PET

High resolution PET Imaging of the Brain Using BresTome

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Abstract

We present BresTome with a focus on clinical brain cases and outline its usefulness. FDG-PET demonstrated clear delineation of gyri and distinct contrast between gray and white matter, allowing depiction of minute structures. In MCI, clear cortical hypometabolism of the cerebral cortex was observed. In amyloid (Flutemetamol) PET, normal cases showed non specific accumulation in cerebral white matter, whereas amyloid positive cases demonstrated clear accumulation in the gray matter. Tau (MK 6240) PET images did not show intracerebral off target binding in normal cases. In tau accumulation positive cases, accumulation was observed from the entorhinal cortex and hippocampus to the cerebral cortex. Amino acid (fluciclovine) PET images showed clear accumulation in parts of gliomas. BresTome is expected to contribute substantially to the evaluation of brain PET ligands and to the development of therapeutic agents and treatment methods.

1. Introduction

According to a 2024 nationwide survey of PET examinations and facilities conducted by the Japan Isotope Association[1)], there are more than 300 PET facilities across Japan. PET/CT systems accounted for the largest share with 399 units (87.9%); among these, semiconductor detector systems numbered 86 units, breast-specific PET systems numbered 11 units (4.0%), dedicated head PET systems numbered 2 units (0.4%), and combined head/breast PET systems numbered 3 units (0.7%). Additionally, target indications were overwhelmingly malignant tumors (97.6%), whereas epilepsy accounted for 0.3% and dementia 2.3%, indicating that brain examinations are relatively few. Given that most facilities perform oncologic studies (97.6%), it is understandable that PET/CT systems whose primary purpose is whole-body tumor PET imaging and CT imaging using 2-[^{18}F]fluoro-2-deoxy-D-glucose (FDG) predominate.

As an imaging biomarker for Alzheimer's disease, amyloid (A), tau (T), and neurodegeneration (N) form the ATN classification. In Japan, cerebral metabolic assessment by FDG is not covered by health insurance; therefore, unlike some foreign countries, N evaluation is frequently performed with cerebral blood flow SPECT. Historically, however, PET brain imaging has been fundamental: NIH's Sokoloff and colleagues developed the 2-[14C] deoxyglucose (2DG) autoradiography method to measure glucose metabolism, on which subsequent development of FDG by Ido and others was based. The first organ imaged by PET, in 1976 by Kuhl et al., was the brain; thereafter, FDG has been used extensively for studies of brain function, brain development, cerebrovascular disease, and more. Domestic development of PET in Japan has also been pursued early on by organizations such as the Akita Prefectural Cerebrovascular Research Center (at that time) with Shimadzu Corporation and the National Institute of Radiological Sciences (at that time) with Hitachi.

Domestic and historical context continued Wagner et al. reported imaging of dopamine D2 receptors using 3-N-[^{11}C] methylspiperone (NMSP) in 1983, after which many imaging agents for brain receptors and transporters have been researched and developed. Recently, with the approval and clinical application of drugs for Alzheimer's disease, the need for early diagnosis, treatment indication assessment, and evaluation of therapeutic efficacy has increased the clinical demand for amyloid PET, thereby renewing attention to brain PET examinations. ^{18}F-labeled agents are available via delivery; FDG is reimbursed, but because physiological accumulation in normal brain tissue is high, assessment of tumor extent in the brain can sometimes be difficult. Historically, ^{11}C-methionine showing low physiological brain uptake has been used for brain tumor imaging, but its short half-life (≈20 minutes) restricts use to cyclotron-equipped facilities. Recently, the amino acid agent ^{18}F-fluciclovine has been approved for brain tumor diagnosis and is available by delivery.

