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Detecting radiation esophagitis using ^{18}F-FAPI-04 PET/CT in patients with LA-ESCC treated with concurrent chemoradiotherapy

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Abstract

Purpose This prospective study examined whether ^{18}F-AlF-NOTA-fibroblast activation protein inhibitor (FAPI)-04 (denoted as ^{18}F-FAPI-04) positron emission tomography/computed tomography (PET/CT) can detect the development and severity of radiation esophagitis (RE) in patients with locally advanced esophageal squamous cell carcinoma (LA-ESCC) treated with concurrent chemoradiotherapy.

Materials and methods From June 2021 to March 2022, images were collected from LA-ESCC patients who underwent ^{18}F-FAPI-04 PET/CT examinations before and during radiotherapy. The development of RE was evaluated weekly according to Radiation Therapy Oncology Group criterion. The target-to-background ratio in blood (TBR_{blood}) was analyzed at each time point and correlated with the onset and severity of RE. Factors that predicted RE were identified by multivariate logistic analyses.

Results Thirty patients were evaluated. Significantly higher TBR_{blood} (during radiotherapy, $P=0.003$) and change in TBR_{blood} compared with pre-RT (ΔTBR_{blood}, $P=0.002$) were observed in patients with RE than patients without RE. Those with grade 3 RE had a significantly higher TBR_{blood} (during radiotherapy, $P=0.003$) and ΔTBR_{blood} ($P=0.003$) compared with those with RE < grade 3. On multivariate analysis, ΔTBR_{blood} was identified as a significant detection of any grade RE ($P=0.021$) and grade 3 RE ($P=0.038$).

Conclusion The ΔTBR_{blood} on ^{18}F-FAPI-04 PET/CT may be effective at identifying patients with RE, especially grade 3 RE.

Keywords Fibroblast activation protein, Positron emission tomography, Chemoradiotherapy, Esophageal squamous cell carcinoma, Radiation esophagitis

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Introduction

Esophageal cancer is one of the most common malignant tumors of the digestive system globally, ranking seventh in terms of incidence and sixth in mortality overall in 2020 [1, 2]. Squamous cell carcinoma is the main histological type of esophageal cancer among patients in central and Southeast Asia [3], and definitive concurrent chemoradiotherapy (CCRT) is the standard of care currently available for unresectable locally advanced esophageal cancer (LA-ESCC) [4–8]. However, radiation esophagitis (RE) is a common adverse reaction in esophageal cancer patients treated with radiotherapy (RT) [9]. The typical clinical features of RE include dysphagia, odynophagia and substernal pain, which causes great pain to patients and may even interrupt radiotherapy treatment [10]. To our knowledge, there is currently a lack of effective early detection methods for RE in clinical practice.

Fibroblast activation protein (FAP) is a member of the dipeptidyl peptidase (DPP) 4 protein family and has both endopeptidase and DPP activities [11, 12]. Its expression has been shown to increase significantly during tissue modeling and wound healing as well as in diseases such as arthritis, atherosclerosis and different cancers [13–15]. Recent studies have shown that positron emission tomography (PET)/computed tomography (CT) imaging with a tracer targeting FAP, ^{68}Ga-DOTA-FAP inhibitor (FAPI)-04, offers superior diagnostic efficacy in patients with various types of cancer [16–19]. Recent studies also have shown that ^{18}F-FAPI-04 was proven to be safe and to offer high specificity for FAP imaging [20]. In one case report, a patient with esophagitis showed increased ^{68}Ga-FAPI uptake at the site of esophageal thickening [21]. However, the potential value of ^{18}F-FAPI-04 PET/CT imaging for identifying the development of RE has not been established in the literature.

The aim of the present study was to assess whether ^{18}F-FAPI-04 PET/CT can detect RE in patients with LA-ESCC treated with CCRT, and to explore the prediction parameters for RE.

Methods and materials

Patients

This study was an ongoing prospective clinical study that received ethical approval from the Ethics Committee of Shandong First Medical University Affiliated Cancer Hospital (institutional review board approval no. SDZLEC2021-112-02). This manuscript mainly reports a secondary analysis of this prospective trial. Participants were consecutively recruited from June 2021 to February 2022, and 16 of the 30 patients included herein were also included in a previous study [22].

The inclusion criteria were: (a) newly diagnosed ESCC ($T_{3\sim4}N_{0\sim3}M_0$) with no prior treatment; (b) histologically proven ESCC; and (c) consent to undergo ^{18}F-FAPI-04 PET/CT examinations. The exclusion criteria were: (a) pregnancy; (b) start of treatment before the first ^{18}F-FAPI-04 PET/CT examination; (c) additional primary malignancies or severe hepatic and renal insufficiency at the time of examination; (d) and refusal to undergo ^{18}F-FAPI-04 PET/CT scanning.

