAIR+ lesion (**right**) shows tumor cells with similarly irregularly enlarged nuclei and cytoplasmic processes, but these cells were proliferating more sparsely.

Following surgery, concomitant treatment with temozolomide and radiotherapy was initiated, with the patient receiving 60 Gy over 30 fractions. She tolerated the adjuvant therapy well, with no reported adverse effects. MRI performed 40 days after the biopsy, as part of the interim evaluation during temozolomide maintenance therapy, revealed a newly emerged enhancing lesion. This lesion was located exactly where a high-uptake area had been detected on the preoperative FACBC PET/MRI scan, although no enhancement or CBV increase had been observed at that site prior to surgery (Fig. 5).

Informed Consent

The necessary informed consent was obtained in this study.

Discussion

Observations

In this report, we present the case of a patient with an IDH-wildtype GBM in which preoperative FACBC PET/MRI successfully identified a denser and more malignant tumor region, allowing for accurate histological and molecular characterization. This approach helped avoid underdiagnosis, enabling the selection of the most appropriate treatment strategy. To our knowledge, this is the first study to use FACBC PET/MRI to guide biopsy targeting and differentiate FACBC PET/MRI and FLAIR lesions in a primary GBM case.

Stereotactic biopsy is typically recommended for the histopathological diagnosis of intracerebral lesions, particularly in cases in which tumors are in eloquent brain areas, are deep-seated, diffusely infiltrating, or multifocally distributed. While the minimally invasive nature of stereotactic needle biopsy is a key advantage, its primary limitation is the small sample size, which can lead to diagnostic challenges.

The underdiagnosis of gliomas from stereotactic needle biopsy specimens has been a well-documented issue.[12–15] Studies have

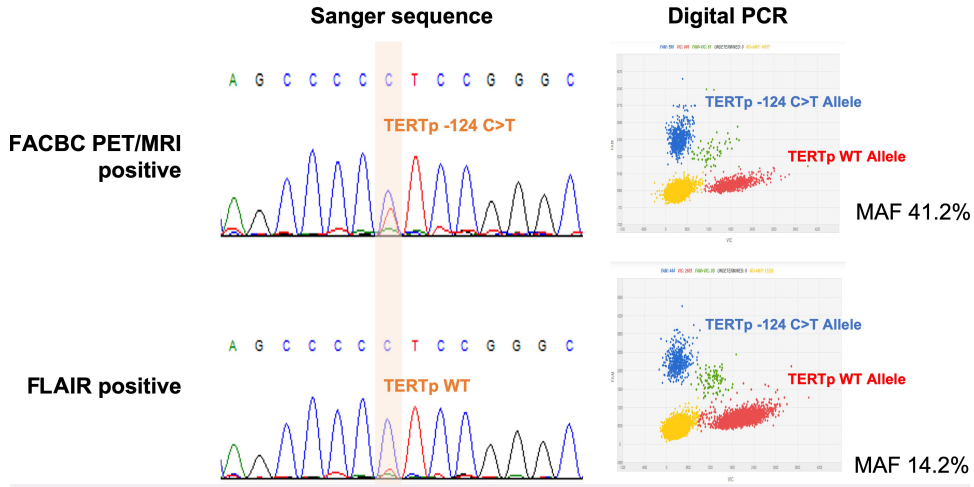

FIG. 4. Molecular analysis of FACBC PET/MRI+ (**upper**) and FLAIR+ (**lower**) lesions. Sanger sequencing (**left**) revealed that the FACBC PET/MRI+ lesion harbors a TERT promoter ($TERT_p$) –124 C>T mutation but the FLAIR+ lesion does not. Digital PCR (**right**) confirms the TERT promoter mutation in both samples, with a low MAF of 14.2% in the FLAIR+ lesion versus a MAF of 41.2% in the FACBC PET/MRI+ lesion. WT = wildtype.

reported a concordance rate of 51%–79% between histopathological diagnoses from biopsy and open resection specimens.[14,16–18] GBM's spatial heterogeneity increases the risk of underdiagnosis when biopsy samples are taken from less malignant regions. For example, one study noted initial misdiagnoses of anaplastic astrocytoma, low-grade astrocytoma, or gliosis based on the initial biopsy, with the correct diagnosis of GBM being made through resected tissue analysis within 60 days.[14] Another study identified diagnostic discrepancies in 12 patients, with 4 cases of GBM initially underdiagnosed as anaplastic astrocytoma or malignant glioma.[18] Given the critical importance of early diagnosis and treatment for GBM prognosis,[19] such diagnostic delays can worsen outcomes. Advanced imaging modalities like FACBC PET/MRI are therefore essential in accurately determining the optimal biopsy targets and improving diagnostic accuracy.

