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Performance of ^{18}F -FAPI PET/CT in assessing glioblastoma before radiotherapy: a pilot study

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Abstract

Background: We aimed to determine the performance of ^{18}F -FAPI PET/CT used for preprocedural assessment of glioblastoma before radiotherapy.

Methods: Twelve glioblastoma patients having undergone incomplete surgical resection or biopsy were examined with ^{18}F -FAPI PET/CT and MRI scanning before radiotherapy. All patients had confirmed tumor residues according to findings of histopathological and/or long-term clinical and radiological follow-ups. Lesion characterization data, including SUV_{max} and tumor-to-background ratio (TBR) on PET/CT were attained. PET/CT and MRI findings were compared in terms of number of lesions. The correlation between immunohistochemistry, molecular expression, and PET/CT parameters was also evaluated.

Results: ^{18}F -FAPI PET/CT detected 16 FAPI-avid out of 23 lesions in 12 patients described on MRI. MRI was statistically different from ^{18}F -FAPI PET/CT for lesion detection according to the exact McNemar statistical test ($P=0.0156$). The SUV_{max} and TBR of the glioblastomas was 7.08 ± 3.55 and 19.95 ± 13.22 , respectively. The sensitivity and positive predictive value (PPV) of ^{18}F -FAPI PET were 69.6% and 100%, respectively. Neither the Ki-67 index nor the molecular expression was correlated with the FAPI-PET/CT parameters.

Conclusion: ^{18}F -FAPI PET/CT detects glioblastomas at a lower rate than MRI. However, the 100% PPV of the examination may make it useful for differentiating controversial lesions detected on MRI. The ^{18}F -FAPI-avid lesions are displayed more clearly probably due to a higher TBR. ^{18}F -FAPI PET/CT imaging might find application in glioblastoma biopsy and radiotherapy planning.

Keywords: Glioblastoma, FAPI, PET/CT, Metabolic parameters, Molecular expression, MRI

Background

Glioblastoma is reported to be the most prevalent primary brain malignancy in adults, which represents one of the most rapidly growing glial tumors, accounting for about 57% of glioma. It is associated with a worse prognosis and a high recurrence rate [1]. Only some 6.8% of glioblastoma patients survive beyond five years [2]. As the most common non-invasive imaging technique to assess glioblastoma [3, 4], magnetic resonance imaging (MRI) has been employed as a diagnostic instrument for glioblastoma diagnosis, prognostication, and monitoring of therapy response [5–9]. Other methods, such as

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diffusion-weighted imaging (DWI), apparent diffusion coefficient (ADC), perfusion-weighted imaging (FWI), and magnetic resonance spectrum imaging (MRS) are also widely used in addition to conventional sequences [4, 6, 7, 10–13].

Positron emission tomography (PET) has been reported to provide additional information, which is helpful for identifying biological characteristics of tumor, differential diagnosis, and tumor size delineation and for an oncologist to plan a surgery, radiotherapy, and/or post-treatment tumor surveillance [14–17]. ^{18}F -fluorodeoxyglucose (^{18}F -FDG) is a commonly used PET tracer in clinical settings, which is known for diminished sensitivity due to increased physiologic uptake in the normal brain tissue [18]. When compared with glucose (^{18}F -FDG), amino acids including ^{11}C -MET, ^{18}F -FET, ^{18}F -FDOPA may be better tracers because they have higher specificity and lower signal/noise ratio [14, 17, 19].

Molecular-based PET-imaging that targets fibroblast activation protein (FAP) has been reported as a novel approach [20–24]. As a new diagnostic instrument, FAP-inhibitor (FAPI) PET imaging has found applications in a number of FAP-positive tumors, including glioblastoma [20, 25–29]. High tracer uptake in glioblastoma has been documented [28, 30, 31]. In this work, we performed ^{18}F -FAPI-PET imaging in 12 glioblastoma patients and attempted to evaluate its performance in pre-chemotherapy tumor assessment by evaluating uptake of FAP ligands in the tumor tissues.

Materials and methods

Patients

Patients with glioblastoma who underwent assessment before radiotherapy in our department between August 2020 and March 2022 were enrolled in this study. The diagnoses were confirmed by biopsy or incomplete surgical resection plus histological study before imaging and/or long-term clinical and radiological follow-up. The immunohistochemistry and molecular expression, such as Ki-67 proliferation index (Ki-67 index), O6-methylguanine-DNA methyltransferase (MGMT) promoter methylation status, Isocitrat Dehydrogenase (IDH) and telomerase reverse transcriptase (TERT) status, were collected. All patients were scanned with ^{18}F -FAPI PET/CT and MRI. The median time between the examinations was 3.5 days (range, 1 to 7 days).