Against this background, high spatial resolution head semiconductor PET systems capable of detailed depiction of brain structures have been developed and marketed domestically and internationally (e.g.,

in Japan and Korea)[2,3]. Shimadzu's high-resolution breast-specific PET device Elmammo has already been used clinically at several domestic centers. BresTome was newly developed as a high-resolution head/breast PET system that adapts that technology to detailed head examinations[4,5]. In institutions such as ours, where clinical departments request oncologic studies and cancer screening as well as referrals from neurology and neurosurgery for head examinations, having a dedicated instrument allows brain examinations to be performed in parallel with PET/CT. This is useful for improving throughput and enables efficient examinations; we anticipate increasing demand.

For preoperative local diagnosis of breast cancer and assessment of accessory lesions, usefulness is already established[6]. Compared with whole-body PET/CT, intra-tumoral heterogeneity is depicted in greater detail. We have also experienced cases in which focal uptake within the contralateral breast undetected on contrast CT and whole-body PET/CT correlated with an enhancing focus on contrast breast MRI **(Fig. 1)**.

In this article, we present primarily the brain clinical cases imaged at our institution and outline the utility of BresTome.

2. BresTome FDG-PET images

As an imaging biomarker within the ATN classification for Alzheimer's disease, FDG-based assessment of cerebral glucose metabolism is important, together with brain MRI, for diagnosing neurodegeneration (N) and differentiating other neurodegenerative disorders. In Japan, because FDG-based diagnosis of cerebral glucose metabolism is not covered by health insurance, cerebral blood flow SPECT is commonly used as an alternative. If CT-based attenuation and absorption correction are properly performed with the triple head-detector SPECT systems developed domestically, images comparable to FDG-PET can, in principle, be obtained. However, according to the national nuclear medicine practice survey[7], dual head-detector SPECT systems represent 83.8% of gamma cameras in Japan, of which only 42.4% are SPECT/CT; thus, sufficient image quality for early diagnosis cannot be guaranteed in many instances. If therapeutics for dementia become widespread, the differential diagnosis of early degenerative dementias will become increasingly important. While insurance coverage remains an issue and FDG brain metabolism imaging will primarily be research-oriented for the time being, FDG-based assessment of cerebral metabolism is expected to grow in importance.

BresTome images **(Fig. 2-1)** clearly depict cortical gyri, with a marked contrast between gray and white matter. The heads of the caudate nucleus and putamen, the thalamus, internal capsule (posterior limb), and other structures are distinctly separable **(Fig. 2-2)**. In the brainstem, the substantia nigra, red nucleus, and superior/inferior colliculi are

