Diagnostic Value of 18F-FACBC PET/MRI in Brain Metastases

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Purpose: The study aims to evaluate whether combined 18F-FACBC PET/MRI could provide additional diagnostic information compared with MRI alone in brain metastases.

Patients and Methods: Eighteen patients with newly diagnosed or suspected recurrence of brain metastases received dynamic 18F-FACBC PET/MRI. Lesion detection was evaluated on PET and MRI scans in 2 groups depending on prior stereotactic radiosurgery (SRS) group or not (no-SRS group). SUVs, time-activity curves, and volumetric analyses of the lesions were performed.

Results: In the no-SRS group, 29/29 brain lesions were defined as “MRI positive.” With PET, 19/29 lesions were detected and had high tumor-to-background ratios (TBRs) (Dmax MR, ≥7 mm; SUVmax, 1.2–8.4; TBR, 3.9–25.9), whereas 10/29 lesions were undetected (Dmax MR, ≤8 mm; SUVmax, 0.3–1.2; TBR, 1.0–2.7). In the SRS group, 4/6 lesions were defined as “MRI positive,” whereas 2/6 lesions were defined as “MRI negative” indicative of radiation necrosis. All 6 lesions were detected with PET (Dmax MR, ≥15 mm; SUVmax, 1.4–4.2; TBR, 3.6–12.6). PET volumes correlated and were comparable in size with contrast-enhanced MRI volumes but were only partially congruent (mean DSC, 0.66). All time-activity curves had an early peak, followed by a plateau or a decreasing slope.

Conclusions: 18F-FACBC PET demonstrated uptake in brain metastases from cancer of different origins (lung, gastrointestinal tract, breast, thyroid, and malignant melanoma). However, 18F-FACBC PET/MRI did not improve detection of brain metastases compared with MRI but might detect tumor tissue beyond contrast enhancement on MRI. 18F-FACBC PET should be further evaluated in recurrent brain metastases.

Key Words: brain metastases, 18F-FACBC, PET, contrast enhancement, MRI, detection

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It is estimated that 10% to 40% of patients with cancer will develop 1 or more brain metastases. These originate most frequently from lung cancer, followed by breast cancer and malignant melanoma. Patients with brain metastases have a poor prognosis with a median survival of 6 months and a 2-year survival of 8.1%. Stereotactic radiosurgery (SRS) is frequently the preferred treatment for patients with brain metastases, but whole-brain radiation therapy, neurosurgical resection, and/or systemic treatments such as chemotherapy, immunotherapies, and targeted therapy can also be considered. Late diagnosis may limit treatment options, and early identification and accurate localization of brain metastases are therefore important for treatment planning and preventing further deterioration of the patient. Precise tumor delineation and tools to differentiate brain metastases from treatment-related changes, such as radiation necrosis, are also of high importance.

Contrast-enhanced MRI (ce-MRI) is currently the recommended imaging modality for the detection of brain metastases. MRI provides high-resolution anatomical images with excellent soft tissue contrast, and contrast agents increase visibility of pathology when the blood-brain barrier (BBB) is disrupted. Brain metastases are considered to be well delineated on ce-MRI, and the sensitivity for detection is high also for small metastases. However, contrast enhancement is a marker for BBB disruption, which may be caused by radiotherapy, infection, inflammation, ischemia, and other affiliations. Contrast enhancement is therefore not specific for malignancy, and ce-MRI has limitations for instance in separating recurrence of brain metastases from treatment-related changes, a challenge regularly occurring in clinical practice. The accuracy may be improved with perfusion-weighted MRI, but the literature is still limited, and alternative tools for diagnosing recurrent brain metastases after treatment are warranted.

Amino acid (AA) PET may add complementary information to MRI in the management of patients with brain metastases. Brain malignancies accumulate AAs through overexpression of AA transporter systems, which is a result of alterations in tumor vasculature and proliferation. Amino acid PET tracers do not accumulate as much in normal brain parenchyma as the most commonly used PET tracer, the glucose analog 18F-FDG. This results in improved tumor-to-normal brain contrast for AA tracers over 18F-FDG. The transport of AAs across the BBB is facilitated by specific AA transporter systems, which is a result of alterations in tumor vasculature and proliferation.
that the literature is still limited.\textsuperscript{11} 18F-FET has shown to differentiate recurrence of brain metastases from radiation necrosis with high accuracy, especially when supplemented with dynamic PET acquisitions.\textsuperscript{17–19}