FACBC is a PET tracer developed for diagnosing malignant tumors. It is a tumor-avid amino acid, 1-amino-3-fluorocyclobutane-1-carboxylic acid, labeled with ^{18}F for nuclear imaging, first developed by a research team at Emory University in 1999.[7] FACBC shows high accumulation in glioma tissue while maintaining a low background in normal brain tissue.[7] A multicenter phase 3 trial demonstrated that the positive predictive value of FACBC PET/MRI in gadolinium-negative regions was 88.0%.[20] Recently, Henderson and colleagues reported that FACBC PET/MRI was useful in distinguishing recurrent GBM from treatment effects,[21] showing that biopsies guided by FACBC PET/MRI

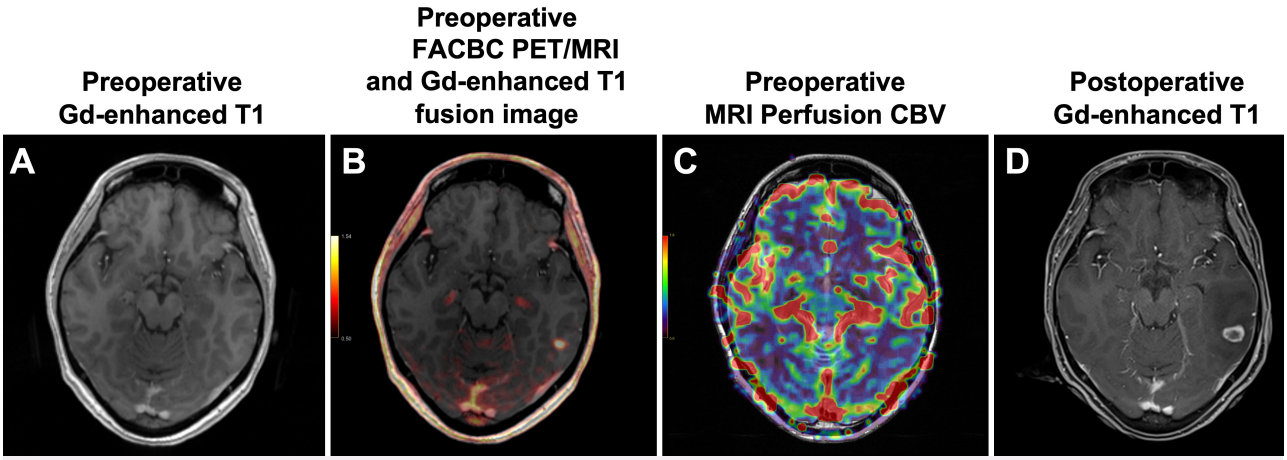

FIG. 5. The preoperative Gd-enhanced T1-weighted image (**A**) reveals no contrast-enhanced lesion, whereas the FACBC PET/MRI fusion image (**B**) demonstrates a high-uptake lesion in the left temporal lobe. The preoperative MRI perfusion image (**C**) shows no increase in CBV within the PET+ lesion. Postoperative Gd-enhanced T1-weighted image (**D**) exhibiting a newly emerged enhancing lesion located where the high-uptake area has been detected on preoperative FACBC PET/MRI.

successfully targeted high tumor content. Their findings are consistent with ours, further supporting that FACBC PET/MRI is more sensitive than contrast-enhanced MRI.

However, the clinical impact of FACBC PET/MRI remains unproven. Further research is essential to determine whether FACBC PET/MRI contributes to longer survival by enabling more accurate diagnoses. Our case report should be considered a preliminary feasibility study. A large prospective study will help clarify the diagnostic value of FACBC PET/MRI, particularly in the context of GBM diagnosis via biopsy.

Lessons

FACBC PET/MRI proved useful in identifying the optimal biopsy target region, helping to avoid underdiagnosis in patients with GBM. This imaging modality demonstrated high sensitivity in detecting tumor lesions with high cell density. Further prospective research is needed to validate its prognostic impact on patients with GBM, particularly in improving diagnostic accuracy and guiding treatment decisions.