Radiopharmaceutical preparation

Radiosynthesis was as follows [32, 33]: ^{18}F -FAPI was automatically synthesized with modified AllinOne module (Trasis, Ans, Belgium). ^{18}F -was attained on-site on a Sumitomo HM-10 cyclotron system (Sumitomo Heavy Industries, Tokyo, Japan), where $[^{18}\text{O}]\text{H}_2\text{O}$ was irradiated

with 10 MeV protons, and reacted with 0.15 mg NOTA-FAPI-04 (Paite Biotech, Beijing, China) (130 °C, 8 min, pH 4.0). An HLB cartridge (Waters Corporation) was used to collect the purified products. Quality of the final ^{18}F -FAPI product was tested by HPLC (Shimadzu LC-15, Suzhou, China). Radiochemical purity was >95%. Appearance, color, pH, and other quality controls were performed according to the current pharmacopoeias.

PET/CT imaging

The patients were not specially prepped on the day of ^{18}F -FAPI PET/CT scanning. A Biograph mCT-64 scanner (Siemens, Germany) was used. The scanning was performed about 60 min after intravenous injection of ^{18}F -FAPI (0.12 millicurie/kg). The localizer was positioned with a scout head view. Low-dose CT (120 kV/110 mA) was then performed for anatomical localization and attenuation correction. Single-bed emission scans were obtained in 3-dimensional mode (acquisition time, 3 min). Reconstruction of data was done using an ordered subset expectation maximization iterative reconstruction algorithm (three iterations, 21 subsets). The emission data were corrected for random, scatter, and decay.

MRI acquisition

MRI scans were acquired at 3 T. The sequences were: T1-weighted, T2-weighted, T2-weighted fluid-attenuated inversion recovery (FLAIR), T1-weighted gadoterate meglumine contrast-enhanced (CE-T1), MRS, ADC and DWI. Gadoterate meglumine (Gd-DOTA, DOTAREM, Guerbet, France) was intravenously administered in CE-T1 (pre-bolus dose, 0.1 mmol/kg).

Image analysis

Two physicians with ten years of experience in brain tumor imaging evaluated the MRI images. Two nuclear medicine physicians who were experienced in PET/CT image assessment evaluated the PET/CT images. Disagreements were resolved by consensus. An abnormal focus of increased ^{18}F -FAPI uptake as compared with the background activity in the brain parenchyma was defined as positive on PET/CT. Standardized uptake values (SUV) were quantified using regions of interest (ROI). Should an area be found with increased uptake compared with the surrounding parenchyma, we drew a circular ROI over it where cystic or necrotic portions of the lesion was identified and avoided. Additionally, we drew an identical ROI over the contralateral normal cerebral cortex as a background. Tumor-to-background ratio (TBR) was calculated as the SUV_{max} of the lesion divided by the SUV_{max} of the contralateral normal cortex. The Response Assessment in Neuro-oncology (RANO) guidelines were used as the MRI reference. Lesions that

were Gd-DOTA-enhancing, predominantly hyperintense with surrounding edema on the FLAIR sequence, or with a CHO/NAA ratio > 1.5 were considered positive on MRI images.

Statistical analysis

We performed the statistical analyses using SPSS (version 22.0; IBM). Continuous variables are expressed as mean ± SD and categorical variables as numbers and percentages. The number of positive lesions was compared using exact McNemar statistical test. Inter-parameter correlations were calculated with the Spearman test. *P* < 0.05 was statistically significant.

Results

Patients’ characteristics

Twelve patients (aged 34–73 yrs, average 52 yrs) with glioblastomas confirmed by incomplete surgical resection or biopsy were enrolled in this study before radiotherapy. The characteristics are displayed in Table 1. The Ki-67 index of the glioblastomas was 42.92 ± 21.58%.

According to the molecular expression, MGMT promoter methylation was found in 7 patients (58.3%), TERT mutation in 8 patients (66.7%), and IDH mutation only in 1 patient (8.3%).

MRI image and ¹⁸F-FAPI PET/CT characteristics

MRI detected 23 lesions in 12 patients, whereas ¹⁸F-FAPI PET/CT detected 16 FAPI-avid lesions (Table 1; Figs. 1

and 2). Performance of MRI and ¹⁸F-FAPI PET/CT was significantly different in terms of lesion detection (*P* = 0.0156). The SUV_{max} and TBR were 7.08 ± 3.55 and 19.95 ± 13.22 in the FAPI-avid lesions, respectively (Table 2).