The artificial AA anti-1-amino-3-\(^{18}\)F-fluorocyclobutane-1-carboxylic acid (\(^{18}\)F-FACBC),\textsuperscript{20} also known as fluciclovine (\(^{18}\)F) or Axumin (Blue Earth Diagnostics Ltd, United Kingdom), was initially developed for the assessment of brain tumors but is most commonly used for prostate cancer.\textsuperscript{21} Recent studies have demonstrated increased \(^{18}\)F-FACBC uptake in gliomas compared with normal brain parenchyma, especially for high-grade gliomas.\textsuperscript{22–28} Several glioma studies have reported \(^{18}\)F-FACBC uptake in areas without contrast enhancement, in addition to generally larger tumor volumes with \(^{18}\)F-FACBC than ce-MRI.\textsuperscript{22,24,27,29} In addition, in studies exploring glioma, \(^{18}\)F-FACBC provides greater visual contrast than \(^{11}\)C-MET due to lower uptake in healthy brain tissue.\textsuperscript{25,26,29} This high contrast has likely also allowed for the detection of small satellite gliomas not visualized with MRI.\textsuperscript{25}

\(^{18}\)F-FACBC PET has only been evaluated in a limited number of patients with brain metastases.\textsuperscript{30,31} The results are promising with relatively high tumor-to-background ratios (TBRs) compared with \(^{18}\)F-FET and \(^{11}\)C-MET. This may increase the possibility to detect small brain metastases. \(^{18}\)F-FACBC PET has also shown potential to differentiate recurrence from radiation necrosis.\textsuperscript{30} The potential of \(^{18}\)F-FACBC in the management of brain metastases should therefore be further explored. The aims of this study were to assess the diagnostic value of static and dynamic \(^{18}\)F-FACBC PET in patients with brain metastases and to compare tumor volumes between \(^{18}\)F-FACBC PET and ce-MRI.

**PATIENTS AND METHODS**

**Subjects**

Between January 2020 and July 2021, 18 patients (7 female) were recruited to a multicenter study at St. Olavs Hospital, Trondheim University Hospital, and the University Hospital of Northern Norway for simultaneous brain \(^{18}\)F-FACBC PET/MRI examinations. Patients were eligible for inclusion if they had a known or confirmed cancer and MRI findings consistent with a new metastatic brain lesion and/or suspected recurrence if previously treated with surgery or SRS in this location.

The average age of the subjects was 64.5 years (range, 51–77 years), and their primary cancers were lung (n = 9), gastrointestinal (GI) (n = 5), malignant melanoma (n = 2), breast (n = 1), and thyroid (n = 1) (Tables 1 and 2). The patients had a median graded tumor volume of 212 cm\(^3\) (range, 3–1795 cm\(^3\)). The patients had ongoing glucocorticosteroid treatment at the time of the examination. The study was approved by the Regional Ethics Committee (REC, reference number: 2018/2243). All patients gave written informed consent to participate in the study.

**PET/MRI**

The patients underwent a simultaneous brain PET/MRI examination (Siemens Biograph mMR, Erlangen, Germany) after at least 4 hours of fasting. \(^{18}\)F-FACBC (3.0 ± 0.2 MBq/kg; average activity, 234 ± 50 MBq) was manually injected at \(t = 0\) of the PET acquisition (list mode; 0–35 minutes post injection). Two patients (ID 10 and 11) had a shorter acquisition (30 minutes) due to delays and expiration of the tracer. MRI sequences acquired were ultrashort echo time (UTE) for PET attenuation correction, 3D fluid-attenuated inversion recovery, and contrast-enhanced 3D T1 magnetization-prepared rapid gradient echo. One patient (ID 12) was examined on a PET/CT system (Siemens Biograph Vision 600) due to technical problems with the PET/MRI system (only static acquisition 20–35 minutes post injection). This patient had a separate MRI examination later the same day.