Imaging protocol

Participants were scanned within 1 week before RT (pre-RT) and after delivery of approximately 40 Gy (during-RT). The during-RT scan was performed once approximately 40 Gy of the total prescribed dose had been delivered, with the intent that a dose to this threshold would provide control of microscopic disease but still leave a reasonable amount of treatment remaining to alter the RT plan to include an additional RT boost. The total RT dose ranged from 50.4 to 69.4 Gy, and intensity-modulated RT was delivered to all patients with X-ray (6 MV). RT was given according to the conventionally fractionated regimen of 1.8–2.0 Gy/fraction for 5 days per week.

^{18}F-FAPI-04 was synthesized as described in recent study [23]. Fasting and blood glucose measurement were not needed before scanning. After intravenous injection of ^{18}F-FAPI-04 (4.81 MBq/kg), patients rested for about 60 min before scanning was performed with an integrated in-line PET/CT system (GEMINI TF Big Bore; Philips Healthcare, Cleveland, OH, USA). Whole-body CT scans were obtained using a low-dose protocol (300 mAs, 120 kV, 512 × 512 matrix, rotation time of 1.0 s, and pitch index of 0.688; reconstruction with a soft-tissue kernel to a slice thickness of 2 mm) for attenuation correction. PET data were acquired in three-dimensional mode using a 200 × 200 matrix with an imaging time of 1 min per bed position. During image acquisition, the patients continued normal shallow breathing. Body-ctac-SB. Lstcln, BioGraph 3D iterative reconstruction software with time-of-flight correction was used for attenuation and correction of PET and CT images.

Image analysis

The attenuation-corrected PET, CT, and fused PET/CT images, which were displayed as coronal, sagittal, and transaxial slices, were viewed and analyzed on a Nuclear Medicine Information System (Beijing Mozi Healthcare Ltd, Beijing, China). All ^{18}F-FAPI-04 PET/CT images were reviewed independently by two experienced nuclear medicine physicians with more than 8 years of nuclear oncology experience.

Multiple planes for the same patient were superimposed via the MIM system to obtain a series of parameters: primary gross tumor volume (GTV, cc), RT dose, maximal esophageal dose, mean esophageal dose, volume of esophagus receiving ≥ 50 Gy (V50), and volume

of esophagus receiving ≥ 60 Gy (V60). PET/CT data for all patients were transmitted to the MIM system. The GTV and esophagus (from cricoid to gastroesophageal junction) were contoured on the first PET/CT, and this area was fused with the second PET/CT. We analyzed the esophageal area delineated after excluding the region within 5 mm of the GTV, and defined it as regions of interest (ROI), to reduce confounding ^{18}F-FAPI-04 PET/CT changes related to tumor response, as shown in Fig. 1.

^{18}F-FAPI-04 PET/CT parameters were generated by the MIM system. ROIs were normalized to the injected dose per kilogram of body weight to derive standardized uptake values (SUVs), which were calculated as: [measured activity concentration (Bq/mL) × body weight (g)]/injected activity (Bq). Normalized SUVs were used to represent FAPI activity in each ROI to improve reproducibility. For calculation of the SUVs, ROIs were automatically adapted to a 3-dimensional volume with a 30% isocontour. The ratio of the maximum SUV of a ROI to the mean SUV of the pulmonary aorta was calculated and denoted as the target-to-background ratio (TBR_{blood}). The change in TBR_{blood} from pre-RT to during-RT was denoted as ΔTBR_{blood}. For controversial lesions, discussion among the imaging experts was carried out with consideration of results from other imaging modalities proceeded until a final consensus was reached.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows version 25.0 (IBM, Armonk, NY, USA). Descriptive statistics were used to summarize the demographics and disease characteristics. The Mann-Whitney *U* test was used to test the associations of ^{18}F-FAPI-04 PET/CT, clinical, and dosimetric parameters with the development of any grade of RE and grade 3 RE. Logistic regression analyses were performed to identify which of these parameters could predict development of any grade of RE (grade > 1) or specifically grade 3 RE. Spearman's rank correlation coefficients were calculated to assess the relationships between parameters. Receiver operating characteristic curve analysis was used to determine the threshold values and accuracy of the parameters for toxicity prediction. All tests were two-sided, and $P < 0.05$ was considered statistically significant.