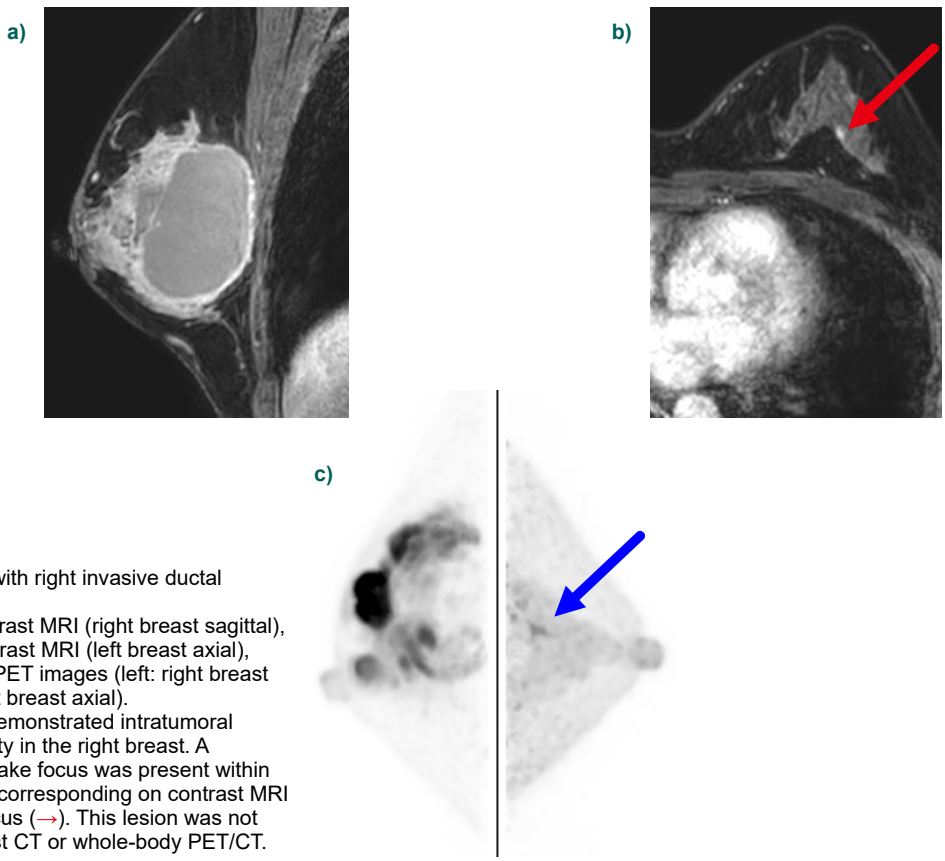

Fig. 1 Female in her 40s with right invasive ductal carcinoma
a) Early phase contrast MRI (right breast sagittal),
b) Early phase contrast MRI (left breast axial),
c) FDG BresTome PET images (left: right breast sagittal, right: left breast axial).
BresTome clearly demonstrated intratumoral uptake heterogeneity in the right breast. A polygonal small uptake focus was present within the left breast (→), corresponding on contrast MRI to an enhancing focus (→). This lesion was not detected on contrast CT or whole-body PET/CT.

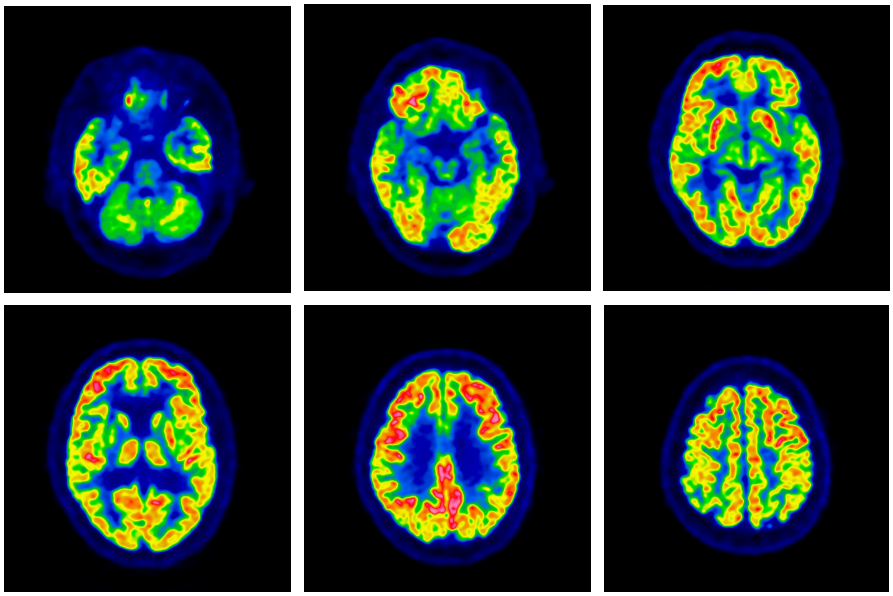

Fig. 2-1 Normal subject. BresTome FDG-PET axial image from cerebellum to thalamus–basal ganglia level. Cortical gyri and the contrast between gray and white matter are clearly depicted.