**PET Reconstruction**

Static and dynamic PET image reconstructions were performed using iterative OSEM reconstruction (PET/MRI reconstruction: 5 iterations, 21 subsets, 344 image matrix, 4 mm Gaussian filter; PET/CT reconstruction: 8 iterations, 5 subsets, 440 image matrix, 4 mm Gaussian filter, TOF), point spread function modeling, and relative scatter correction. MR-based attenuation correction was performed with a deep learning–based method (DeepUTE) using the UTE MR sequence as input for making MR-based attenuation correction maps.\textsuperscript{33} Static PET reconstructions were generated from the last 15 minutes of the list mode data, whereas the dynamic reconstructions were performed with frames of 12 × 5 seconds, 6 × 10 seconds, 6 × 30 seconds, 5 × 60 seconds, and 5 × 300 seconds, based on recommendations for dynamic \(^{18}\)F-FET PET imaging of gliomas.\textsuperscript{16}

**Image Evaluation**

The PET and MR images were jointly investigated by an experienced nuclear medicine physician (years of experience: H.J., 5 years; T.V., 20 years) and an experienced neuroradiologist (years of experience: E.M.B., 7 years; J.A.T., 8 years). As both recurrence and radiation necrosis show contrast enhancement, the MRI interpretation differed depending on whether the lesions were treated with SRS before PET/MRI or not, and the lesions were divided in 2 groups. Lesions without previous SRS in the same location (no-SRS group) were categorized as “MRI positive” if they showed contrast enhancement and were not present on previous MRIs or if no previous MRIs were available, thus radiologically evident a metastasis. Contrast-enhancing lesions in operation cavities were also defined as “MRI positive.” Lesions with previous SRS in the same location (SRS group) were categorized as “MRI positive” if showing contrast enhancement and progressive enlargement according to the RANO criteria for brain metastasis\textsuperscript{14} (>20% enlargement in largest diameter) compared with previous MRI scans. On the contrary, if the lesions had been stable or decreased in size compared with previous MRIs and thus indicative of radiation necrosis, they were categorized as “MRI negative.” A follow-up status of the lesions in the SRS group was assessed based on follow-up MRIs after the PET/MRI, to serve as a surrogate marker for separating true recurrence from radiation necrosis in the lack of histopathological verification. PET findings with \(^{18}\)F-FACBC uptake distinctly higher than surrounding tissue were defined as detected on PET.

**Image Analysis**

Image analysis was performed with the software PMOD (version 4.203; PMOD Technologies LLC, Zürich, Switzerland). A volume of interest (VOI) was drawn on the static PET images to encompass the lesion of interest to extract the SUV\(_{\text{max}}\) of the lesion. For lesions not detected on PET, SUV\(_{\text{max}}\) was measured in the volume defined on ce-MRI. To measure reference tissue, a crescent-shaped area was defined on the normal brain adjacent to the lesion of interest.

**RESULTS**

PET/MRI images were analyzed jointly by an experienced radiologist and a neuroradiologist. The PET/MRI examination was interpreted as positive if PET uptake was detected (minimum SUV\(_{\text{max}}\) of 1.5). The SUV\(_{\text{max}}\) of the lesion was measured by drawing a VOI encompassing the lesion of interest. The SUV\(_{\text{max}}\) of the normal brain adjacent to the lesion was measured as a reference. The SUV\(_{\text{max}}\) of the lesion was compared with the SUV\(_{\text{max}}\) of the normal brain to determine whether the lesion was positive or negative.

**DISCUSSION**

PET/MRI is a powerful tool for the management of brain metastases. The advantages of PET/MRI include the ability to detect small lesions and to differentiate recurrence from radiation necrosis. PET/MRI is particularly useful in the assessment of patients with brain metastases who have undergone prior SRS. PET/MRI provides valuable information for the management of brain metastases, including the detection of lesions not visible on MRI, the differentiation of recurrence from radiation necrosis, and the assessment of lesion response to treatment.
threshold-based method of 41% of SUV\textsubscript{max} was found to visually perform best for all lesion sizes and was applied in this study. Manual modifications were made to include necrotic areas inside tumors and to exclude nontumor tissue, such as veins. Contrast-enhanced MRI volumes were manually delineated in accordance with an experienced neuroradiologist, and necrotic areas inside tumors were included. The maximum diameter of the lesions (in any direction) on ce-MRI (D\textsubscript{max MR}) was automatically calculated in PMOD. The spatial similarity of PET and MRI tumor volumes was evaluated using the Dice similarity coefficient (DSC).\textsuperscript{36}

\[
\text{DSC} = \frac{2(V_{\text{MRI}} \cap V_{\text{PET}})}{V_{\text{MRI}} + V_{\text{PET}}}
\]

The VOIs drawn on static PET were transferred to the dynamic PET images to generate time-activity curves (TACs) for SUV\textsubscript{max} and SUV\textsubscript{mean}. The SUV\textsubscript{max} curve was assigned to one of the following slope characteristics, as defined by Galldiks et al\textsuperscript{17}: (I) constantly increasing uptake without identifiable peak, (II) uptake peaking early (<20 minutes) followed by a plateau, and (III) uptake peaking early (<20 minutes) followed by a constant decrease. Only PET detected lesions with D\textsubscript{max MR} >10 mm were included in the dynamic analyses, due to generally poor activity recovery for small lesions.\textsuperscript{37}

