Comparison of [68Ga]Ga-DOTA-FAPI-04 PET/CT and [18F]FDG PET/CT for diagnosis of metastasis in differentiated thyroid cancer with negative iodine scintigraphy

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Abstract

Purpose Evaluation of the potential value of [^{68}Ga]Ga-DOTA-FAPI-04 positron emission tomography/computed tomography (PET/CT) and [^{18}F]FDG PET/CT in detection of differentiated thyroid cancer (DTC) metastases.

Methods [^{68}Ga]Ga-DOTA-FAPI-04 and [^{18}F]FDG PET/CT scans were performed on suspected metastatic DTC patients. Maximum standard uptake value (SUVmax) was used to quantify the uptake of positive lesions. Histopathology or follow-up images were used as the standard for final diagnosis.

Results A total of 35 DTC patients underwent [^{68}Ga]Ga-DOTA-FAPI-04 and [^{18}F]FDG PET/CT scans in the same time period. Average SUVmax of [^{68}Ga]Ga-DOTA-FAPI-04 uptake by DTC lesions was low (average SUVmax<7). The difference in detection rate of SUVmax of[^{68}Ga]Ga-DOTA-FAPI-04compared with that of[^{18}F]FDG in bone metastases was statistically significant (P=0.000, 0.049). There were differences in the detection rate of other distant and lymph node metastases, and SUVmax, with no statistical significance (*P*>0.05). The specificity, accuracy, and positive predictive value of [^{68}Ga]Ga-DOTA-FAPI-04 in the diagnosis of lymph node lesions were higher than those of [^{18}F]FDG PET/CT, and the difference was statistically significant (c^2=16.583，c^2=9.910，c^2=7.548，c^2=2.781, *P*＜0.05). There were no statistically significant differences in sensitivity, specificity, accuracy, and positive and negative predictive value of the two groups in the diagnosis of distant metastases (c^2=0.440，c^2=4.956，c^2=0.013，c^2=1.194，c^2=2.618，*P*＞0.05).

Conclusion [^{68}Ga]Ga-DOTA-FAPI-04 has certain advantages over [^{18}F]FDG PET/CT in detecting lymph node and bone metastases. It has the same ability to detect other distant metastases and can be used as a supplementary imaging method for DTC.

Introduction

Differentiated thyroid cancer (DTC) is one of the tumours with the best prognosis in malignant tumours. However, the overall risk of recurrence is about 20% [1]. In case of suspicion of DTC persistence/recurrence, the lack of consistency between negative routine imaging tests and high or gradually increasing serum thyroglobulin (Tg) levels prompted attempts to detect DTC recurrence and metastasis.

Fibroblast activation protein (FAP) is highly expressed in cancer associated fibroblasts (CAFs) in more than 90% of malignant epithelial tumours [2].It promotes the disease progression in different types of cancers, thereby, worsening the prognosis [3]. Therefore, FAP is considered to be a promising target that can be used for radionuclide-based tumour diagnosis and treatment [4]. FAP-inhibitors (FAPI) are caused in tumours with characteristics of high uptake and very low accumulation in normal tissues and rapid circulatory clearance [5]. Studies have shown that [^{68}Ga]Ga-DOTA-FAPI-04 positron emission tomography/computed tomography (PET/CT) has advantages in the detection of initial staging,

recurrence, and metastasis of some tumours [6-8].Some studies reported that [^{68}Ga]Ga-DOTA-FAPI-04 PET/CT has limited research value in the recurrence and metastasis of DTC[7,9], however,the sample size of the above-mentioned literature studies is small. Therefore, the purpose of this study is to compare [^{68}Ga]Ga-DOTA-FAPI-04 PET/CT and[^{18}F]FDG PET/CT for the detection of recurrence and metastasis of DTC.

Materials And Methods

Selection of patients

This prospective study was approved by our hospital's Institutional Review Board (AHSWMU-2020-035). After approval and determination of the eligibility of the patient by an oncologist and was conducted in accordance with the 1964 Helsinki Declaration and its subsequent revisions or similar ethical standards. between March 2020 to July 2020, patients were enrolled in our institute for participation in this study. The inclusion criteria were as follows: (i)All patients who underwent total thyroidectomy, with or without neck lymph node dissection, followed by oral iodine-131 (^{131}I) for ablative treatment; (ii)Elevated Tg and/or anti-thyroglobulin autoantibody (TgAb) level at clinical follow-up, and indication of lymph node metastasis on neck colour Doppler ultrasound or clinically suspected metastasis; (iii)postoperative time>6 months; (iv)age>18 years old; (v)Patients who received [^{68}Ga]Ga-DOTA-FAPI-04 PET/CT additionally; (vi)Patients who provided informed consent (signed by the participant, parent, or legal representative) and consent in accordance with the guidelines of the clinical research ethics committee. The exclusion criteria were: (i)Patients during pregnancy and lactation; (ii)Patients with liver and kidney dysfunction; (iii)Study participants, parents, or legal representatives who were unable or unwilling to provide written informed consent. Criteria for diagnosis: Histopathological results were considered as the gold standard for diagnosis. In case of no pathological diagnosis, follow-up results, including imaging, laboratory examination results, and clinical comprehensive judgment (follow-up time ≥ 6 months) were considered. Recurrence or metastasis was diagnosed during follow-up based on the following criteria: (i)Typical imaging features of malignancy on CT, MRI, and neck ultrasound; (ii)Malignant progression of the lesion occurring in the later follow-ups, and gradual increase in serum Tg or TgAb levels;□iii□After treatment with ^{131}I, radiotherapy, or targeted therapy, the size of the lesion reduced significantly or the disease stabilized without further progression.

All patients underwent both PET/CT scans within 3 days.

Preparation of [^{18}F]FDG and [^{68}Ga]Ga-DOTA-FAPI-04

[^{18}F]FDG was produced according to standard methods. ^{18}F was produced by Siemens eclipse HP/RD cyclotron at our institute, and [^{18}F]FDG was synthesized using FDG-N automatic synthesis module of Beijing Paite Company. FAPI-04 precursor (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid; 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraaceticacid, DOTA) -FAPI-04 was purchased from CSBio (Shanghai, China). The radio labelling of [^{68}Ga]Ga-DOTA-FAPI-04wascarried out according to the literature

protocol. Ultraviolet high performance liquid chromatography and radio frequency high performance liquid chromatography were used for quality control of the radioactive composition. The radiochemical purity of [^{18}F]FDG and [^{68}Ga]Ga-DOTA-FAPI-04wasmore than 95% and the final product was sterile and pyrogen-free.