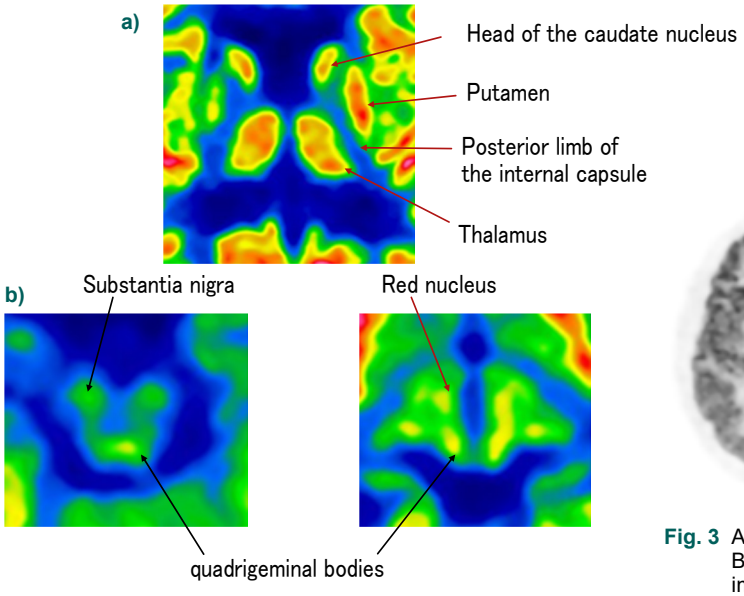

Fig. 2-2 Normal subject. BresTome FDG-PET enlarged axial images: **a)** thalamus–basal ganglia level, **b)** midbrain level. Minute structures are visualized.
a) Caudate head, putamen, posterior limb of internal capsule, thalamus
b) Substantia nigra, red nucleus, quadrigeminal bodies

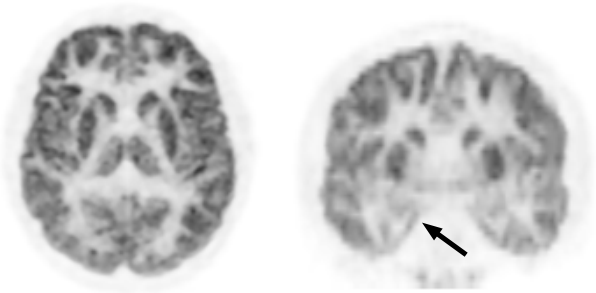

Fig. 3 Adolescent male (early teens), epilepsy workup. BresTome FDG-PET axial (left) and coronal (right) images. Coronal image clearly depicts bilateral hippocampi and parahippocampal gyri (→). No epileptic focus was detected.

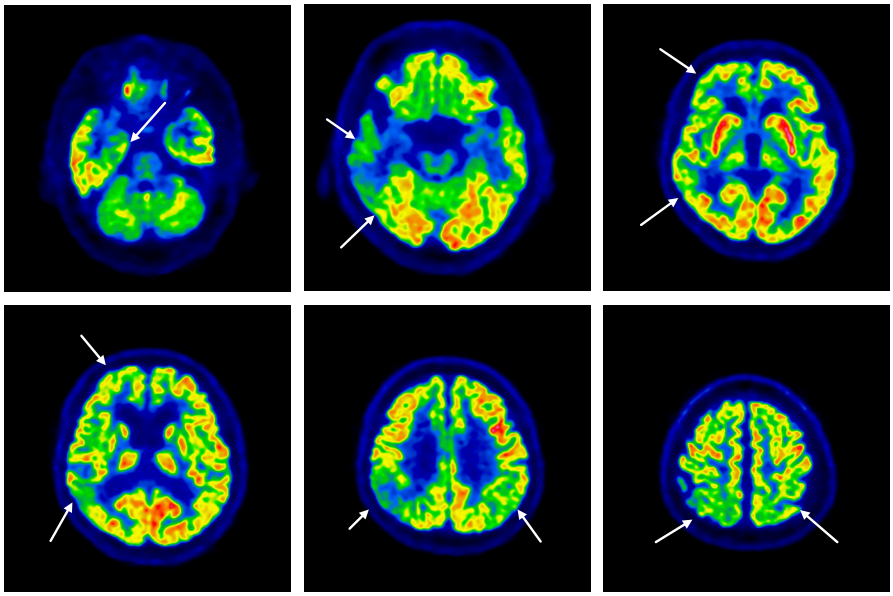

Fig. 4 MCI case. BresTome FDG-PET axial image from cerebellum to thalamus–basal ganglia level. Right-dominant cortical hypometabolism is clearly depicted (→).

also separable **(Fig. 2-2)**. In an epilepsy workup performed in an adolescent, coronal images clearly depicted the medial inferior temporal lobe hippocampus and parahippocampal gyrus **(Fig. 3)**. In an MCI case, decreased cortical uptake in the right inferior temporal to right frontal/lateral temporal and bilateral parietal lobes was clearly depicted **(Fig. 4)**.