### Statistics

Statistical analyses were performed with MATLAB (R2021a, The MathWorks). The Wilcoxon rank sum test was used to test

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**TABLE 1. Patient Information and Results From Evaluations of Brain Lesions Not Treated With Stereotactic Radiosurgery (No-SRS Group) Before PET/MRI**

| Patient ID | Age | Primary Cancer | GPA | Lesion Number | PET Positive* | MRI Positive† | D\textsubscript{max MR} (mm) | V\textsubscript{MRI} (mL) | V\textsubscript{PET} (mL) | DSC | SUV\textsubscript{max} | SUV\textsubscript{mean} | TBR | TAC Slope |
|------------|-----|----------------|-----|---------------|---------------|---------------|--------------------------|-----------------|-----------------|-----|-----------------|-----------------|-----|-----------|
| 1‡         | 54  | Breast         | 2.5 | 1             | Yes           | Yes           | 19                       | 1.68            | 1.7             | 0.76 | 3.2           | 0.3             | 12.3| III       |
| 2          | 61  | Esophagus (GI) | 0   | 1§            | Yes           | Yes           | 55                       | 5.00            | 9.3             | 0.55 | 3.9           | 0.4             | 9.0 | III       |
| 3          | Yes | No             | 5   | 0.03          | —             | 1.0           | 2.2                       | 0.6             | 1.2             | 0.4  | 1.4           | 0.4             | 2.2 | II        |
| 4          | 66  | Lung           | 1.5 | 1             | Yes           | Yes           | 10                       | 0.32            | 1.0             | 0.50 | 1.8           | 0.3             | 5.4 | —         |
| 5          | Yes | No             | 5   | 0.02          | —             | 0.5           | 0.4                       | 0.4             | 0.6             | 0.4  | 1.2           | 0.4             | 1.2 | —         |
| 6‡         | 74  | Melanoma       | 3   | 1             | Yes           | Yes           | 30                       | 5.38            | 3.7             | 0.77 | 7.4           | 0.3             | 21.9| III       |
| 8§         | 73  | Melanoma       | 3   | 1§            | Yes           | Yes           | 13                       | 0.36            | 0.5             | 0.58 | 6.9           | 0.3             | 19.8| II        |
| 9‡         | 51  | Coli (GI)      | 0   | 1             | Yes           | Yes           | 24                       | 4.18            | 6.6             | 0.76 | 2.3           | 0.4             | 5.8 | II        |
| 12‡        | 56  | Esophagus (GI) | 0   | 1             | Yes           | Yes           | 49                       | 27.02           | 29.6            | 0.90 | 5.2           | 0.4             | 13.2| —         |
| 13‡        | 69  | Thyroid        | NA  | 1             | Yes           | Yes           | 8                        | 0.14            | 0.9             | 0.24 | 1.2           | 0.3             | 3.9 | —         |
| 14‡        | 58  | Lung           | 3   | 1             | Yes           | Yes           | 26                       | 4.47            | 3.6             | 0.86 | 8.4           | 0.3             | 25.9| III       |
| 15‡        | 67  | Rectal (GI)    | 0   | 1             | Yes           | Yes           | 33                       | 7.83            | 10.7            | 0.83 | 3.8           | 0.4             | 10.6| II        |
| 16         | 74  | Lung           | 1.5 | 1             | Yes           | Yes           | 51                       | 25.60           | 30.9            | 0.88 | 4.3           | 0.3             | 16.4| II        |
| 17‡        | 63  | Lung           | 0.5 | 1             | Yes           | Yes           | 38                       | 12.85           | 10.8            | 0.76 | 6.5           | 0.3             | 21.7| III       |
| 18‡        | 63  | Lung           | 3   | 1             | Yes           | Yes           | 38                       | 11.30           | 11.7            | 0.78 | 2.8           | 0.3             | 9.2 | II        |

*"Yes" if new contrast-enhancing lesion.
†"Yes" if visually detected on PET, "no" otherwise.
‡Ongoing steroid treatment.
§Prior resection at same location.
||Chemotherapy last month.
¶Immunotherapy last month.
#Most likely lung cancer.