The lesions were subsequently validated with biopsy (3, 13.0%), biopsy after complete or incomplete resection (10, 43.5%), and/or radiological follow-up (10, 43.5%). The sensitivity and positive predictive value (PPV) of ¹⁸F-FAPI PET/CT were 69.6% and 100%, respectively.

Neither the Ki-67 index nor the molecular expression was correlated with the ¹⁸F-FAPI-PET/CT parameters. (*P* > 0.05, Table 2)

Discussion

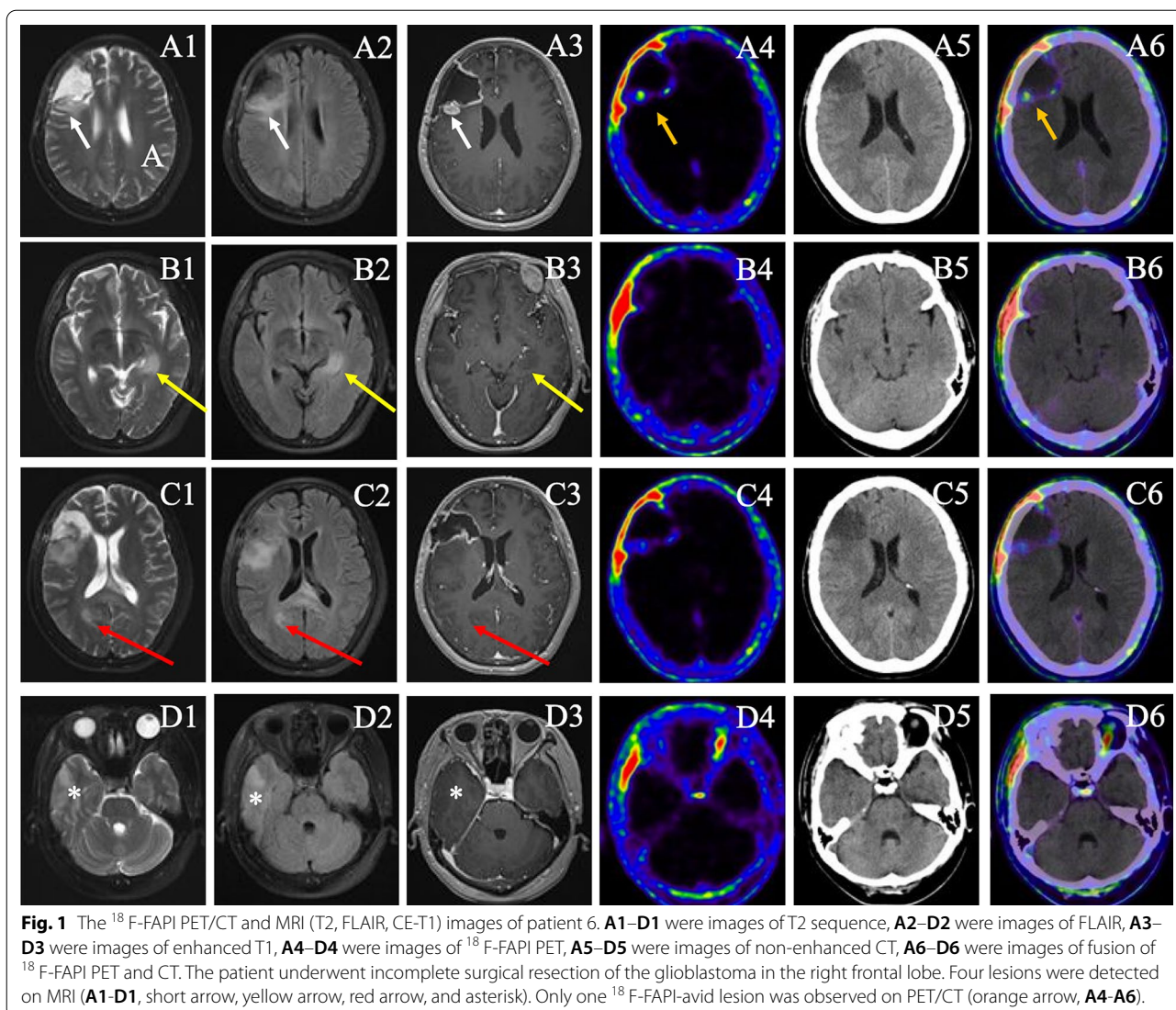
FAP overexpression and cancer associated fibroblasts (CAFs) found in tumor stroma are believed to cause the FAP-positive signaling in extracranial tumors [21, 34]. Imaging techniques that target FAP are novel promising instruments for visualizing tumor stroma. Excellent performance of FAPI PET/CT has been reported in various tumors including glioblastoma [21, 28].