Results

Patients' characteristics

From June 2021 to March 2022, 30 LA-ESCC patients (22 men, 18 women; median age: 66.5 years [interquartile

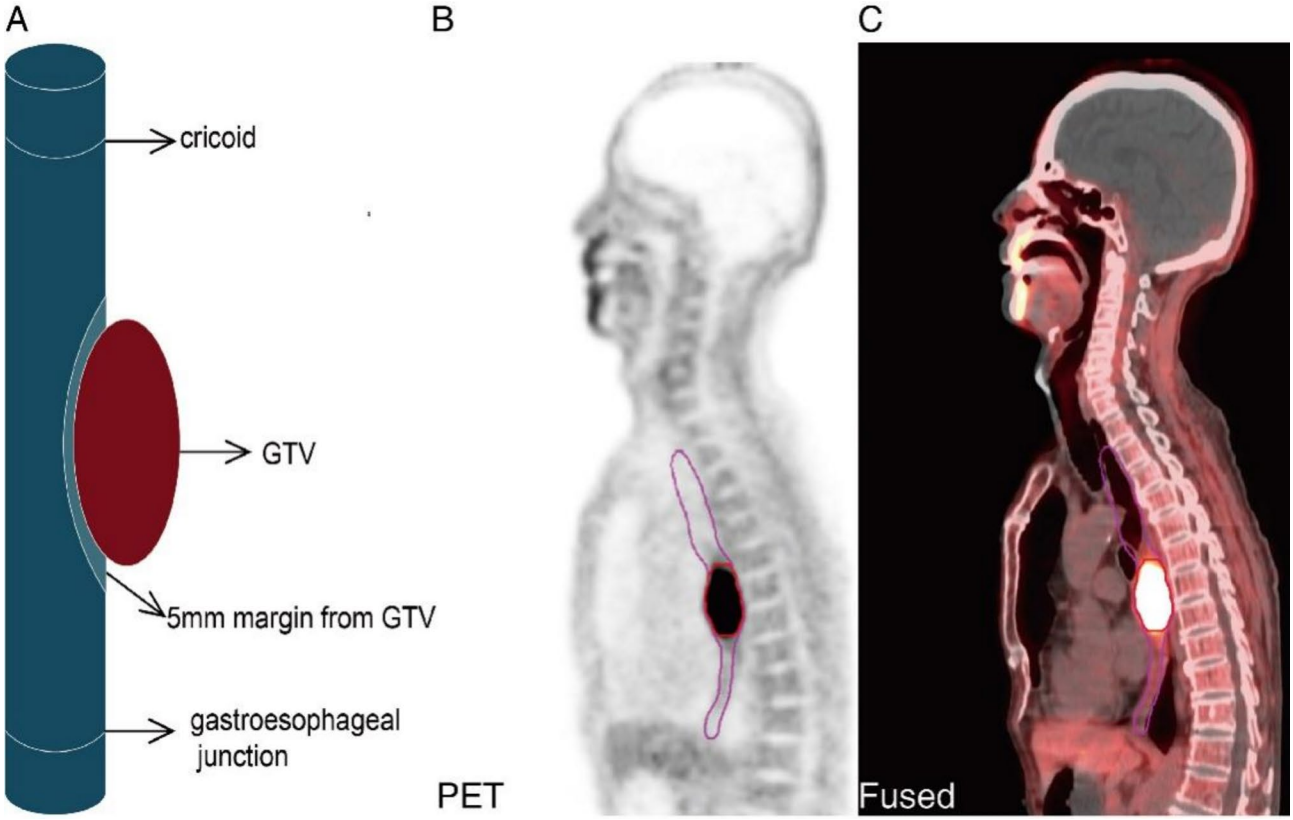

Fig. 1 (**A**) Esophagus segmentation for evaluation. (**B**-**C**) Scans for a patient with locally advanced esophageal squamous cell carcinoma before radiotherapy. The purple outlines indicated the endangered organ (esophagus), and the red area shows the GTV. (Abbreviations: GTV = gross tumor volume)

range: 56–71 years]) were enrolled. The study flow diagram is presented in Fig. 2. All 30 patients were treated with CCRT, with a median RT dose of 59.9 Gy (interquartile range: 54–60 Gy) in fractions of 1.8–2.0 Gy. The specific chemotherapy regimens followed are listed in Supplemental Table 1. Overall, 21 of 30 (70%) patients developed RE, and 6 of 30 (20%) patients developed grade 3 RE according to the Radiation Therapy Oncology Group (RTOG) criteria (Table 1). Figure 3 shows representative PET/CT imaging results for a patient without RE, and Fig. 4 provides representative PET/CT imaging results for a patient with grade 3 RE.

Correlations between ^{18}F-FAPI-04 PET/CT parameters and radiation esophagitis

As shown in Table 2, the patient groups with or without RE showed no differences in age, sex, Eastern Cooperative Oncology Group (ECOG) performance score, N stage, primary GTV, RT dose, maximal esophageal dose, mean esophageal dose, V50, and V60. T stage was significant correlated with RE ($P = 0.047$), and V50 was significantly increased in association with grade 3 RE ($P = 0.021$).