PET/CT imaging

The dose of [^{18}F]FDG/[^{68}Ga]Ga-DOTA-FAPI-04was injected intravenously (FDG 3.7 MBq [0.1 mCi]/kg; FAPI was 1.8-2.2 MBq [0.05-0.06 mCi]/kg). Before the intravenous administration of[^{18}F]FDG PET/CT, the patient was required to fast for more than six hours, maintain blood glucose less than 11.1moml/L, and take rest for one hour. The PET/CT scanner of China United Imaging Corporation was then used for imaging. The above preparations were not required before a[^{68}Ga]Ga-DOTA-FAPI-04 PET/CT scan. First CT scan (scanning range from the top of the skull to the middle and lower 1/3rd of the femur) was done at a tube voltage of120kv, tube current of 100mA, and layer thickness of5.0mm; followed by PET scan in 3D acquisition modeat 6-8 beds ([^{18}F]FDG 4.0-4.5 min/bit; [^{68}Ga]Ga-DOTA-FAPI-04: 3.0-3.5min/bit). The PET image was reconstructed by OSEM iterative method.

PET/CT imaging review

In order to prevent bias, image 1 group consisted of all [^{18}F]FDG PET/CT scans and image 2 group consisted of all [^{68}Ga]Ga-DOTA-FAPI-04 PET/CT scans (each group consisted of two different nuclear medicine doctors with deputy senior titles). In the absence of other clinical in vestigations, double-blind reading was carried out in the case of image data and a consensus was reached through consultation on differingopinions. The lesions with activity exceeding that of the adjacent background tissue were marked as positive and the cross-section with the highest metabolism was selected to record the maximum standardized uptake value (SUVmax) of the lesion. If the number of lesions in a certain organ was not clear on recording the SUVmax, mean, and sum of the positive lesions at each site scope, the organ was excluded. According to the stage and anatomical structure of differentiated thyroid cancer, the lymph nodes weredivided into cervical area VI (pretracheal, paratracheal, and prelaryngeal lymph nodes), and other areas of the neck (I-V Regional lymph nodes or supraclavicular fossa), mediastinum (including epicardium, bilateral internal mammary area, etc.), axilla, abdomen (including para-aortic, hilar, retroperitoneum, abdominal cavity), and inguinal lymph nodes. Brain, lung, liver, bone, and other involvements were classified as separate parts.

Statistical analyses

All statistical analysis was done using SPSS 25.0 software. Continuous data were expressed as mean ± standard deviation and categorical data were expressed as percentages. The Wilcoxon paired signed-rank test was used to compare the SUVmax values of [^{18}F]FDG and [^{68}Ga]Ga-DOTA-FAPI-04, and to assess if their difference was statistically significant. A comparison of the results of PET/CT visual interpretation with the results of histopathology (biopsy or surgery) was used as the gold standard for diagnosis. The

detection rate was compared using Fisher's exact probability method. Comparisons of the sensitivity, specificity, accuracy, and positive- (PPV) and negative predictive value (NPV) of [^{18}F]FDG and [^{68}Ga]Ga-DOTA-FAPI-04 were done for evaluation of the diagnostic effect. Two-tailed *p* values of less than 0.05 were considered statistically significant.

Results

Characteristics of the patients

Between March 2020 to July 2020, a total of 46 DTC patients were enrolled in the initial stage of the study; of these 11 patients were excluded from analysis due to the following reasons:7 patients were unwilling to undergo further [^{68}Ga]Ga-DOTA-FAPI-04 PET/CT examination, while 4 patient shad no pathological results and/or had a follow-up time of less than 6 months. In the end, a total of 35 DTC patients (12 males, 23 females) were enrolled, 17 patients (17/35, 48.57%) had high serum Tg level or progressive increase for more than half a year, three patients had high TgAb level (3/35, 8.57 %), while 15 cases had suspected lymph node metastasison neck colour Doppler ultrasound (15/35, 42.86%); average age of participants was 52.6 years (age range 27-76 years); pathology type included were: 32 cases of papillary carcinoma and three cases of follicular carcinoma. The previous cumulative dose of ^{131}I was 100~750mci. According to the later pathological organization and follow-up results, out of 35 DTC patients,including14 cases of lymph node metastasis (14/35, 40.00%), 10 cases of lung metastasis (10/35, 28.57%), three cases of bone metastasis (3/35, 8.57%),two cases of other (pleural) problems(2/35, 5.71%), and one case of brain metastasis (1/35, 2.86%), ,one case of liver metastasis (1/35, 2.86%). 24 cases of metastasis were finally confirmed (4 males and 17 females, aged 27-71 years, average 54.3±11.0 years). A representative case showing the different SUVs of differentiated thyroid cancer metastasis in the two types of scans is presented in Fig.1.

Adverse events

All patients tolerated the [^{68}Ga]Ga-DOTA-FAPI-04 PET/CT well. There were no signs of drug-related pharmacologic effects or physiological responses. All observed vital signs (including blood pressure, heart rate, and body temperature)remained within normal limits during and after [^{68}Ga]Ga-DOTA-FAPI-04 PET/CT. None of the patients reported any abnormal symptoms.

Comparison of semi-quantitative parameters and diagnostic performance of [^{68}Ga]Ga-DOTA-FAPI-04PET/CT and [^{18}F]FDGPET/CT for lymph node metastasis

In this study, very few patients showed positive lymph nodes in the inguinal and axillary areas, hence, PET-positive lymph nodes were divided depending on 4 locations: the central area of the neck (pretracheal, paratracheal, and prelaryngeal lymph nodes), other areas of the neck (the I-V area lymph nodes or supraclavicular fossa), mediastinum (including epicardium, internal mammary area, etc.), and abdomen (including abdominal aorta, hilar, retroperitoneum, abdominal cavity). As shown in Table 1,

there was no statistically significant difference in SUVmax uptake in positive lymph nodes between the two groups (*P*=0.054). Specific analysis of SUVmax uptake of each regional lymph node found that the uptake of [^{18}F]FDG and [^{68}Ga]Ga-DOTA-FAPI-04 SUVmax in the central neck area was basically the same, while the uptake of [^{18}F]FDG and [^{68}Ga]Ga-DOTA-FAPI-04 in other regional lymph nodes had statistically different significance. Among these, lymph nodes in lateral neck and mediastinum had a significantly higher uptake of [^{18}F]FDG than that of [^{68}Ga]Ga-DOTA-FAPI-04, while the uptake of latter in the abdominal area was significantly higher than that of the former.

Among the 15 patients, 71 suspected lymph node metastases were found and finally 39 lymph nodes of 14 patients were confirmed as metastatic by pathology or at later follow-up. Although the diagnostic sensitivity and negative predictive value of [^{68}Ga]Ga-DOTA-FAPI-04 PET/CT were not statistically different from that of[^{18}F]FDG PET/CT(c^2=0.083，c^2=2.781，*P*＞0.05), the specificity, accuracy, and positive predictive value were all high compared with that of[^{18}F]FDG PET/CT, and the difference wasstatistically significant (c^2=16.583，c^2=9.910，c^2=7.548，c^2=2.781，*P*＜0.05) (Table 2). However, the detection rate difference between the two groups was not statistically significant (P=0.774) (Table 3). A representative case showing the different SUVs of lymph nodes metastasis in the two types of scans is presented in Fig.2.