Although fibroblasts do not exist in the brain, FAP-positive vessels in glial tumors, FAP-positive foci of neoplastic cells in gliomas, as well as FAP-positive stromal cells that function similarly to CAFs in epithelial cancers have been reported by several researchers[35–38]. FAP and FAP mRNA are overexpressed in most glioblastomas, especially in the mesenchymal subtype [37]. Some 65%

Table 1 Radiological and molecular characteristics of patients

Pt	Age, yr/Sex	Lesions (MRI)	Lesions (FAPI)	TBR	SUV _{max}	Ki-67 index (%)	MGMT	TERT	IDH
1	48/M	4	1	16.76 [#]	7.88	30	+	+	–
2	48/M	1	1	8.28 [#]	7.52	60	+	–	–
3	59/M	1	1	19.21 [#]	8.32	20	–	+	–
4	58/F	4	3	9.43 [#]	7.99	40	–	+	–
				19.56	2.82	N/A	N/A	N/A	N/A
				22.03	3.48	N/A	N/A	N/A	N/A
5	34/F	1	1	8.88 [#]	6.82	10	+	–	+
6	56/F	4	1	26.59 [#]	8.64	50	–	+	–
7	48/F	2	2	10.98 [#]	7.20	80	–	+	–
				21.05	1.94	N/A	N/A	N/A	N/A
8	36/F	1	1	61.69 [#]	8.27	60	+	–	–
9	73/M	1	1	27.38 [#]	8.63	20	+	+	–
10	58/M	1	1	13.06 [#]	7.50	70	+	–	–
11	49/F	2	2	7.90 [#]	3.41	35	+	+	–
				16.19	5.49	N/A	N/A	N/A	N/A
12	55/M	1	1	30.21 [#]	17.34	40	+	–	–
Total		23	16	19.95 ± 13.22	7.08 ± 3.55				

Pt, patient; MGMT: MGMT promoter methylation; TERT: TERT mutation; IDH:IDH mutation; #: specimen undergoing biopsy or surgical resection for immunohistochemistry, and molecular expression



of glioblastomas are FAP-positive intraparenchymally. In our pilot study, ^{18}F -FAPI PET/CT detected 69.6% (16/23) of all lesions, which could be attributed to the varying FAP expressions in different molecular glioblastoma subtypes [37] or the status of the blood-brain barrier [19]. Although its sensitivity was not high, the PPV of ^{18}F -FAPI PET/CT was up to 100%, which may be useful for differentiating controversial lesions detected on MRI. However, prospective studies based on larger samples are still needed to validate the findings.

To this day MRI remains the most used imaging modality for glioblastoma diagnosis and evaluation of treatment response and prognosis [1, 4, 10]. A number of advanced MRI techniques such as functional MRI (fMRI), diffusion tensor imaging (DTI), and MRS have been adopted for tumor treatment including preoperative surgical planning or as an instrument to distinguish

post-operative vascular damage from residual enhancing tumor[9, 12, 13, 39]. However, it is highly challenging to assess sub-regions of tumors in MRI scans visually because of their anatomic complexity. This can be even more true in post-operative settings[13]. It is a time-consuming task for clinicians to delineate the targets and critical structures, where observer biases are probable. Up to 20% intra- and 28% inter-rater variability have been reported for determining glioma boundaries[40]. As a result, boundary delineation of radiotherapy target volume could be inaccurate. Advanced molecular imaging could be helpful at this point[41]. Although the lesion detection rate was lower on ^{18}F -FAPI PET/CT than on MRI in our study, the TBR of the lesion was high (range 7.90-30.21) and the boundaries were better visualized due to the low FAPI distribution in the normal cerebral tissues. FAPI PET/