Patients who developed RE had significantly higher TBR_{blood} (during-RT) ($P = 0.003$) and ΔTBR_{blood} ($P = 0.002$) values than those who did not develop RE (Table 2). Additionally, patients who experienced grade 3 RE also had significantly higher TBR_{blood} (during-RT) ($P = 0.003$) and ΔTBR_{blood} ($P = 0.003$) values than those who developed RE rated lower than grade 3 (Table 2).

Receiver-operating characteristic curves were generated to evaluate the predictive accuracy of ^{18}F-FAPI-04 PET/CT parameters for identifying any grade RE and grade 3 RE. High TBR_{blood} (during-RT) (area under the curve [AUC] = 0.902; cut-off = 1.53) and ΔTBR_{blood} (AUC = 0.911; cut-off = 4.19) significantly predicted any grade RE, and with higher cut-off values, TBR_{blood} (during-RT) (AUC = 0.912; cut-off = 6.61) and ΔTBR_{blood}

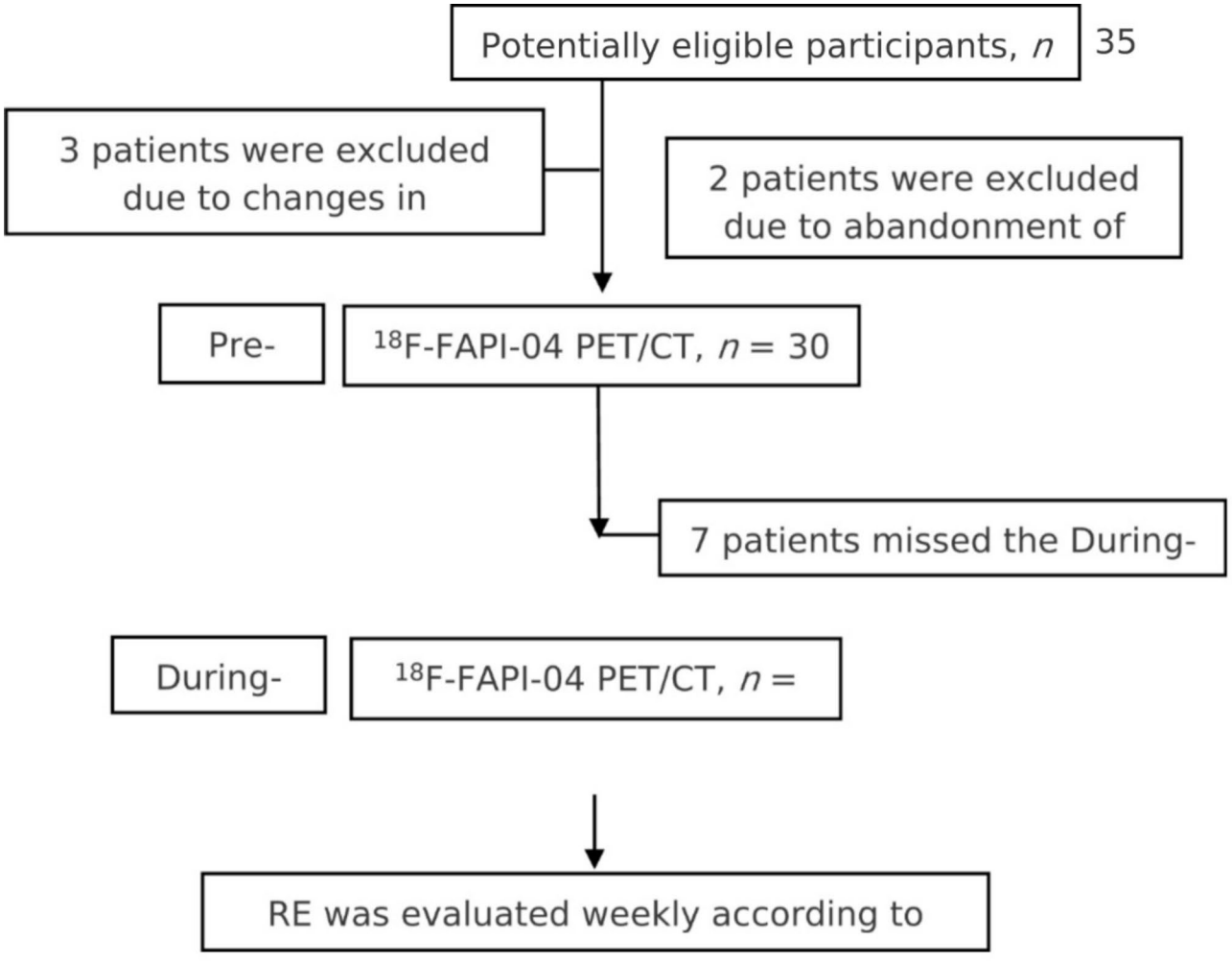

Fig. 2 Study flowchart. (Abbreviations: FAPI = fibroblast-activation protein inhibitor; ^{18}F = fluorine 18; RE: radiation esophagitis; RT: radiotherapy; RTOG: Radiation Therapy Oncology Group)