Comparison of semi-quantitative parameters and diagnostic performance of distant metastases between [^{68}Ga]Ga-DOTA-FAPI-04 PET/CT and [^{18}F]FDG PET/CT

The SUVmax uptake of [^{68}Ga]Ga-DOTA-FAPI-04 distant metastases were higher than that of [^{18}F]FDG, and the difference was statistically significant (P<0.001). Specific analysis of the comparison of the detection of metastases in each organ showed that although there was only one case of brain metastasis, the absolute value of SUVmax in brain metastasis [^{68}Ga]Ga-DOTA-FAPI-04 was lower than that of [^{18}F]FDG (0.89:2.08). However, uptake of [^{68}Ga]Ga-DOTA-FAPI-04was lower in normal brain tissue, and its tumour/background ratio was higher than that of [^{18}F]FDG, which led to a higher contrast of the image and easier detection. In the detection of bone metastases, [^{68}Ga]Ga-DOTA-FAPI-04 intake SUVmax was significantly higher than [^{18}F]FDG intake, and the difference was statistically significant (*P*<0.001) (Table 1). The value of [^{68}Ga]Ga-DOTA-FAPI-04 in the detection of other metastases is basically the same as that of [^{18}F]FDG.

Among the 17 patients who had high serum Tg level or progressive increase for more than half a year, 77 suspected distant metastases were found, and finally a total of 55 lesions in 12 patients were confirmed to be metastatic by pathology or at later follow-up. Compared with [^{68}Ga]Ga-DOTA-FAPI-04 PET/CT, [^{18}F]FDG PET/CT has higher specificity, accuracy, and positive and negative predictive value for distant metastasis, but the difference is not statistically significant (c^2=0.440, c^2= 4.956,c^2=0.013, c^2=1.194, c^2=2.618, *P*>0.05) (Table 2). [^{68}Ga]Ga-DOTA-FAPI-04 has no significant difference in the detection rate of distant metastases compared with [^{18}F]FDG (*P*=0.742). However, [^{68}Ga]Ga-DOTA-FAPI-04 can detect more

bone metastases than [^{18}F]FDG. The difference between the two groups was statistically significant (p=0.049), (Table 3). In this study, [^{68}Ga]Ga-DOTA-FAPI-04 had more false positives in the diagnosis of distant metastasis than [^{18}F]FDG. The false positives included twocases of arthritis, twocases of breast fibromatosis, one case each of esophagitis, mumps, pancreatitis, and benign bone lesions.

Table 1 Comparison of semi-quantitative parameters of [^{68}Ga]Ga-DOTA-FAPI-04 and [^{18}F]FDG on lymph node and distant metastasis

Area	Tracer	Positive lesions*	SUV mean	SUV range	*P value*
Central neck	FAPI	5	5.39±1.90	3.43-7.50	0.735
	FDG	5	7.05±5.87	2.29-17.14	
Lateral neck	FAPI	10	8.38±6.03	2.06-18.86	0.019
	FDG	17	9.96±6.27	3.18-27.38	
Mediastinum	FAPI	14	4.56±2.30	1.09-9.67	0.026
	FDG	24	6.26±10.55	2.36-54.95	
Abdomen	FAPI	6	7.82±2.67	4.41-11.03	0.028
	FDG	4	3.21±0.67	2.47-3.98	
Nodal metastasis	FAPI	35	6.15±4.10	1.09-18.86	0.054
	FDG	50	7.36±5.07	2.29-54.95	
Brain	FAPI	1	-	0.89	-
	FDG	1	-	2.08	
Lung	FAPI	24	3.29±2.34	0.73-17.06	0.757
	FDG	28	3.40±3.35	2.01-14.75	
Liver	FAPI	1	-	18.8	-
	FDG	1	-	4.7	
Bone	FAPI	30	6.98±5.78	1.45-22.77	0.000
	FDG	21	2.94±2.18	1.43-10.02	
Other	FAPI	6	9.33±3.64	4.77-14.49	0.116
	FDG	3	6.17±4.21	2.48-13.79	
Distant metastasis	FAPI	60	5.64±4.89	0.73-22.77	0.000
	FDG	48	3.51±3.13	0.65-14.75	

*Calculate the number of [^{68}Ga]Ga-DOTA-FAPI-04 and [^{18}F]FDG PET/CT positive lesions in patients with countable lesions; the number of lesions with many to countless lesions are excluded from the analysis, *p* Comparison of the SUVmax value of the number of positive lesions with the two imaging agents.

Table 2 Comparison of the efficacy of [^{68}Ga]Ga-DOTA-FAPI-04 and [^{18}F]FDG in diagnosing metastases

Area	Tracer	Sensitivity □%□	Specificity □%□	Accuracy □%□	PPV□%□	NPV□%□
Lymph nodes	FAPI	82.05	84.38	83.10	86.49	79.41
	FDG	**79.49**	**34.38**	**60.56**	**59.62**	**57.89**
Distant metastasis	FAPI	91.07	50.00	80.52	82.26	73.33
	FDG	89.09	81.82	87.01	92.45	75.00

Table 3 Comparison of the detection rates of [^{68}Ga]Ga-DOTA-FAPI-04 PET/CT and [^{18}F]FDG PET/CT in metastases

Area	^{68}Ga-FAPI-04 PET/CT	^{18}F-FDG PET/CT	*p*
Lymph nodes	82.05%(32/39)	79.49%(31/39)	0.774
Distant metastasis	91.07%(51/55)	89.09%(49/55)	0.742
Bone metastasis	96.00%(24/25)	72.00%(18/25)	0.049

The lesions with [^{18}F]FDG and/or [^{68}Ga]Ga-DOTA-FAPI-04 uptake were compared with whole body imaging using atherapeutic dose or diagnostic dose of ^{131}I. An interesting phenomenon was found in this study. Acomparison of SUVmax measuredforthe two imaging agents in lung metastases without iodine uptake showed that when the same lesion had a higher [^{18}F]FDG uptake, it was only on [^{68}Ga]Ga-DOTA-FAPI-04. On the contrary, it showed mild uptake in the lesion on [^{18}F]FDG, and a higher uptake of[^{68}Ga]Ga-DOTA-FAPI-04. In addition, in the twocases of pleural metastases in this study, a comparison of the imaging agents in the two groups, the SUVmax uptake showed the same imaging characteristics as the lung metastases, that is, the lesions with high [^{68}Ga]Ga-DOTA-FAPI-04 uptake had lower [^{18}F]FDG uptake. While [^{68}Ga]Ga-DOTA-FAPI-04 showed mild uptake lesions with significantly increased [^{18}F]FDG uptake, there was no such observation in lymph node metastases and other distant metastases. A representative case showing the different SUVs of lung metastasis in the two types of scans is presented in Fig.3. Fig.4.