D\textsubscript{max MR}, maximum lesion diameter on ce-MRI; V\textsubscript{MRI}, tumor volume defined on ce-MRI; V\textsubscript{PET}, tumor volume defined on \textsuperscript{18}F-FACBC PET; NA, not available, GPA not defined for thyroid cancer.
differences in PET and MRI volumes, whereas Spearman ρ, rs, was calculated to evaluate the correlation between the volumes.

**RESULTS**

**Static PET Versus MRI**

The results in the no-SRS group are presented in Table 1. Twenty-nine lesions were identified with MRI in the no-SRS group, and all lesions were defined as “MRI positive.” Nineteen of 29 lesions were detected with 18F-FACBC PET and had in general high 18F-FACBC uptake and TBR (SUVmax: mean, 4.2 ± 2.2; range, 1.2–8.4; TBR: mean, 12.0 ± 6.5; range, 3.9–25.9). All PET detected lesions had Dmax MR ≥ 7 mm. Ten of 29 lesions were undetected with 18F-FACBC PET due to low 18F-FACBC uptake and TBR (SUVmax: mean, 0.6 ± 0.3; range, 0.3–1.2; TBR: mean, 1.6 ± 0.6; range, 1.0–2.7). PET undetected lesions were small with Dmax MR ≤ 8 mm.

Figure 2 shows the smallest PET detected lesion (Dmax MR = 7 mm) and 2 lesions undetected with PET (Dmax MR = 6 mm and 5 mm).

The results in the SRS group are presented in Table 2. Six lesions were identified in the SRS group of which 4/6 lesions were defined as “MRI positive” and suspected as metastatic tissue, whereas 2/6 lesions were defined as “MRI negative” and hence indicative of radiation necrosis (1 example shown in Fig. 3). All 6 lesions had 18F-FACBC uptake (SUVmax: mean, 3.2 ± 1.1; range, 1.4–4.2; TBR: mean, 8.4 ± 3.2; range, 3.6–12.6) and were detected with PET (Dmax MR ≥ 15 mm). The 2 patients with “MRI-positive” lesions deceased 5 months after the PET/MRI examination. The 2 lesions defined as “MRI negative” were stable at the time of follow-up (10 and 7 months after PET/MRI), but 1 of the patients had 7 new brain lesions consistent with new metastasis.

PET parameters (SUVmax, TBR) for all lesions detected and not detected with PET are shown in Figure 4, demonstrating that all PET detected lesions had SUVmax ≥ 1.2 and TBR ≥ 3.6. Lesions from all included tumor origins showed 18F-FACBC uptake, and the distributions of the PET parameters for the different tumor origins (lung cancer [n = 11], GI cancer [n = 8], malignant melanoma [n = 4], breast cancer [n = 1], thyroid cancer [n = 1]) are presented in Figure 5. No clear differences in SUVmax or TBR between the tumor origins were observed, but statistical tests of group differences were not performed due to small group sizes.

The MRI and PET tumor volumes for the PET detected lesions correlated significantly (rs = 0.95, P < 0.001) and were not

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**TABLE 2. Patient Information and Results From Evaluations of Brain Lesions Treated With Stereotactic Radiosurgery (SRS Group) Before PET/MRI**

| Patient ID | Age | Primary Cancer | GPA | Lesion Number | MRI-DT | PET-DT | Follow-up Status† | Dmax MR (mm) | VMRI (mL) | VPET (mL) | DSC | SUVmax | SUVmean | TBR | TAC | Slope |
|------------|-----|----------------|-----|---------------|--------|--------|------------------|-------------|-----------|----------|-----|--------|---------|-----|-----|-------|
| 7          | 60  | Lung           | 1.5 | 1§||          | 1 y    | No     | Yes              | 36          | 3.2       | 4.4      | 0.57| 4.1    | 0.4     | 10.6| II  |       |
| 9‡         | 51  | Coli (GI)      | 0   | 2§||          | 2 y    | Yes    | Yes              | 20          | 1.6       | 2.2      | 0.59| 3.0    | 0.4     | 7.6 | III |       |
| 3§         | 6 mo|                  |     |              | Yes    | Yes    | Yes              | 15          | 0.8       | 2.4      | 0.52| 1.4    | 0.4     | 3.6 | II  |       |
| 4§         |      |                  |     |              | Yes    | Yes    | Yes              | 31          | 6.5       | 10.1     | 0.76| 2.5    | 0.4     | 6.5 | II  |       |
| 10¶        | 66  | Lung           | 2   | 1§           | 2.5 y  | Yes    | Yes              | 34          | 5.9       | 6.5      | 0.80| 4.2    | 0.3     | 12.6| II  |       |
| 11¶        | 77  | Lung           | 1   | 1§           | 1 y    | No     | Yes              | 23          | 1.7       | 3.0      | 0.58| 3.8    | 0.4     | 9.3 | II  |       |