3. BresTome amyloid (^{18}F-Flutemetamol) PET images

In Japan, novel Alzheimer's disease treatments such as lecanemab and donanemab have been approved in recent years. Determination of treatment indication and, in the case of donanemab, efficacy assessment require evaluation of amyloid-β accumulation. Amyloid PET is less invasive than cerebrospinal fluid testing and is expected to see wider clinical use.

BresTome amyloid images show, in normal subjects **(Fig. 5)**, pronounced non-specific uptake in cerebral white matter, with negative uptake in gray matter. An amyloid-positive case (the same MCI case imaged with FDG; **Fig. 6**) demonstrated clear gray matter accumulation in the frontal, temporal, parietal lobes, striatum, and posterior cingulate. Ishii et al.[4,5] reported cases in which gray matter uptake that was ambiguous on whole-body PET could be judged negative on high-resolution BresTome amyloid (Flutemetamol) PET images.

4. BresTome tau (^{18}F-MK-6240) PET images

Neurofibrillary tangles (NFTs) resulting from hyperphosphorylation of tau (T) are, along with amyloid (A) and neurodegeneration (N), imaging biomarkers within the ATN classification for Alzheimer's disease. The ^{18}F-MK-6240 agent used

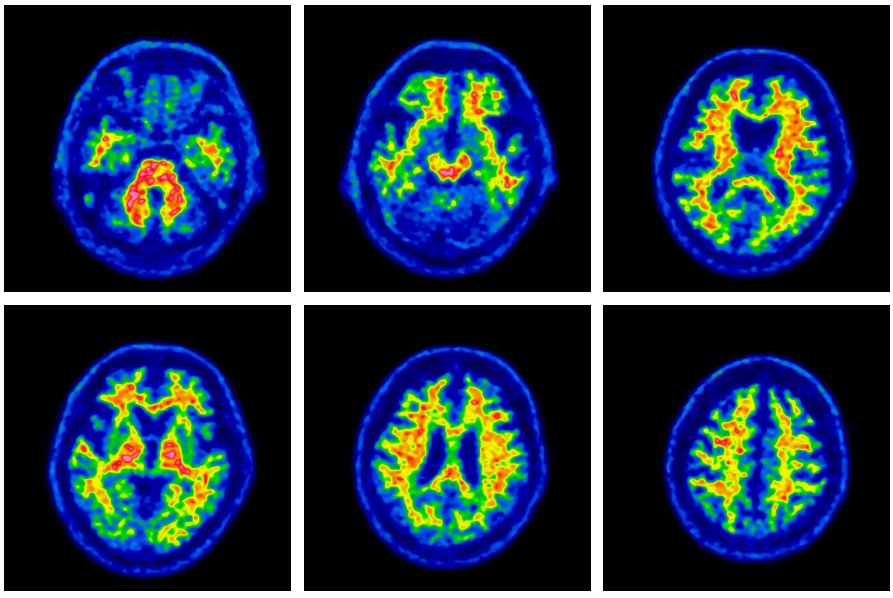

Fig. 5 Normal subject. BresTome amyloid (Flutemetamol) PET axial image from cerebellum to thalamus–basal ganglia level. Marked accumulation in cerebral white matter is seen; gray matter uptake is negative.