Discussion

The purpose of this prospective study was to compare the potential value of [^{68}Ga]Ga-DOTA-FAPI-04 PET/CT and [^{18}F]FDG PET/CT in the detection of DTC disease metastases.

Differentiated thyroid cancer (DTC) is the commonest thyroid cancer (>90% of all thyroid cancers). In the majority of cases, the prognosis is excellent with 97% cause-specific 10-year survival. Because DTC is not sensitive to radiotherapy and chemotherapy, ^{131}I is the first choice for adjuvant therapy after surgery, especially for patients with metastases [10]. However, about 33%-50% of patients with DTC metastasis eventually progress to radioiodine refractory during the course of the disease. Such patients generally have a poor prognosis, with a survival period of only 3-6 years [11]. In order to optimize the benefit of each patient's treatment, while minimizing the treatment risks associated with radiation exposure, early identification of suitable treatment options for DTC patients and formulation of appropriate treatment strategies from a long-term perspective should be done. It will help improve long-term expectations of DTC patients.

[^{18}F]FDG PET imaging plays an essential role in the diagnosis and management of varieties of malignancy; [^{18}F]FDG PET/CT is suitable for DTC patients with ^{131}I-WBS negative and elevated Tg [12]. In contrast, patients with well-differentiated DTC subtypes have lower sensitivity [13]. [^{68}Ga]Ga-DOTA-FAPI-04 has the advantages of shorter half-life and less injection dose, which can shorten the waiting and scanning time of patients after intravenous injection, and reduce the burden of inspection radiation [5]. Therefore, in the case of limited use of [^{18}F]FDG, use of [^{68}Ga]Ga-DOTA-FAPI-04 for the diagnosis of DTC seems to be a promising new method. Kratochwil *et al.* [5] found that the intake of [^{68}Ga]Ga-DOTA-FAPI-04in DTC cases was mild (average SUVmax<6). In this study, whether it was lymph node metastasis or distant metastasis, the uptake of [^{68}Ga]Ga-DOTA-FAPI-04wasin line with literature reports. Because the expression of FAP is closely related to the aggressiveness of tumours [14], considering that the reason for low uptake is related to malignant tumours with indolent progression, the diagnostic value of semi-quantitative parameter analysis in DTC is not higher than that of [^{18}F]FDG. However, because [^{68}Ga]Ga-DOTA-FAPI-04 has a better tumour/background ratio, it has certain advantages in the detection of lesions and can be used as a supplementary imaging method for DTC.

In this study, the number of positive lymph nodes detected by [^{68}Ga]Ga-DOTA-FAPI-04 was less than those detected by[^{18}F]FDG, but there was no statistically significant difference in the detection rate between the two. The specificity, accuracy, and positive predictive value of [^{68}Ga]Ga-DOTA-FAPI-04 lymph node diagnosis were higher than that of [^{18}F]FDG, and the differences were statistically significant. According to the results of later pathological tissue biopsy and follow-up, it is considered that more inflammatory lymph nodes take up FDG, resulting in lower specificity. This may be because DTC lymph node metastasis is usually located in the neck, which is also a popular area for inflammatory lymph nodes. Therefore, the false positive rate of [^{18}F]FDG increases, which is consistent with previous literature reports [15]. Although it is reported in literature that inflammation can also lead to the false positive uptake of [^{68}Ga]Ga-DOTA-FAPI-04, the false positive rate of [^{68}Ga]Ga-DOTA-FAPI-04 uptake in inflammatory lymph nodes in this study is lower than that of [^{18}F]FDG, which may suggest that inflammation and fibrosis are not necessarily interconnected. Because lymph node metastasis is the

most common form of DTC metastasis, it seems that [^{68}Ga]Ga-DOTA-FAPI-04 is more suitable for follow-up of DTC lymph node metastasis than [^{18}F]FDG.

The uptake of ^{18}[F]FDG is closely related to the degree of differentiation and proliferation of tumours. The lower the degree of differentiation, the higher the uptake of FDG. Previous studies have shown that radioactive iodine therapy(RAI) is inversely proportional to the accumulation of [^{18}F]FDG in cancer cells (i.e., "trigger phenomenon") [16]. According to the relationship between the uptake of [^{68}Ga]Ga-DOTA-FAPI-04 and [^{18}F]FDG by DTC distant metastases, the analysis of RAI and the accumulation of [^{68}Ga]Ga-DOTA-FAPI-04 in cancer cells has a similar “triggering phenomenon”. However, [^{18}F]FDG and [^{68}Ga]Ga-DOTA-FAPI-04 have opposite uptake in lung metastases and pleural metastases, that is, when the same lesion has a higher [^{18}F]FDG uptake, the uptake of [^{68}Ga]Ga-DOTA-FAPI-04 is lower, and vice versa. Considering this opposite phenomenon, it may be considered that different tumour cells in metastases have different levels of differentiation during the dedifferentiation process (that is, different degrees of different metastases occur in the same patient). Functional hypothesis can explain this phenomenon. The low glucose metabolism and radioactive iodine uptake of normal DTC cells gradually turn into corresponding high glucose metabolism during the course of disease progression, suggesting that cancer cells have gradually increased aggressiveness, leading to a gradual increase in FAP expression, and increased intake of [^{68}Ga]Ga-DOTA-FAPI-04. Therefore, the differentiation state of DTC can also be inferred based on the degree of uptake of [^{68}Ga]Ga-DOTA-FAPI-04 in the lesion. Different from [^{18}F]FDG uptake, the lesions with high [^{68}Ga]Ga-DOTA-FAPI-04 uptake may be cells that are in the initial stages of the dedifferentiation process. It is considered that the prognosis of these cells is better than that of the lesions with high [^{18}F]FDG uptake. Perhaps it has a higher guiding effect on the suitability of ^{131}I treatment. In DTC, [^{68}Ga]Ga-DOTA-FAPI-04 uptake is not mutually exclusive with [^{18}F]FDG uptake, which may represent the different differentiation states of DTC cancer cells, which helps to distinguish thepatients who still benefit from ^{131}I treatment.