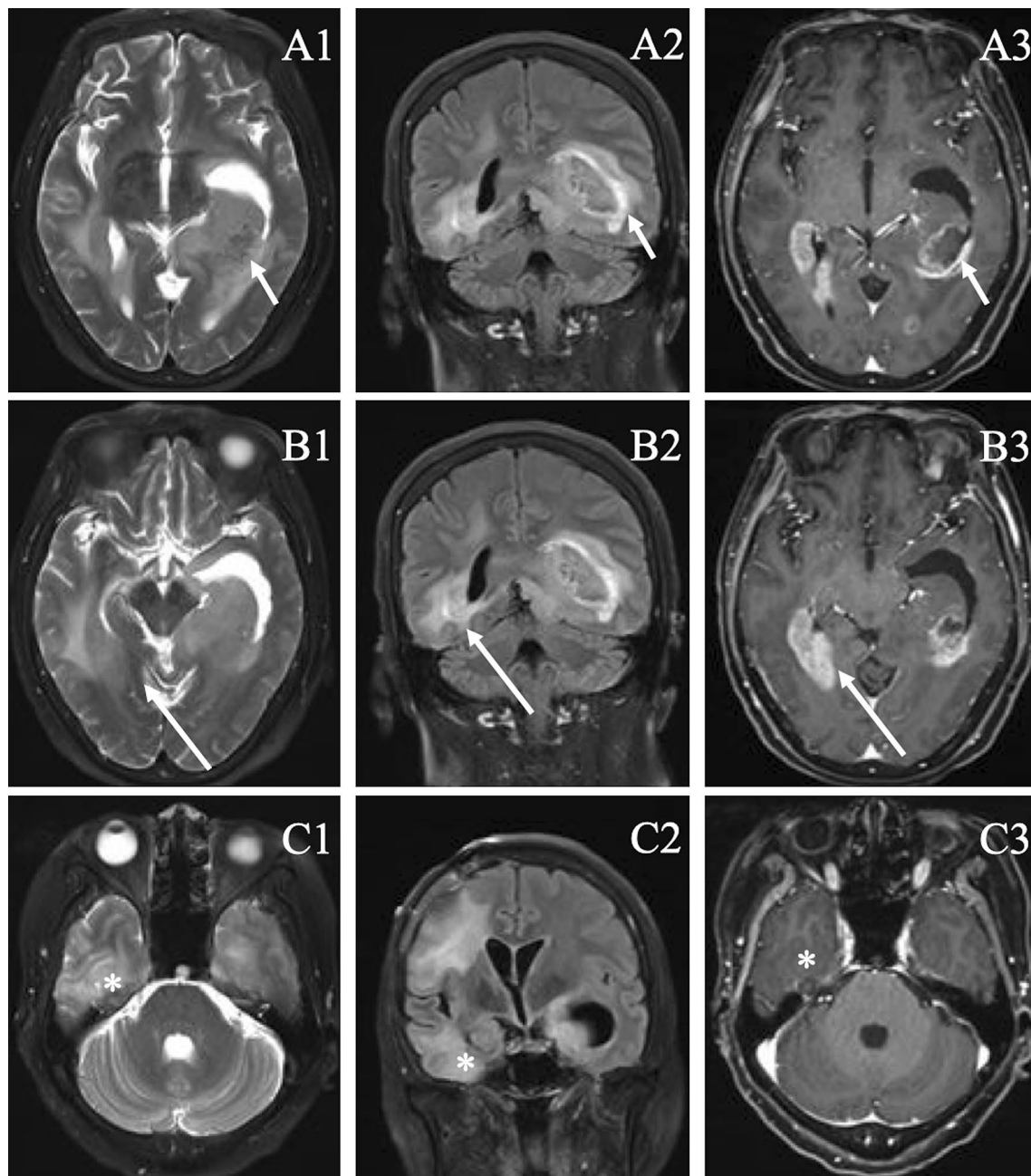


Fig. 2 The non-FAPI-avid lesions were confirmed by follow-up MRI (T2, FLAIR, CE-T1) 6 months later. **A1–C1** were images of T2 sequence, **A2–C2** were images of FLAIR, **A3–C3** were images of enhanced T1. All enlarged and partially mixed signals were heterogeneously enhanced (short arrow, long arrow, and asterisk), indicating disease progression

Table 2 Correlations between Ki-67 index, molecular expression, and FAPI-PET/CT parameters

	TBR	SUV _{max}
Ki-67	$r = 0.018, P = 0.957$	$r = -0.095, P = 0.769$
MGMT status	$r = 0.269, P = 0.397$	$r = 0.073, P = 0.821$
TERT status	$r = -0.073, P = 0.821$	$r = 0.073, P = 0.821$
IDH status	$r = -0.306, P = 0.334$	$r = -0.393, P = 0.206$

CT shows potential for application in biopsy and radiotherapy planning for glioblastoma [28, 30, 42]. According to a Polish study, target volume delineation based on MRI and FAPI PET is differentiated[30]. Gross tumor volumes (GTVs) delineated using FAPI PET plus MRI is significantly higher compared with MRI alone[30]. Unfortunately, the metabolic GTVs were not calculated in this study due to the threshold value

of MTV in FAPI PET/CT was still indeterminate. The further study is needed to analyze the different threshold value of MTV in FAPI PET/CT compared with the GTVs on MRI or RT planning.