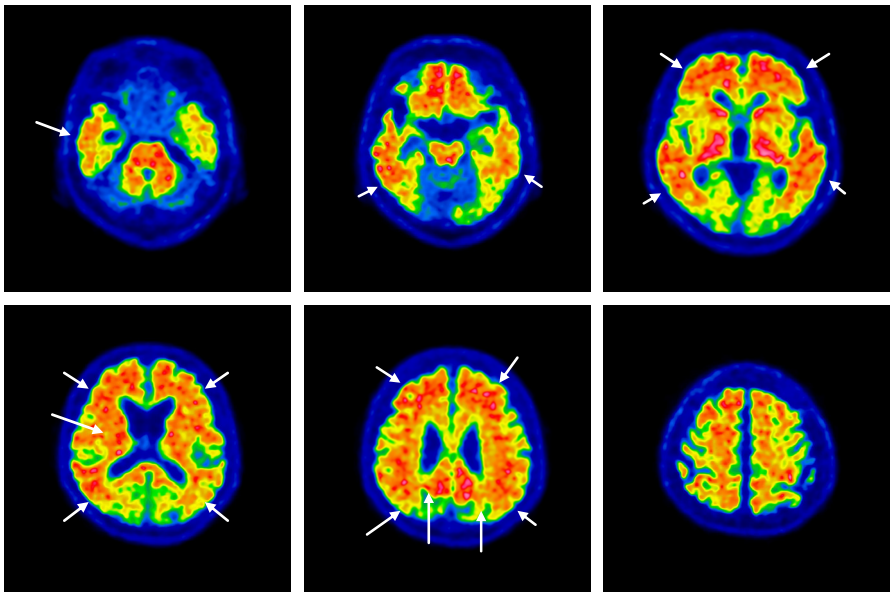

Fig. 6 MCI case. BresTome amyloid (Flutemetamol) PET axial image from cerebellum to thalamus–basal ganglia level. Clear gray matter accumulation is noted in the cerebral cortex, striatum, and posterior cingulate (→).

in our institution is currently an unapproved drug. Nonetheless, because tau spreads with Alzheimer's disease progression, the ability of modern tau PET tracers to detect early lesions starting from the entorhinal cortex in the medial temporal lobe (Braak stage I) and then the hippocampus (stage II) could provide a crucial marker for treatment strategy.

BresTome images in normal subjects **(Fig. 7)** revealed faint off-target binding in the ethmoid sinuses and cranial bones, but no intracerebral accumulation in basal ganglia or choroid plexus. In a tau accumulation-positive case (the same MCI case imaged with FDG and amyloid; **Fig. 8**), right-dominant accumulation was observed in the medial temporal lobe entorhinal cortex and hippocampus, extending from the inferior to the middle temporal and parietal cortices. Compared with normal subjects, these findings are considered to represent specific binding to tau.

5. BresTome amino acid (^{18}F-fluciclovine) PET images

^{18}F-fluciclovine was included in the National Health Insurance coverage in 2024 for visualization of tumors in patients with suspected primary malignant glioma[9]. This tracer is taken up into cells via amino acid transporters; because tumor cells generally exhibit enhanced amino acid metabolism relative to normal cells, increased accumulation is visualized.

Referring to standard protocols for brain tumor PET imaging[10], our institution conducted basic studies with BresTome using a BT phantom. Detection of a 5-mm hot sphere required more than 20 minutes of acquisition; however, a 10 minute acquisition enabled detection of a 7.5 mm hot sphere **(Fig. 9)**. Fusion images of BresTome and head MRI **(Fig. 10)** in a glioma case showed that fluciclovine PET accumulation corresponded to parts of the high-