*Yes* if lesion showed contrast enhancement and progressive enlargement compared with previous MRIs, “no” if lesion was stable or decreased in size compared with previous MRIs.
†“Yes” if visually detected on PET.
‡Based on follow-up MRI.
§Prior SRS at same location.
||Prior resection at same location.
¶Ongoing steroid treatment.
GP A, graded prognostic assessment; TP, time period, Dmax MR, maximum lesion diameter on ce-MRI; VMRI, tumor volume defined on ce-MRI; VPET, tumor volume defined on 18F-FACBC PET.
significantly different ($P = 0.49$) (MRI: mean, 6.0 ± 7.8 mL; range, 0.1–27.0 mL; PET: mean, 6.9 ± 8.6 mL; range, 0.5–30.9 mL) (Fig. 6). The average spatial similarity of PET and MRI volumes measured by DSC was 0.66 ± 0.18 (range, 0.24–0.90). The lesion with lowest DSC is shown in Figure 7.

**DISCUSSION**

This study evaluated the use of $^{18}$F-FACBC PET/MRI in 18 patients with brain metastases and is to our knowledge the largest study using $^{18}$F-FACBC in this patient group. The majority of brain metastases demonstrated high uptake of $^{18}$F-FACBC and low $^{18}$F-FACBC uptake in normal brain tissue, resulting in generally high TBR. However, small brain metastases (<7 mm) were only detected by ce-MRI and not by $^{18}$F-FACBC PET. Consequently, our findings demonstrated an inferior detection of brain metastases using $^{18}$F-FACBC PET compared with ce-MRI.

The poor spatial resolution of PET imaging likely explains why ce-MRI performed better than $^{18}$F-FACBC PET in the detection of small brain metastases. The limited spatial resolution causes reduced lesion uptake in small lesions (approximately 10 mm and smaller) in PET images due to partial volume effects, which limits the detectability.38,39 Interestingly, a study by Bogsrud et al23 reported

![FIGURE 2. Upper row, Two “MRI-positive” lesions with $D_{\text{max, MR}}$ of 6 mm and 5 mm (left, ce-MRI) not detected on PET (middle, $^{18}$F-FACBC PET), shown on fused PET and MRI (right) (ID 132, SUV scale from 0 to 1.6). Lower row, The smallest PET detected lesion with $D_{\text{max, MR}}$ of 7 mm (ID 82, SUV scale from 0 to SUV$_{\text{max}}$).](image1)

![FIGURE 3. “MRI-negative” finding indicative of radiation necrosis on ce-MRI due to missing progression in a location with prior resection and SRS (ID 7, lung cancer) (left). $^{18}$F-FACBC PET showed high uptake (middle) (SUV scale from 0 to SUV$_{\text{max}}$). Fused PET and ce-MRI (right).](image2)
detection of small satellite tumors of 2 to 4 mm in patients with suspected high-grade gliomas. All these tumors had high TBRs that probably enabled detection below PET spatial resolution. The satellite tumors were undetectable on MRI, although this may be explained by the 5 to 14 days delay between MRI and PET/CT examinations. It can be noted that the PET/CT system (Biograph mCT) used in the study by Bogsrud et al has shown a slightly improved detectability over the PET/MRI system (Biograph mMR) used in the current study, which may have further impacted the results.

Brain metastases below 10 mm that were detected with $^{18}$F-FACBC PET in our study had TBR approximately 4 to 5, whereas PET undetected metastases had TBR up to 2.7. Hence, for $^{18}$F-FACBC PET detection of lesions with diameters below 10 mm, a TBR of approximately 4 may be required. The generally high TBR in the study by Bogsrud et al (median, 21.6) may be due to the inclusion of high-grade gliomas, as TBR tends to increase with glioma tumor grade. In studies using $^{11}$C-MET and $^{18}$F-FET in both gliomas and brain metastases, the average TBR was slightly
lower for brain metastases than for gliomas\textsuperscript{40,41}; however, it is uncertain whether this difference is significant and whether it is unique for specific PET tracers. If brain metastases generally have lower AA uptake than gliomas, this may contribute to a reduced detectability for brain metastases.