Table 1 Summary of patient characteristics

Characteristics	Value
No. of participants	30
Median age (interquartile range), years	66.5 (56–71)
Sex, *n*	
Male	22
Female	8
ECOG score	
0	19
1	11
T stage	
T2	1
T3	24
T4	5
N stage	
N0	6
N1	16
N2	8
Median radiotherapy dose (interquartile range), Gy	59.9 (54–60)
Chemotherapy regimen	
Docetaxel + Carboplatin/Nedaplatin	4
Paclitaxel + Nedaplatin/Carboplatin/Cisplatin	16
Paclitaxel	7
Capecitabine	1
Tegafur	2

Abbreviation: ECOG: Eastern Cooperative Oncology Group

(AUC = 0.922; cut-off = 4.21) also significantly predicted grade 3 RE (Fig. 5).

Correlations between biomarkers

The correlations between ^{18}F-FAPI-04 PET/CT biomarkers, ECOG performance score, and dosimetric parameters are presented in Fig. 5. Except for a significant positive correlation between TBR_{blood} (during-RT) and ΔTBR_{blood} ($r = 0.984$; $P < 0.01$), no correlations were found between these variables (Fig. 5).

Associations between ^{18}F-FAPI-04 PET/CT parameters, clinical variables, dosimetric parameters, and development of radiation esophagitis

According to univariate logistic regression analyses, V50 ($P = 0.108$), TBR_{blood} (during-RT) ($P = 0.020$) and ΔTBR_{blood} ($P = 0.019$) were significantly associated with the development of RE (Table 3). Additionally, V50 ($P = 0.146$), TBR_{blood} (during-RT) ($P = 0.022$) and ΔTBR_{blood} ($P = 0.022$) were significantly associated with the development of grade 3 RE (Table 3). Because of the significant positive correlation between TBR_{blood} (during-RT) and ΔTBR_{blood}, we only included ΔTBR_{blood} and V50 in the subsequent multivariate analysis (Table 3), which showed that ΔTBR_{blood} was independently associated with the development of RE ($P = 0.021$) as well as the development of grade 3 RE specifically ($P = 0.038$; Table 3).

Discussion

This prospective study demonstrated the first time that ^{18}F-FAPI-04 PET/CT can be used as an effective detection method for RE. TBR_{blood} and ΔTBR_{blood} could be independent prediction parameters of RE, especially

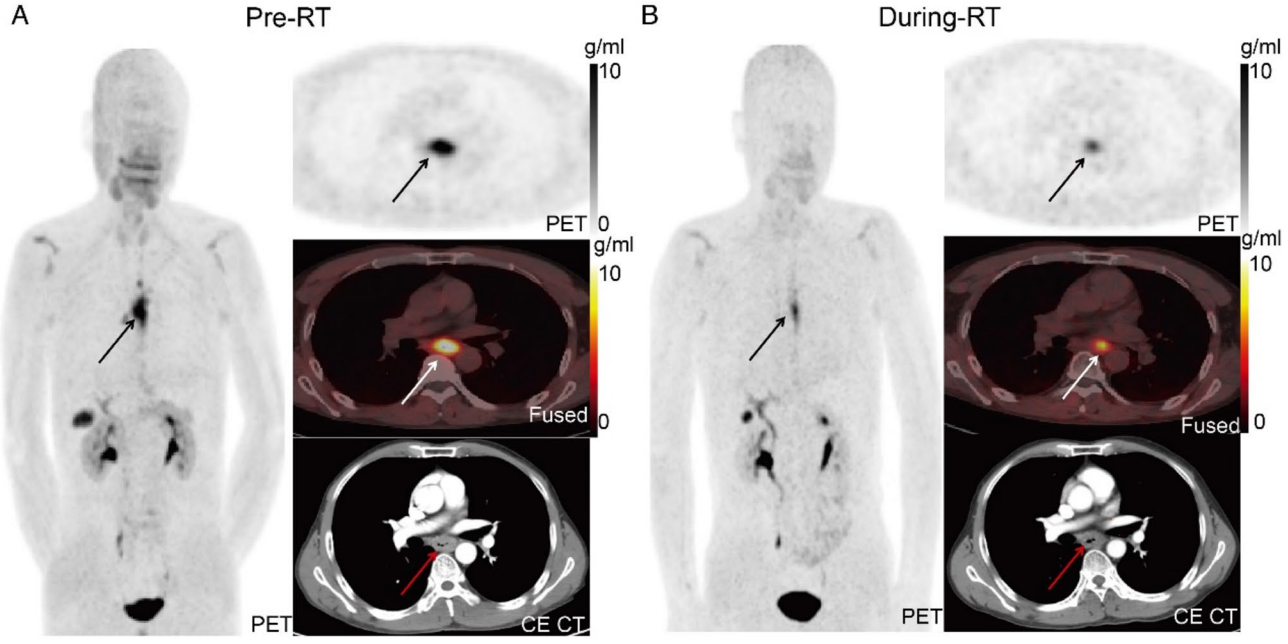

Fig. 3 ^{18}F-FAPI-04 PET/CT scans for a patient with radiation esophagitis classified as grade 0 according to Radiation Therapy Oncology Group criteria