References

1. Louis DN, Perry A, Wesseling P, et al. The 2021 WHO Classification of Tumors of the Central Nervous System: a summary. *Neuro Oncol*. 2021;23(8):1231-1251.
2. Sottoriva A, Spiteri I, Piccirillo SG, et al. Intratumor heterogeneity in human glioblastoma reflects cancer evolutionary dynamics. *Proc Natl Acad Sci U S A*. 2013;110(10):4009-4014.
3. Aubry M, de Tayrac M, Etcheverry A, et al. From the core to beyond the margin: a genomic picture of glioblastoma intratumor heterogeneity. *Oncotarget*. 2015;6(14):12094-12109.
4. Okudaira H, Shikano N, Nishii R, et al. Putative transport mechanism and intracellular fate of trans-1-amino-3-18F-fluorocyclobutanecarboxylic acid in human prostate cancer. *J Nucl Med*. 2011;52(5):822-829.
5. Kaira K, Oriuchi N, Imai H, et al. l-type amino acid transporter 1 and CD98 expression in primary and metastatic sites of human neoplasms. *Cancer Sci*. 2008;99(12):2380-2386.
6. Oka S, Okudaira H, Ono M, et al. Differences in transport mechanisms of trans-1-amino-3-[18F]fluorocyclobutanecarboxylic acid in inflammation, prostate cancer, and glioma cells: comparison with L-[methyl-11C]methionine and 2-deoxy-2-[18F]fluoro-D-glucose. *Mol Imaging Biol*. 2014;16(3):322-329.
7. Shoup TM, Olson J, Hoffman JM, et al. Synthesis and evaluation of [18F]1-amino-3-fluorocyclobutane-1-carboxylic acid to image brain tumors. *J Nucl Med*. 1999;40(2):331-338.
8. Tsuyuguchi N, Terakawa Y, Uda T, Nakajo K, Kanemura Y. Diagnosis of brain tumors using amino acid transport PET imaging with ^{18}F-fluciclovine: A comparative study with L-methyl-^{11}C-methionine PET imaging. *Asia Ocean J Nucl Med Biol*. 2017;5(2):85-94.
9. Wakabayashi T, Iuchi T, Tsuyuguchi N, et al. Diagnostic performance and safety of positron emission tomography using 18F-Fluciclovine in patients with clinically suspected high- or low-grade gliomas: a multicenter Phase IIb trial. *Asia Ocean J Nucl Med Biol*. 2017;5(1):10-21.
10. Hadjipanayis CG, Widhalm G, Stummer W. What is the surgical benefit of utilizing 5-aminolevulinic acid for fluorescence-guided surgery of malignant gliomas? *Neurosurgery*. 2015;77(5):663-673.
11. Tsiatis AC, Norris-Kirby A, Rich RG, et al. Comparison of Sanger sequencing, pyrosequencing, and melting curve analysis for the detection of KRAS mutations: diagnostic and clinical implications. *J Mol Diagn*.2010;12(4):425-432.
12. Chandrasoma PT, Smith MM, Apuzzo ML. Stereotactic biopsy in the diagnosis of brain masses: comparison of results of biopsy and resected surgical specimen. *Neurosurgery*. 1989;24(2):160-165.
13. Glantz MJ, Burger PC, Herndon JE, 2nd, et al. Influence of the type of surgery on the histologic diagnosis in patients with anaplastic gliomas. *Neurology*. 1991;41(11):1741-1744.
14. Jackson RJ, Fuller GN, Abi-Said D, et al. Limitations of stereotactic biopsy in the initial management of gliomas. *Neuro Oncol*. 2001;3(3):193-200.
15. Woodworth G, McGirt MJ, Samdani A, Garonzik I, Olivi A, Weingart JD. Accuracy of frameless and frame-based image-guided stereotactic brain biopsy in the diagnosis of glioma: comparison of biopsy and open resection specimen. *Neurol Res*. 2005;27(4):358-362.
16. Bruner JM, Inouye L, Fuller GN, Langford LA. Diagnostic discrepancies and their clinical impact in a neuropathology referral practice. *Cancer*. 1997;79(4):796-803.
17. McGirt MJ, Villavicencio AT, Bulsara KR, Friedman AH. MRI-guided stereotactic biopsy in the diagnosis of glioma: comparison of biopsy and surgical resection specimen. *Surg Neurol*. 2003;59(4):277-281.
18. Reithmeier T, Lopez WO, Doostkam S, et al. Intraindividual comparison of histopathological diagnosis obtained by stereotactic serial biopsy to open surgical resection specimen in patients with intracranial tumours. *Clin Neurol Neurosurg*. 2013;115(10):1955-1960.
19. Kawauchi D, Ohno M, Miyakita Y, et al. Early diagnosis and surgical intervention within 3 weeks from symptom onset are associated with prolonged survival of patients with glioblastoma. *Neurosurgery*. 2022;91(5):741-748.
20. Wakabayashi T, Hirose Y, Miyake K, et al. Determining the extent of tumor resection at surgical planning with ^{18}F-fluciclovine PET/CT in patients with suspected glioma: multicenter phase III trials. *Ann Nucl Med*. 2021;35(12):1279-1292.
21. Henderson F Jr, Brem S, O'Rourke DM, et al. ^{18}F-Fluciclovine PET to distinguish treatment-related effects from disease progression in recurrent glioblastoma: PET fusion with MRI guides neurosurgical sampling. *Neurooncol Pract*. 2020;7(2):152-157.

Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Narita, Kawauchi, Ohno. Acquisition of data: Kawauchi, Ito, Yoshida, Yanagisawa, Ohmura, Aoki, Kawanishi, Sakuramachi, Igaki. Analysis and interpretation of data: Narita, Kawauchi, Sugino, Kubo. Drafting the article: Narita, Kawauchi, Ito. Critically revising the article: Narita, Kawauchi, Ohno, Ito, Yoshida, Igaki. Reviewed submitted version of manuscript: Narita, Kawauchi, Ohno, Sugino, Ito, Yoshida, Igaki. Approved the final version of the manuscript on behalf of all authors: Narita. Statistical analysis: Kawauchi. Administrative/technical/material support: Ito, Fuse, Honda-Kitahara. Study supervision: Narita.

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