Our findings suggest that $^{18}$F-FACBC can produce significantly higher TBR for brain metastases ($11.1 \pm 6.0$) than has been reported for $^{11}$C-MET and $^{18}$F-FET.\textsuperscript{17–19,40,42–46} This potentially allows for detection of smaller brain metastases with $^{18}$F-FACBC than for other AA PET tracers. However, brain metastases as small as 6 mm have been reported $^{18}$F-FET positive in a study by Unterrainer et al.\textsuperscript{44} They used a quantitative definition of $^{18}$F-FET–positive metastases (TBR $\geq 1.6$), whereas a visual definition was used in the current study as no such guideline exists for $^{18}$F-FACBC. A visual definition is subjective, and a faint uptake could in some cases be observed, although not distinctly higher than surrounding tissue.

Although not all lesions were detected with PET, brain metastases from all the included primary cancers showed $^{18}$F-FACBC uptake. No remarkable differences in $^{18}$F-FACBC uptake were observed between the metastases of different tumor origins, but the groups were too small for statistical testing. The results are consistent with the $^{18}$F-FET study by Unterrainer et al\textsuperscript{44} where brain metastases originating from lung, breast, and melanoma did not show significantly different uptake. Larger groups are required to verify that brain metastases originating from different primary cancer show similar AA uptake.

In concordance with previous studies, $^{18}$F-FACBC stands out among AA PET tracers by exhibiting uniquely low uptake in healthy brain tissue.\textsuperscript{22,24,26–28,31,47} This difference is likely due to slight differences in the transport mechanisms by which the AA tracers cross the BBB. For accumulation in cancer cells, the primary mode of transport for $^{11}$C-MET and $^{18}$F-FET is the system L AA transport (LAT1) system.\textsuperscript{20,48–51} Although $^{18}$F-FACBC also uses LAT1, it has higher affinity to ASCT2 (alanine-serine-cysteine transporter 2).\textsuperscript{51–53} A lack of and presence of ASCT2 expression on the luminal and abluminal side of BBB endothelial cells, respectively, may contribute to low $^{18}$F-FACBC uptake by resulting in a low luminal uptake of $^{18}$F-FACBC from blood and an increased abluminal $^{18}$F-FACBC uptake from normal brain tissue. The low background uptake of $^{18}$F-FACBC clearly allows for high tumor contrast.

MRI evaluations of brain tumors following radiation treatment present a clinical challenge, as MRI may not be able to distinguish malignant tissue from radiation necrosis as both show contrast enhancement.\textsuperscript{54} Amino acid PET can potentially play an important role.

**FIGURE 6.** Volume of PET detected lesions defined in ce-MRI ($V_{\text{MRI}}$) versus $^{18}$F-FACBC PET ($V_{\text{PET}}$). Significant correlation ($\rho = 0.95$, $P < 0.001$) between $V_{\text{MRI}}$ and $V_{\text{PET}}$.

**FIGURE 7.** Fused PET/MRI scans of the lesion with the lowest spatial similarity between volumes defined on $^{18}$F-FACBC (blue) and ce-MRI (cerise). The DSC for the volumes was 0.24 (SUV scale from 0 to SUV$_{\text{max}}$).
In this situation, metabolic information provided by 18F-FACBC PET can help detect malignancies when MRI findings are equivocal. All 6 lesions in the SRS group had 18F-FACBC uptake, but 2 lesions were initially suspected as radiation necrosis due to no progressive enlargement compared with MRI scans before PET/MRI. Follow-up MRI also showed that these 2 lesions remained stable, but one of the patients developed 7 new brain lesions. Follow-up MRI as a reference might be insufficient in patients treated with SRS as radiation necrosis can occur up to several years after radiation therapy and may also increase in size.55,56 This exemplifies the diagnostic challenge in these patients, which is even more difficult as it is shown that radiation necrosis and viable metastatic tissue can coexist.55 Without histopathological verification and with the small cohort in the SRS group, our study yields inconclusive results regarding the value of 18F-FACBC PET for differentiation between brain metastasis recurrence and radiation necrosis.