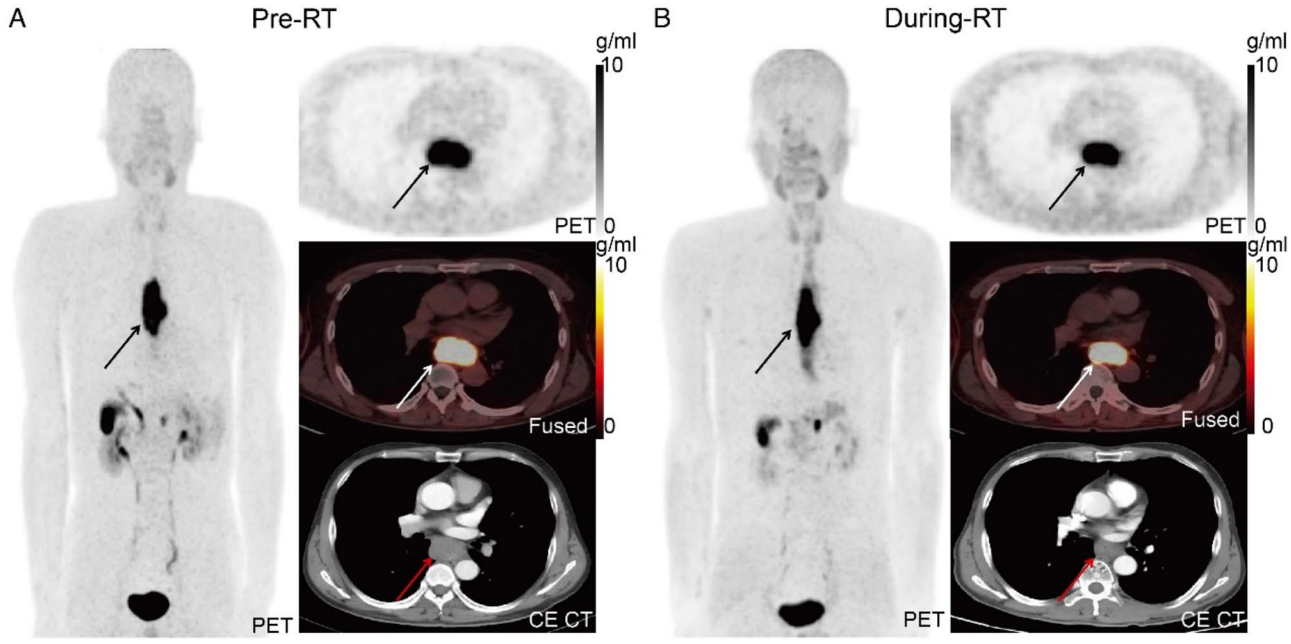

Fig. 4 ^{18}F-FAPI-04 PET/CT scans for a patient with radiation esophagitis classified as grade 3 according to Radiation Therapy Oncology Group criteria

Table 2 Comparison of volumetric, dosimetric, and ^{18}F-FAPI-04 PET/CT parameters with any grade and grade 3 radiation esophagitis