Ki-67 index is a quantitative measure of cell proliferation in histopathological assessment of glioblastoma and many other tumors [43]. Ki-67 index and TERT or IDH mutation are positively associated with overall survival of glioblastoma patients and a lower Ki-67 index and IDH-wildtype are linked with poor prognosis [43, 44]. However, our findings failed to establish any correlations between the Ki-67 index or the molecular expression with the FAPI-PET/CT parameters, such as MGMT promoter methylation, TERT, and IDH mutation. Yet, only one of the glioblastoma patients in our study had IDH mutation. A larger sample may be needed in future research to further investigate our finding.

Limitation

Our sample size was limited with 12 patients and 23 lesions. As a pilot study, our findings are preliminary and should be interpreted with caution. Another limitation to our study was that some of the lesions were not labeled with FAP on immunohistochemistry. This prevented us from evaluating the correlation between FAP expression and the PET/CT parameters. Further studies with larger samples are needed to validate our results, especially the correlation findings.

Conclusion

Despite a lower lesion detection rate than MRI, the PPV of ¹⁸F-FAPI PET/CT was 100%, suggesting it as a useful examination for indeterminate lesions detected on MRI. ¹⁸F-FAPI PET/CT visualizes lesions more clearly with a high TBR, possibly because of lower FAPI distribution in the normal cerebral tissues. The technique may find applications in target volume delineation in radiotherapy of glioblastoma.

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Authors contributions

All authors contributed to study conception and design. YY, XT, JY, WY, YK, XW, XJ, SC, YL and JD collected, reviewed and analyzed the data. YY, XT, WY, YK, JY, and ZC wrote and revised the manuscript. All authors approved the submitted version of manuscript.

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Availability of data and materials

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Declarations

Ethics approval and consent to participate

This study was carried out in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Sichuan cancer hospital (NO: SCCHEC-04-2020-001). The informed consent was obtained from all subjects.

Consent for publication

Not applicable.

Competing interests

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

- McKinnon C, Nandhabalan M, Murray SA, Plaha P. Glioblastoma: clinical presentation, diagnosis, and management. *BMJ*. 2021;374:n1560.
- Wen PY, Weller M, Lee EQ, Alexander BM, Barnholtz-Sloan JS, Barthel FP, et al. Glioblastoma in adults: a Society for Neuro-Oncology (SNO) and European Society of Neuro-Oncology (EANO) consensus review on current management and future directions. *Neuro Oncol*. 2020;22(8):1073–113.
- Kim JY, Park JE, Jo Y, Shim WH, Nam SJ, Kim JH, et al. Incorporating diffusion- and perfusion-weighted MRI into a radiomics model improves diagnostic performance for pseudoprogression in glioblastoma patients. *Neuro Oncol*. 2019;21(3):404–14.
- Wolf RL. MRI of Recurrent Glioblastoma. *Reliab Real Radiol*. 2019;290(2):477–8.
- Strauss SB, Meng A, Ebani EJ, Chiang GC. Imaging glioblastoma post-treatment: progression, pseudoprogression, pseudoresponse, radiation necrosis. *Radiol Clin North Am*. 2019;57(6):1199–216.
- Bai R, Wang B, Jia Y, Wang Z, Springer CS Jr, Li Z, et al. Shutter-Speed DCE-MRI analyses of human Glioblastoma Multiforme (GBM) Data. *J Magn Reson Imaging*. 2020;52(3):850–63.
- Park CJ, Han K, Kim H, Ahn SS, Choi D, Park YW, et al. MRI features may predict molecular features of Glioblastoma in Isocitrate Dehydrogenase Wild-Type Lower-Grade Gliomas. *AJNR Am J Neuroradiol*. 2021;42(3):448–56.
- Pak E, Choi KS, Choi SH, Park CK, Kim TM, Park SH, et al. Prediction of prognosis in Glioblastoma using Radiomics features of dynamic contrast-enhanced MRI. *Korean J Radiol*. 2021;22(9):1514–24.
- Kasper J, Hilbert N, Wende T, Fehrenbach MK, Wilhelmy F, Jahne K, et al. On the prognosis of Multifocal Glioblastoma: an evaluation incorporating volumetric MRI. *Curr Oncol*. 2021;28(2):1437–46.
- De Barros A, Attal J, Roques M, Nicolau J, Sol JC, Charni S, et al. Glioblastoma survival is better analyzed on preradiotherapy MRI than on postoperative MRI residual volumes: a retrospective observational study. *Clin Neurol Neurosurg*. 2020;196:105972.
- Woo PYM, Ho JMK, Tse TPK, Lam SW, Mak CHK, Chan DTM, et al. Determining a cut-off residual tumor volume threshold for patients with newly diagnosed glioblastoma treated with temozolomide chemoradiotherapy: a multicenter cohort study. *J Clin Neurosci*. 2019;63:134–41.