In this study, [^{68}Ga]Ga-DOTA-FAPI-04 and [^{18}F]FDG PET/CT have the same diagnostic performance for distant metastases, but the former has better diagnostic value for bone metastases than the latter. [^{68}Ga]Ga-DOTA-FAPI-04 detected almost all bone metastases (96.00%, 24/25) , and the detection of bone micrometastases was more sensitive, while [^{18}F]FDG detected only (72.00%, 18/25)of the metastases. In addition, in bone metastases, the uptake of [^{68}Ga]Ga-DOTA-FAPI-04 in SUVmax was significantly higher than that of [^{18}F]FDG, considering that the high detection rate of lesions is correlated with the higher uptake of [^{68}Ga]Ga-DOTA-FAPI-04. [^{68}Ga]Ga-DOTA-FAPI-04 PET/CT surprisingly detected several small pelvis lesions highly suspected of metastases in one patients which were missed by[^{18}F]FDG PET/CT in this study. The reasons may be related to the component of activated fibroblasts and/or myofibroblasts in the osseous lesions [17]. A recent study also reported more bone metastases with higher uptake were observed on [^{68}Ga]Ga-DOTA-FAPI-04 PET/CT than [^{18}F]FDG in Some neoplastic diseases [18-19].Therefore, [^{68}Ga]Ga-DOTA-FAPI-04 may be superior to [^{18}F]FDG in detecting small bone metastases.Finally, although the absolute value of [^{68}Ga]Ga-DOTA-FAPI-04 SUVmax is lower than that

of[^{18}F]FDG (0.89:2.08), [^{68}Ga]Ga-DOTA-FAPI-04 PET resulted in images with exceptionally clear tumor delineation and higher image contrast than [^{18}F]FDG PET, [^{68}Ga]Ga-DOTA-FAPI-04 PET shows much higher tumor-to-background contrast of primary tumor and reveals more metastatic lesions, the former has good tumour/background contrast and better contour imaging (Fig.5), which can improve the detection of brain metastases efficacy. Furthermore, compared to[^{18}F]FDG, the lower hepatic background of [^{68}Ga]Ga-DOTA-FAPI-04 may be a promising feature for evaluation of liver metastases(Fig.1) as Shi *et al*[20] research reported.

The DOTA chelating agent contained in [^{68}Ga]Ga-DOTA-FAPI-04 tracer ligand can be used for various therapeutic radionuclide labelling. At present, the preclinical study of the ^{177}Lu-labelled internalization antibody against FAP has been tested in preclinical experiments and proved to be effective [21]. Targeting [^{68}Ga]Ga-DOTA-FAPI-04 also provides a promising new method for the treatment of these FAP-positive tumours. Therefore, further research on the use of [^{68}Ga]Ga-DOTA-FAPI-04 PET/CT in DTC may result in its greater utility in the future.

However, [^{68}Ga]-FAPI-04 is not more tumour-specific than [^{18}F]FDG. It has been reported in literature that [^{68}Ga]Ga-DOTA-FAPI-04 false positive uptake may occur in patients with fibrosis or fibrotic activity [22]. In this study, the false positive intake of [^{68}Ga]Ga-DOTA-FAPI-04 PET/CT included: (i) inflammatory diseases, such as arthritis and pancreatitis; (ii) fibroproliferative diseases such as breast fibroids; and (iii) bone benign degeneration. Therefore, the image analysis of patients with tumours and inflammation should integrate with clinical results. In addition, studies have shown that fibrosis induced after radiotherapy and surgery also shows strong uptake of [^{68}Ga]Ga-DOTA-FAPI-04 [23]. Therefore, [^{68}Ga]Ga-DOTA-FAPI-04 PET/CT is not recommended in the postoperative or early stage of radiotherapy and chemotherapy.

Limitations

There are several limitations to this study. (i) There were very few cases of distant metastasis among the patients included in this study, especially lack of patients with other metastatic sites. thus, the superior values for sensitivity and specificity of FAPI PET could differ in other Metastatic lesions. Thus, he sample size of the study will be further expanded in the follow-up study to make the detection of metastases more valuable; (ii) The number of patients included in this study was small, therefore, the SUVmax of[^{68}Ga]Ga-DOTA-FAPI-04 intake of patients with different DTC subtypes that was analysed for correlation may not be correct. The difference in statistical significance of SUVmax intake of patients with different differentiation status needs to be further studied. (iii) The other limitation was that not all positive findings were confirmed histopathologically. Therefore, all the results must be confirmed in a greater number of patients and biopsy-proven lesions.

Conclusion

[^{68}Ga]Ga-DOTA-FAPI-04 PET/CT is of great value in distinguishing whether the lymph nodes of DTC patients are metastatic or benign lesions, thereby, reducing unnecessary panic and invasive procedures (such as ultrasound-guided Fine-needle aspiration(FNA)); Furthermore, the uptake of [^{68}Ga]Ga-DOTA-FAPI-04 in bone metastases was significantly higher than that of [^{18}F]-FDG, demonstrating a larger extent of the lesions and it has advantages over [^{18}F]FDG PET/CT in the detection of distant metastases in small bones. Its ability to detect other distant metastases is equivalent, and it can be used as a supplementary imaging method for DTC.

Declarations

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethics approval All procedures involving human participants were performed in accordance with the ethical standards of the institutional committee, as well as the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This article does not contain any animal experiments.

Consent to participate Informed consent was obtained from all participants included in the study

Consent for publication Informed consent was obtained from all participants included in the study