Variable	No RE	RE	*P* value	Grade < 3RE	Grade 3RE	*P* value
	n = 9	*n* = 21		*n* = 24	*n* = 6	
Median age (range), years	67 (52–76)	67 (48–78)	0.406	67 (52–78)	57.5 (48–74)	0.057
Sex, *n* (%)						
Female	3 (33.3)	5 (23.8)	0.595	7 (29.2)	1 (16.7)	0.543
Male	6 (66.7)	16 (76.2)		17 (70.8)	5 (83.3)	
ECOG score						
0	7 (77.8)	12 (57.1)	0.291	16 (66.7)	3 (50.0)	0.456
1	2 (22.2)	9 (42.9)		8 (33.3)	3 (50.0)	
T stage*, *n* (%)						
T2	1 (11.1)	0	0.047	1 (4.2)	0	0.852
T3	8 (88.9)	16 (76.2)		19 (79.2)	5 (83.3)	
T4	0	5 (23.8)		4 (16.7)	1 (16.7)	
N stage, *n* (%)						
N0	2 (22.2)	4 (19.0)	0.550	6 (25.0)	0	0.199
N1	5 (55.6)	11 (52.4)		10 (41.7)	5 (83.3)	
N2	2 (22.2)	6 (28.6)		8 (33.3)	1 (16.7)	
Primary GTV (cc)	28.98 ± 82.41	23.77 ± 72.95	0.414	25.61 ± 77.01	24.23 ± 101.82	0.795
RT dose (Gy)	57.31 ± 4.14	58.43 ± 4.73	0.499	58.12 ± 4.87	58.03 ± 3.13	0.539
Maximal esophageal dose	67.25 ± 33.77	68.17 ± 39.05	0.946	67.63 ± 39.25	68.93 ± 29.13	0.392
Mean esophageal dose	55.03 ± 114.71	52.08 ± 127.46	0.541	52.50 ± 102.99	54.84 ± 225.34	0.568
V50*	66.04 ± 88.81	73.22 ± 119.46	0.099	69.59 ± 130.58	77.72 ± 6.11	0.021
V60	51.91 ± 98.77	57.69 ± 227.62	0.283	55.52 ± 186.18	57.23 ± 243.92	0.965
TBR_{blood}						
Pre-RT	2.37 ± 0.045	2.28 ± 0.13	0.377	2.33 ± 0.12	2.20 ± 0.03	0.468
During-RT*	3.06 ± 2.74	7.11 ± 10.09	0.003	4.55 ± 4.62	9.66 ± 11.70	0.003
$\triangle TBR_{blood}$*	0.67 ± 2.52	4.81 ± 10.84	0.002	2.16 ± 4.44	7.50 ± 12.68	0.003

*$P < 0.05$

$\triangle TBR_{blood} = TBR_{blood}$ (during-RT) – TBR_{blood} (Pre-RT)

Abbreviations: RE: radiation esophagitis; ECOG: Eastern Cooperative Oncology Group; GTV: gross tumor volume; RT: radiotherapy; V50: volume of esophagus receiving ≥ 50 Gy; V60: volume of esophagus receiving ≥ 60 Gy