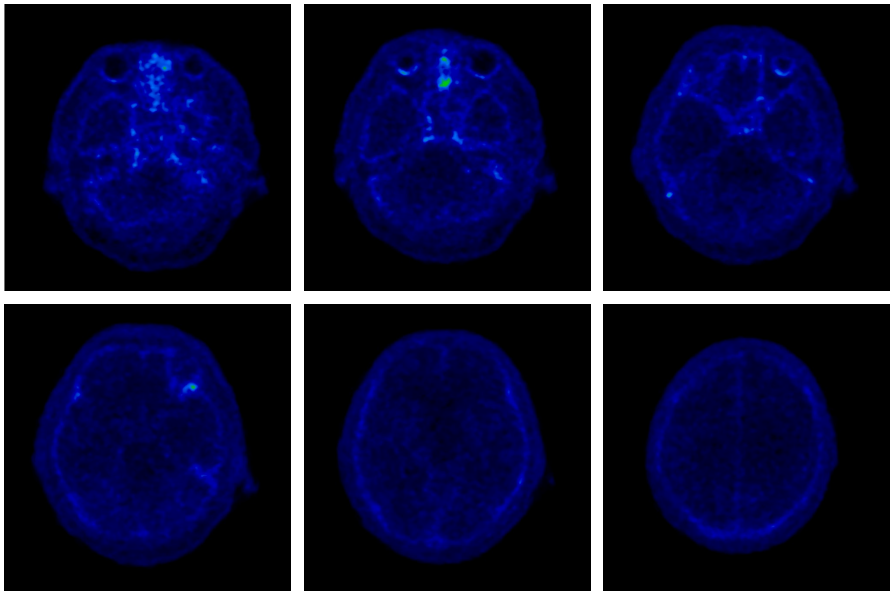

Fig. 7 Normal subject. BresTome tau (MK-6240) PET. (Off-target binding was not observed in the basal ganglia, choroid plexus, or other areas of the brain.
* MK-6240 is an unapproved drug.)

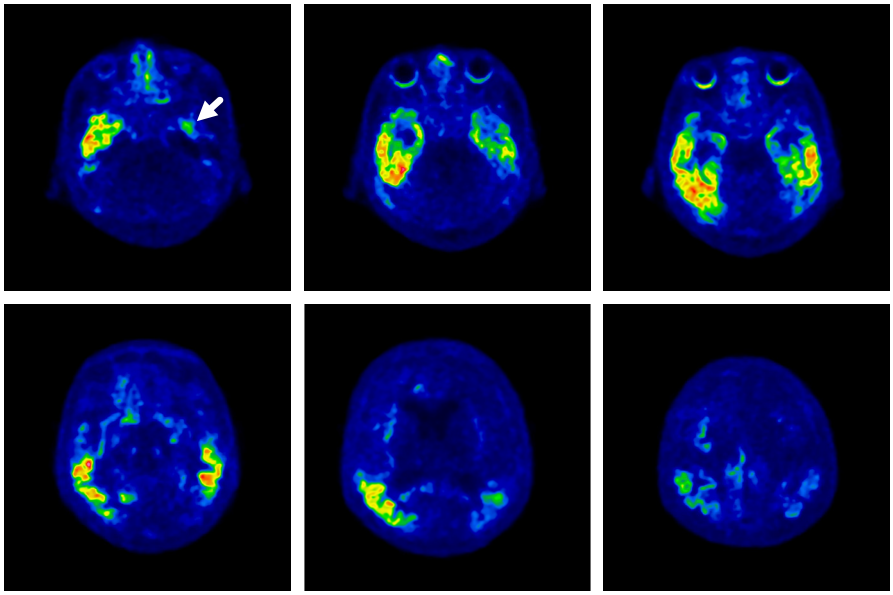

Fig. 8 MCI case. BresTome tau (MK-6240) PET axial image from cerebellum to thalamus basal ganglia level. Right-dominant accumulation is observed in the medial temporal entorhinal cortex (→) and hippocampus, extending to inferior–middle temporal and parietal lobes.
*MK-6240 is an unapproved drug.