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Figures

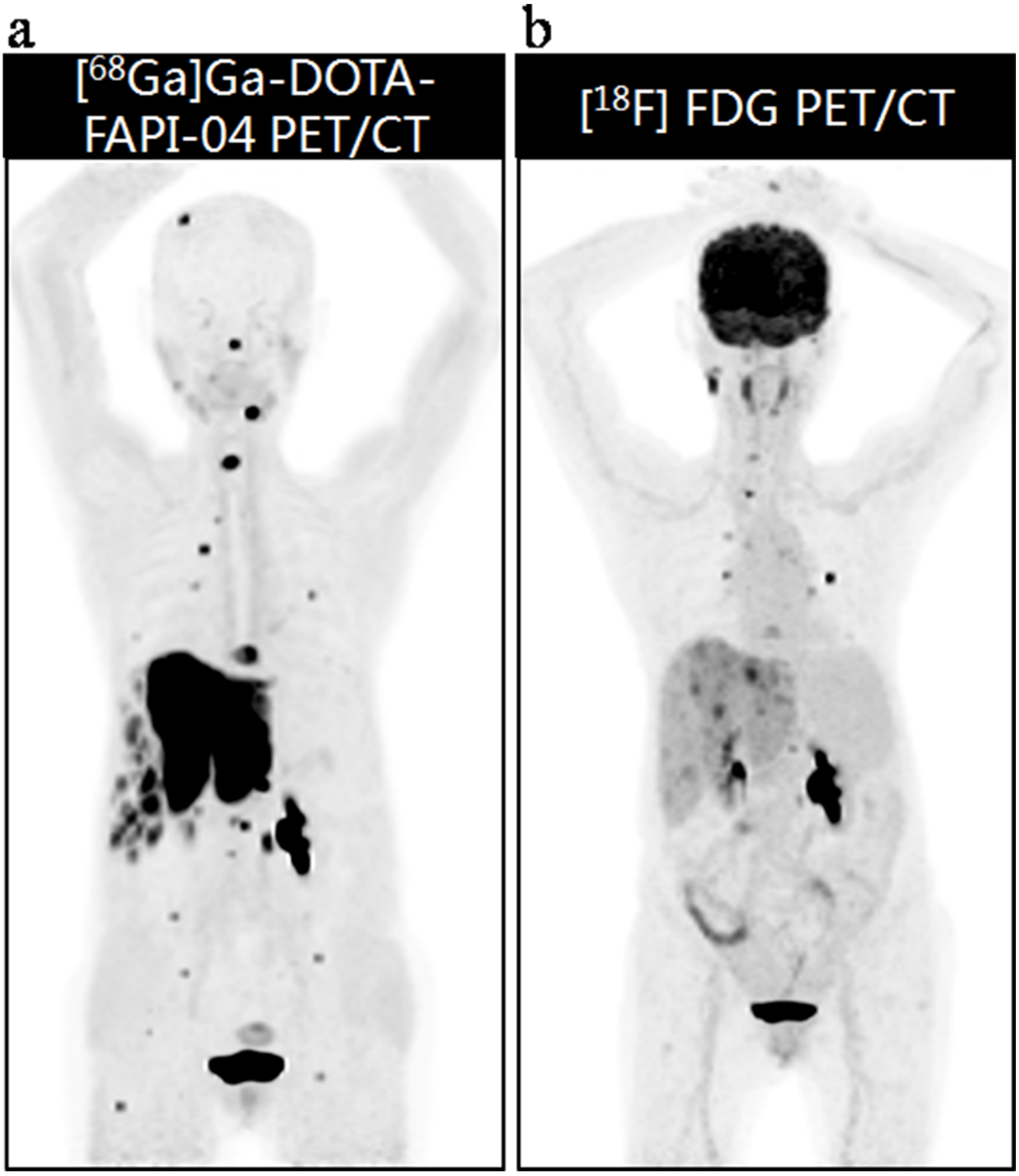

Figure 1

A 75-year-old woman, 15+ years after surgery for papillary thyroid carcinoma，Serum Tg>500ng/ml, received 131I treatment for recurrent thyroid cancer with metastases 1 year ago. she underwent a [18F]FDG PET/CT scan and a [68Ga]Ga-DOTA-FAPI-04 PET/CT scan for evaluation. The MIP image (a) [68Ga]Ga-DOTA-FAPI-04 PET/CT demonstrated multiple FAPI-avid foci in the lung (SUVmax 5.2), bones (SUVmax 10.4), liver (SUVmax 18.8), enlarged retroperitoneal lymph node (SUVmax, 5.6).The MIP image

(b) [18F]FDG PET/CT demonstrated multiple FDG-avid foci in the lung (SUVmax 10.4), bone(SUVmax 3.2) , liver (SUVmax 4.7) and retroperitoneal lymph node with low uptake (SUVmax 1.5). the tracer uptake on [68Ga]Ga-DOTA-FAPI-04 imaging was higher to that on [18F]FDG PET/CT in liver, bones and lymph node and lower to that in [18F]FDG PET/CT in lung. and multiple small bone metastases were detected on the pelvic bone and bilateral upper femur on the [68Ga]Ga-DOTA-FAPI-04 , and on the [18F]FDG Corresponding parts did not see the exact increase in imaging agent uptake.

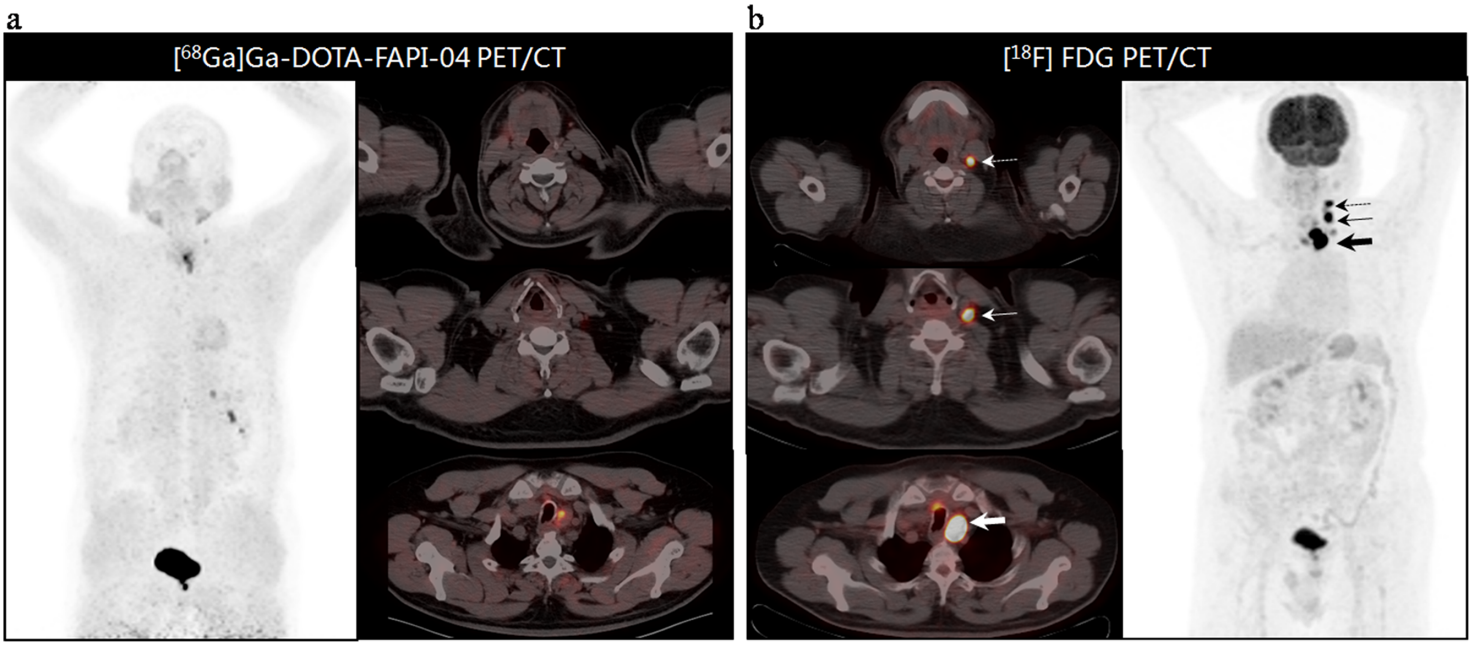

Figure 2

A 63-year-old man, 1+ years after surgery for papillary thyroid carcinoma，Serum Tg 210.5ng/ml. he underwent a [18F]FDG PET/CT scan and a [68Ga]Ga-DOTA-FAPI-04 PET/CT scan for evaluation. The MIP image (a) [68Ga]Ga-DOTA-FAPI-04 PET/CT demonstrated FAPI-avid foci in the upper trachea lymph node with uptake(SUVmax 5.2).The MIP image (b) [18F]FDG PET/CT demonstrated multiple FDG-avid foci in the Left neck lymph node(small arrow SUVmax 10.4), the upper trachea lymph node with Strong uptake (large arrow, SUVmax 3.2). (highly suggestive of metastatic lymph nodes), So a second neck lymph node dissection was performed, Postoperatively, it was confirmed that only the paratracheal lymph nodes were metastatic lymph nodes.