Recently, Parent et al30 showed a significant difference in SUVmax of 18F-FACBC PET between local brain metastasis recurrence and radiation necrosis. They concluded that an SUVmax ≥1.3 differentiated recurrence from radiation necrosis, which points to recurrence for all the lesions in our SRS group. However, their study was limited by few samples (11 recurrent metastases and 4 radiation necrotic lesions). Furthermore, Parent et al did not report a significant difference in TBR between local recurrence and radiation necrosis, which was attributed to a variable tracer uptake in normal brain tissue. SUVmax in a 15-mm spherical background ROI was used as a reference, although SUVmean in a crescent-shaped VOI could possibly have reduced the variability.35 The patients in the no-SRS group in the current study will be followed after SRS treatment to further evaluate the accuracy of 18F-FACBC in distinguishing viable tumor tissue from radiation necrosis. One can hypothesize that 18F-FACBC PET could have a more important role in a follow-up setting than in the primary evaluation of brain metastases, but more studies using histopathology as reference should be performed to fully explore the tracer for this purpose.

Dynamic 18F-FET PET has shown high diagnostic accuracy in differentiating brain metastasis recurrence from radiation necrosis...
when combined with TBR. Radiation necrosis has been associated with slowly increasing TAC curves, whereas recurrence show early peaks followed by a plateau or decreasing slope. 18F-FACBC uptake in radiation necrosis has to our knowledge only been measured in the study by Parent et al., showing a slight increase throughout the acquisition, although with a limited number of time points (5, 10, 30, 55 minutes). In the current study, all lesions showed early peaks followed by either a plateau or decreasing slope, also the lesions suspected as radiation necrosis with MRI. It is still unclear whether dynamic 18F-FACBC PET analyses can be useful for distinguishing recurrent brain metastases from radiation necrosis.

The lack of guidelines for 18F-FACBC PET volumetric analysis of brain tumors has resulted in inconsistent methods throughout the literature. This study used 41% of SUVmax to delineate tumor boundaries as this visually delineated the 18F-FACBC uptake best for all lesion sizes. Previous 18F-FACBC studies on brain metastases and gliomas have used 50% of SUVmax thresholds based on uptake in reference tissue, and manual delineation. In our study, no significant difference in tumor volume for 18F-FACBC PET and ce-MRI was found; however, the spatial distribution was different. The lack of guidelines for 18F-FACBC PET in the SRS group was based on increase in lesion size according to the RANO criteria. However, this criterion can be discussed. It should, however, be noted that the mean time between MRI and PET examinations was 8 days (range, 3–33 days) in that study, which probably impacted the results. To guide guidelines for volumetric 18F-FACBC PET analysis of brain tumors, further research comparing 18F-FACBC PET with data from MRI, tumor resection, and/or image-localized biopsy needs to be conducted.

A strength of this study is the larger sample size of this patient group compared with earlier studies; however, the sample size is still limited, especially for evaluation of radiation necrosis in the SRS group. Differentiation of recurrence from radiation necrosis on MRI in the SRS group was based on increase in lesion size according to the RANO criteria. However, this criterion can be discussed, and it has been shown in a study of more than 500 brain metastases that increase in lesion size after SRS was associated with longer survival compared with lesions exhibiting stable or decreased lesion size. This indicates that lesion enlargement may represent active immune response instead of tumor regrowth, showing that increase in size is not necessarily a good indicator for recurrence. Thus, other features such as enlargement across anatomical boundaries, type of contrast enhancement, conspicuity of tumor margins, and complex evolution such as simultaneous regression and enlargement have been suggested indicative of radiation necrosis rather than tumor progression, but this has not been considered in this study. Biopsy is the criterion standard for distinguishing tumor recurrence from radiation necrosis but was not included in this study because it is invasive and may cause complications. Another limitation is that one patient received immunotherapy the last month before PET/MRI. This can cause an increase in the size and number of metastases in the initial phase of the treatment related to the mechanisms of action of immunotherapy, which are later stabilized or regressed. Furthermore, the study is limited by the patient heterogeneity, with regard to newly diagnosed and recurrent metastases as well as differences in tumor origins. The lack of standardization for volume delineation for 18F-FACBC limits the validity of the volumetric results.

CONCLUSIONS

18F-FACBC showed uptake in brain metastases originating from lung, GI, breast, and thyroid cancer, as well as malignant melanoma. The tracer is unique among AA PET tracers with a characteristic low uptake in healthy brain tissue resulting in a high tumor contrast. However, in small lesions, the 18F-FACBC PET uptake was not sufficient for detection, and PET was inferior to MRI. 18F-FACBC PET should be further evaluated in a follow-up setting for its opportunities to differentiate between tumor recurrence and radiation necrosis. Whether 18F-FACBC PET can detect metastatic tumor tissue beyond ce-MRI should also be further explored.

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