12. Hassanzadeh C, Rudra S, Ma S, Brenneman R, Huang Y, Henke L, et al. Evaluation of interim MRI changes during limited-field radiation therapy for glioblastoma and implications for treatment planning. *Radiother Oncol.* 2021;158:237–43.
13. Shukla G, Alexander GS, Bakas S, Nikam R, Talekar K, Palmer JD, et al. Advanced magnetic resonance imaging in glioblastoma: a review. *Chin Clin Oncol.* 2017;6(4):40.
14. Law I, Albert NL, Arbizu J, Boellaard R, Drzezga A, Galldiks N, et al. Joint EANM/EANO/RANO practice guidelines/SNMMI procedure standards for imaging of gliomas using PET with radiolabelled amino acids and [(18)F]FDG: version 1.0. *Eur J Nucl Med Mol Imaging.* 2019;46(3):540–57.
15. Bolcaen J, Descamps B, Deblaere K, De Vos F, Boterberg T, Hallaert G, et al. Assessment of the effect of therapy in a rat model of glioblastoma using [(18)F]FDG and [(18)F]FCho PET compared to contrast-enhanced MRI. *PLoS ONE.* 2021;16(3):e0248193.
16. Seidlitz A, Beuthien-Baumann B, Lock S, Jentsch C, Platzek I, Zophel K, et al. Final results of the prospective Biomarker Trial PETra: [(11)C]-MET-Accumulation in postoperative PET/MRI predicts outcome after Radiochemotherapy in Glioblastoma. *Clin Cancer Res.* 2021;27(5):1351–60.
17. Ruiz-Lopez E, Calatayud-Perez J, Castells-Yus I, Gimeno-Peribanez MJ, Mendoza-Calvo N, Morcillo MA, et al. Diagnosis of glioblastoma by immuno-positron emission tomography. *Cancers (Basel).* 2021;14(1).
18. Takahashi M, Soma T, Mukasa A, Tanaka S, Yanagisawa S, Momose T. Pattern of FDG and MET distribution in high- and low-grade gliomas on PET images. *Clin Nucl Med.* 2019;44(4):265–71.
19. D'Souza MM, Sharma R, Jaimini A, Panwar P, Saw S, Kaur P, et al. 11 C-MET PET/CT and advanced MRI in the evaluation of tumor recurrence in high-grade gliomas. *Clin Nucl Med.* 2014;39(9):791–8.
20. Meyer C, Dahlbom M, Lindner T, Vauclin S, Mona C, Slavik R, et al. Radiation Dosimetry and Biodistribution of (68)Ga-FAPI-46 PET imaging in Cancer Patients. *J Nucl Med.* 2020;61(8):1171–7.
21. Kratochwil C, Flechsig P, Lindner T, Abderrahim L, Altmann A, Mier W, et al. (68)Ga-FAPI PET/CT: Tracer Uptake in 28 different kinds of Cancer. *J Nucl Med.* 2019;60(6):801–5.
22. Chen H, Pang Y, Wu J, Zhao L, Hao B, Wu J, et al. Comparison of [(68)Ga]Ga-DOTA-FAPI-04 and [(18)F]FDG PET/CT for the diagnosis of primary and metastatic lesions in patients with various types of cancer. *Eur J Nucl Med Mol Imaging.* 2020;47(8):1820–32.
23. Chen H, Zhao L, Ruan D, Pang Y, Hao B, Dai Y, et al. Usefulness of [(68)Ga]Ga-DOTA-FAPI-04 PET/CT in patients presenting with inconclusive [(18)F]FDG PET/CT findings. *Eur J Nucl Med Mol Imaging.* 2021;48(1):73–86.
24. Toms J, Kogler J, Maschauer S, Daniel C, Schmidkonz C, Kuwert T, et al. Targeting fibroblast activation protein: Radiosynthesis and preclinical evaluation of an (18)F-labeled FAP inhibitor. *J Nucl Med.* 2020;61(12):1806–13.
25. Koerber SA, Staudinger F, Kratochwil C, Adeberg S, Haefner MF, Ungerechts G, et al. The role of (68)Ga-FAPI PET/CT for patients with malignancies of the lower gastrointestinal tract: first clinical experience. *J Nucl Med.* 2020;61(9):1331–6.
26. Giesel FL, Kratochwil C, Lindner T, Marschalek MM, Loktev A, Lehnert W, et al. (68)Ga-FAPI PET/CT: Biodistribution and preliminary Dosimetry Estimate of 2 DOTA-Containing FAP-Targeting agents in patients with various cancers. *J Nucl Med.* 2019;60(3):386–92.
27. Jin X, Wei M, Wang S, Wang G, Lai Y, Shi Y, et al. Detecting fibroblast activation proteins in lymphoma using (68)Ga-FAPI PET/CT. *J Nucl Med.* 2021.