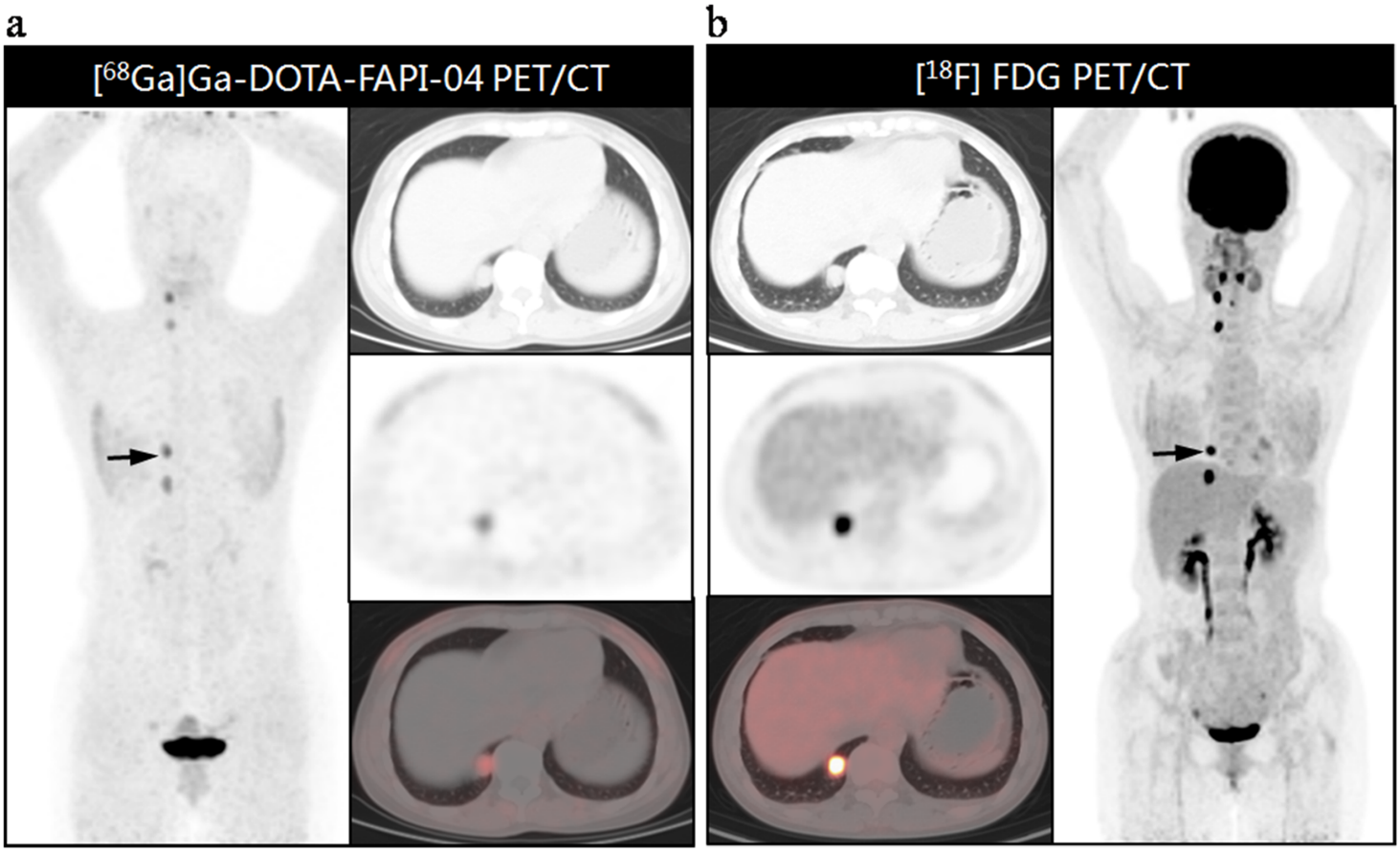

Figure 3

A 48-year-old woman, 10+ years after surgery for papillary thyroid carcinoma. Tg 32.02ng/ml. On [68Ga]Ga-DOTA-FAPI-04 PET/CT and [18F]FDG PET/CT maximum intensity projection (MIP) and axial maps, both lungs can be scattered in round nodules of different sizes with increased imaging agent uptake. [68Ga]Ga-DOTA-FAPI-04 showed only mild uptake (a), and significant uptake in [18F]FDG (b)