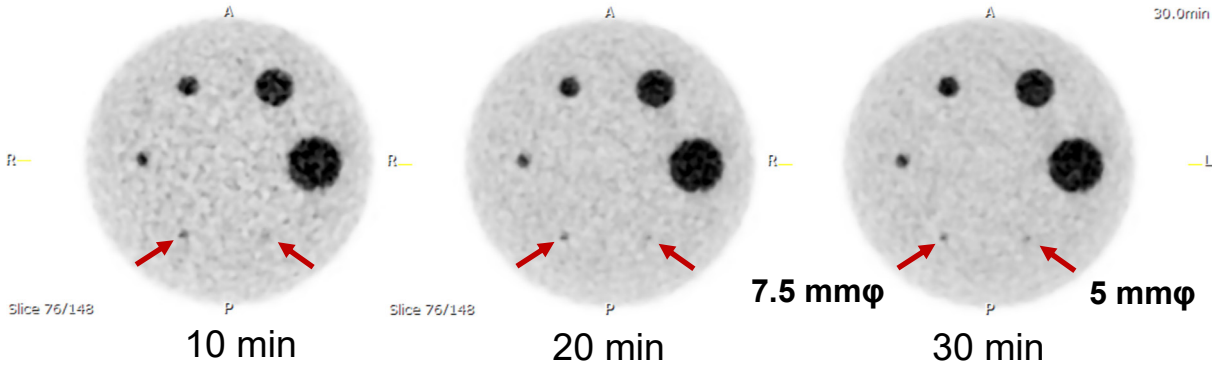

Fig. 9 Basic phantom study with BresTome and BT phantom (Target-to-background ratio (TBR): 5:1, β: 70, NLM intensity: 1.0). While detection of a 5-mm hot sphere required more than 20 minutes of acquisition, a 10-minute acquisition allowed clear depiction of a 7.5-mm hot sphere.

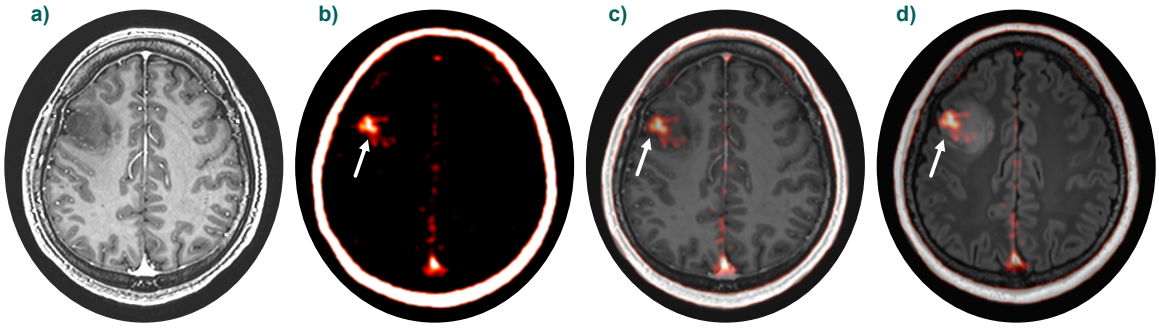

Fig. 10 Glioma (oligodendroglioma, IDH-mutant and 1p/19q-codeleted, WHO grade 2) case:
a) Gadolinium (Gd)-enhanced T1-weighted axial image, **b)** fusion of BresTome ^{18}F-fluciclovine PET and CT (axial), **c)** fusion of fluciclovine PET and Gd-enhanced T1-weighted axial image, **d)** fusion of fluciclovine PET and FLAIR (axial). On fused images with head MRI, fluciclovine demonstrated clear accumulation in portions of the tumor that were Gd-enhancement negative (→).

signal region on FLAIR. Even in gadolinium-enhancing cases, PET-positive regions were often more extensive than the enhancing region, allowing detection of tumor-active portions that were difficult to identify on contrast MRI alone. This information may be useful for tumor biopsy targeting, surgical resection extent, and determination of stereotactic radiotherapy fields.

6. Conclusion

We have presented high-resolution PET images of the brain obtained with BresTome, focusing on clinical cases imaged at our institution, and discussed their utility. This device is expected to make a substantial contribution to the future evaluation of new brain PET ligands and to the development of therapeutic agents and treatment methods.

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