28. Rohrich M, Loktev A, Wefers AK, Altmann A, Paech D, Adeberg S, et al. IDH-wildtype glioblastomas and grade III/IV IDH-mutant gliomas show elevated tracer uptake in fibroblast activation protein-specific PET/CT. *Eur J Nucl Med Mol Imaging.* 2019;46(12):2569–80.
29. Zhao L, Chen S, Chen S, Pang Y, Dai Y, Hu S, et al. (68)Ga-fibroblast activation protein inhibitor PET/CT on gross tumour volume delineation for radiotherapy planning of oesophageal cancer. *Radiother Oncol.* 2021;158:55–61.
30. Windisch P, Rohrich M, Regnery S, Tonndorf-Martini E, Held T, Lang K, et al. Fibroblast activation protein (FAP) specific PET for advanced target volume delineation in glioblastoma. *Radiother Oncol.* 2020;150:159–63.
31. Rohrich M, Floca R, Loi L, Adeberg S, Windisch P, Giesel FL, et al. FAP-specific PET signaling shows a moderately positive correlation with relative CBV and no correlation with ADC in 13 IDH wildtype glioblastomas. *Eur J Radiol.* 2020;127:109021.
32. Jiang X, Wang X, Shen T, Yao Y, Chen M, Li Z, et al. FAPI-04 PET/CT using [(18)F]AIF labeling strategy: automatic synthesis, Quality Control, and in vivo Assessment in Patient. *Front Oncol.* 2021;11:649148.
33. Kou Y, Jiang X, Yao Y, Shen J, Jiang X, Chen S, et al. Physiological tracer distribution and benign lesion incidental uptake of Al18F-NOTA-FAPI-04 on PET/CT imaging. *Nucl Med Commun.* 2022;43(7):847–54.
34. Altmann A, Haberkorn U, Siveke J. The latest developments in imaging of fibroblast activation protein. *J Nucl Med.* 2021;62(2):160–7.
35. Clavreul A, Guette C, Faguer R, Tetaud C, Boissard A, Lemaire L, et al. Glioblastoma-associated stromal cells (GASCs) from histologically normal surgical margins have a myofibroblast phenotype and angiogenic properties. *J Pathol.* 2014;233(1):74–88.
36. Clavreul A, Etcheverry A, Chassevent A, Quillien V, Avril T, Jourdan ML, et al. Isolation of a new cell population in the glioblastoma microenvironment. *J Neurooncol.* 2012;106(3):493–504.
37. Busek P, Balaziova E, Matrasova I, Hilser M, Tomas R, Syrucek M, et al. Fibroblast activation protein alpha is expressed by transformed and stromal cells and is associated with mesenchymal features in glioblastoma. *Tumour Biol.* 2016;37(10):13961–71.
38. Trylcova J, Busek P, Smetana K Jr, Balaziova E, Dvorankova B, Mifkova A, et al. Effect of cancer-associated fibroblasts on the migration of glioma cells in vitro. *Tumour Biol.* 2015;36(8):5873–9.
39. Wang B, Zhang S, Wu X, Li Y, Yan Y, Liu L, et al. Multiple survival outcome prediction of Glioblastoma Patients based on multiparametric MRI. *Front Oncol.* 2021;11:778627.
40. Mazzara GP, Velthuisen RP, Pearlman JL, Greenberg HM, Wagner H. Brain tumor target volume determination for radiation treatment planning through automated MRI segmentation. *Int J Radiat Oncol Biol Phys.* 2004;59(1):300–12.
41. Harat M, Malkowski B, Makarewicz R. Pre-irradiation tumour volumes defined by MRI and dual time-point FET-PET for the prediction of glioblastoma multiforme recurrence: a prospective study. *Radiother Oncol.* 2016;120(2):241–7.
42. Syed M, Flechsig P, Liermann J, Windisch P, Staudinger F, Akbaba S, et al. Fibroblast activation protein inhibitor (FAP) PET for diagnostics and advanced targeted radiotherapy in head and neck cancers. *Eur J Nucl Med Mol Imaging.* 2020;47(12):2836–45.
43. Wong E, Nahar N, Hau E, Varikatt W, Gebksi V, Ng T, et al. Cut-point for Ki-67 proliferation index as a prognostic marker for glioblastoma. *Asia Pac J Clin Oncol.* 2019;15(1):5–9.
44. Sledzinska P, Bebyn MG, Furtak J, Kowalewski J, Lewandowska MA. Prognostic and predictive biomarkers in Gliomas. *Int J Mol Sci.* 2021;22(19).

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