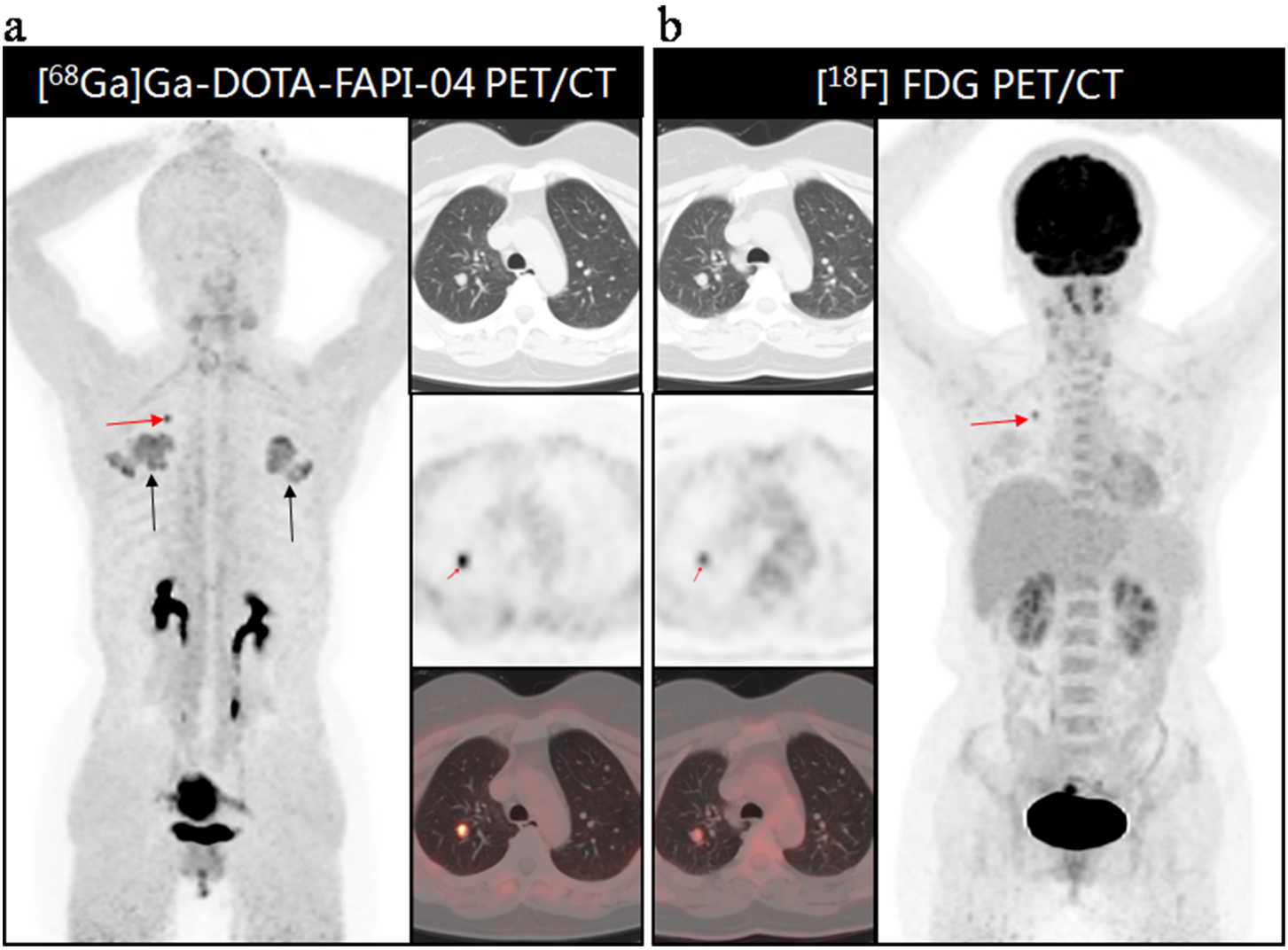

Figure 4

A 48-year-old woman, 1+ year after surgery for papillary thyroid carcinoma, found aright upper lobe node on [68Ga]Ga-DOTA-FAPI-04 PET/CT and [18F]FDG PET/CT maximum intensity projection (MIP) and axial maps.In theshadow of solid nodular tissue, [68Ga]Ga-DOTA-FAPI-04 uptake (a, red arrow) is more obvious than that of [18F]FDG (b, red arrow), postoperative pathology confirmed thyroid cancer lung metastasis. The flaky symmetrical [68Ga]Ga-DOTA-FAPI-04 uptake of the bilateral breast is increased (a, black arrow), and benign breast disease (mammary hyperplasia) is considered after Ultrasonography.

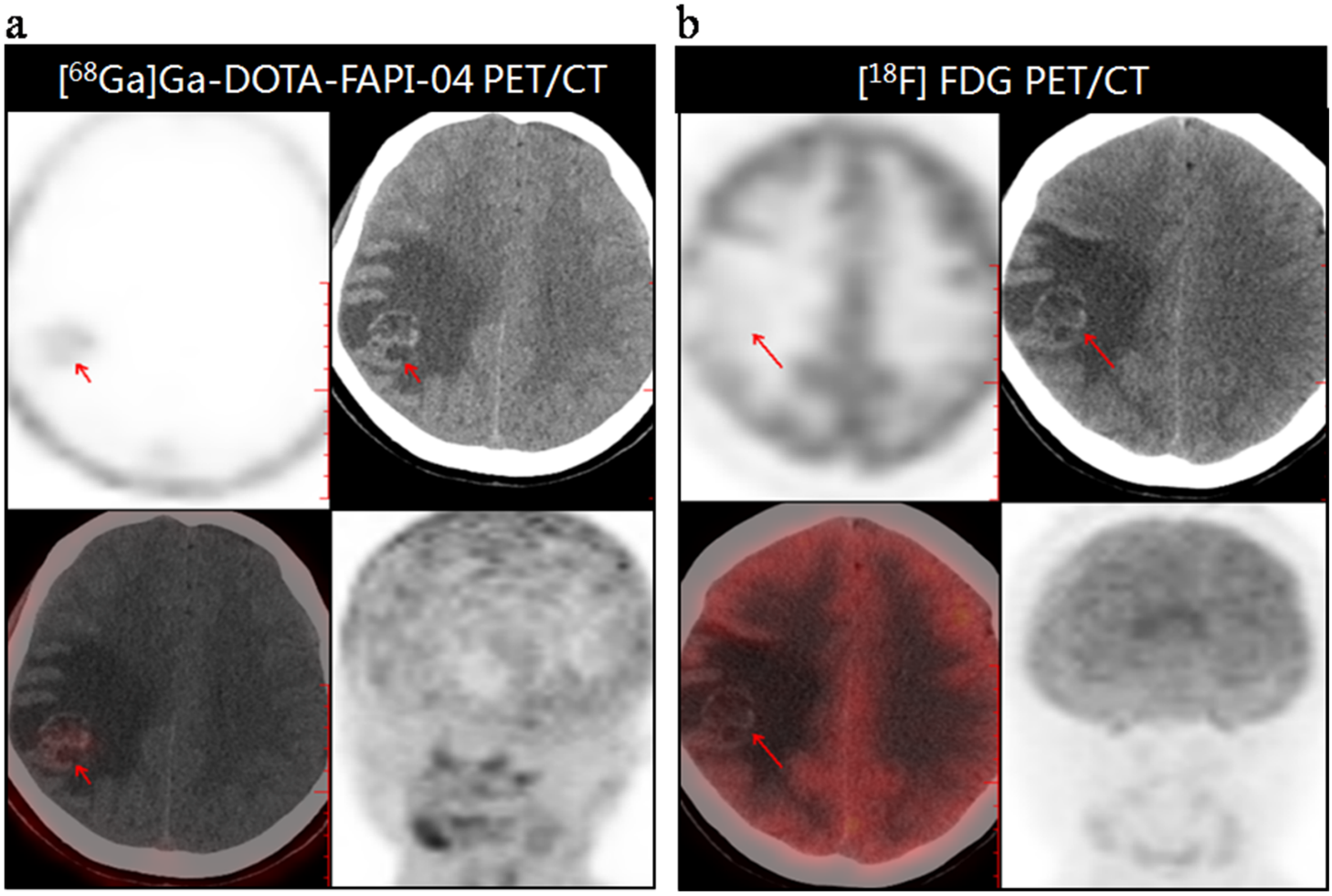

Figure 5

A 49-year-old woman, 20+ years after surgery for papillary thyroid carcinoma. Tg>500ng/ml.[68Ga]Ga-DOTA-FAPI-04 PET/CT axial map (a, red arrow) and [18F]FDG PET/CT axial map (b, red arrow) were done three days apart and the right half was visible. A soft tissue nodule in the centre of the oval, accompanied by light uptake of imaging agent, was confirmed to be a brain metastasis based on the later enhanced MRI and clinical manifestations.