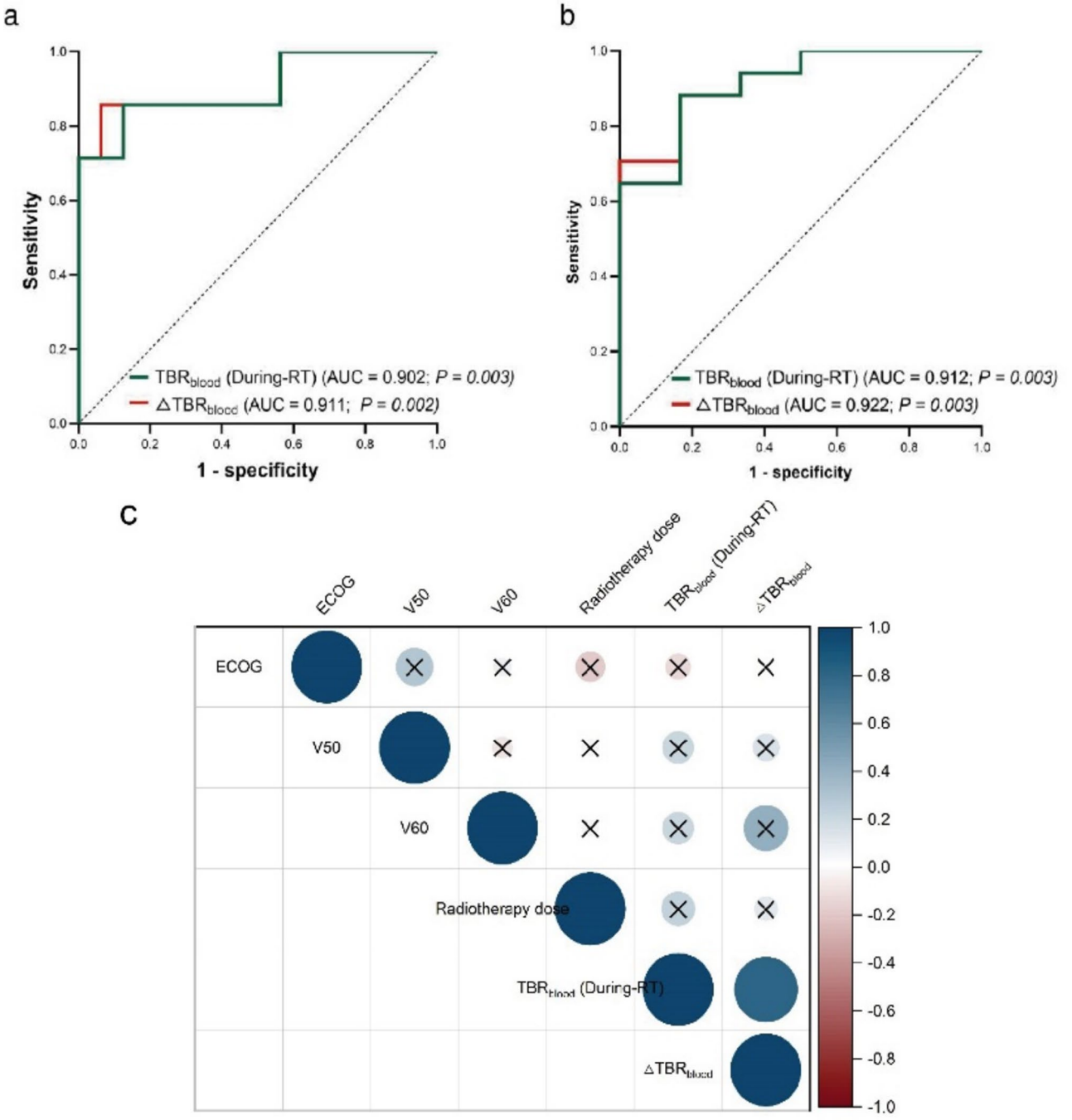

Fig. 5 (**A**-**B**) Receiver-operating characteristic curves for the ability of TBR_{blood} (during-RT) and ΔTBR_{blood} to predict radiation esophagitis after concurrent chemoradiotherapy. (**A**) Receiver-operating characteristic curves for the prediction of any grade of radiation esophagitis. (**B**) Receiver-operating characteristic curves for the prediction of grade 3 radiation esophagitis. (**C**) Correlogram: correlations between TBR_{blood}, clinical and dosimetric variables (Spearman's coefficient). Blue represents a positive correlation between two variables, and red represents a negative correlation between two variables. The stronger the correlation, the darker the color. ($\Delta TBR_{blood} = TBR_{blood}$ (during-RT) - TBR_{blood} (pre-RT); Abbreviations: ECOG: Eastern Cooperative Oncology Group; V50: volume of esophagus receiving ≥ 50 Gy; V60: volume of esophagus receiving ≥ 60 Gy; RE: radiation esophagitis; RT: radiotherapy)

grade 3 RE, in LA-ESCC patients treated with CCRT. The early detection of RE can provide recommendations for clinicians for LA-ESCC patients.

While no studies investigating the use of FAPI-based imaging for RE prediction were found in the literature, a few published studies have explored the correlation between ^{18}F-FDG PET/CT parameters and RE. Study before reported that ^{18}F-FDG uptake is significantly increased in esophagus during RT and that this increase may predict the occurrence of RE later in the course of

Table 3 Predictive ability of biomarkers for any grade of RE (Grade ≥ 1) and grade 3 on univariate and multivariate analyses

Patients	RE of any grade (Grade ≥ 1)				Grade 3 RE			
n = 30	Univariate		Multivariate		Univariate		Multivariate	
Variable	OR (95%CI)	*P* value	OR (95%CI)	*P* value	OR (95%CI)	*P* value	OR (95%CI)	*P* value
ECOG score	2.63 (0.44–15.78)	0.292	-	-	2.00 (0.33–12.24)	0.453	-	-
V50*	1.08 (0.98–1.19)	0.108	1.01 (0.91–1.12)	0.904	1.07 (0.98–1.17)	0.146	1.02 (0.89–1.16)	0.838
V60	1.03 (0.96–1.11)	0.386	-	-	1.01 (0.94–1.09)	0.806	-	-
RT dose (Gy)	1.06 (0.89–1.27)	0.527	-	-	1.00 (0.81–1.22)	0.967	-	-
TBR_{blood}								
During-RT*	2.86 (1.18–6.89)	0.020	-	-	2.09 (1.11–3.92)	0.022	-	-
$\triangle TBR_{blood}$*	3.08 (1.20–7.90)	0.019	3.06 (1.18–7.89)	0.021	2.10 (1.12–3.95)	0.022	2.03 (1.04–3.97)	0.038

*$P < 0.2$

$\triangle TBR_{blood} = TBR_{blood}$ (during-RT)– TBR_{blood} (Pre-RT)

Abbreviations: RE: radiation esophagitis; OR: odds ratio; 95% CI: 95% confidence interval; ECOG: Eastern Cooperative Oncology Group; V50: volume of esophagus receiving ≥ 50 Gy; V60: volume of esophagus receiving ≥ 60 Gy; RT: radiotherapy

treatment [24]. However, the second time point adopted in this study is 40 Gy, earlier than the previous 45 Gy and the prediction AUC of ^{18}F-FAPI-04 is also higher than the previous study. Similarly, Mehmood et al. reported a significant increase in ^{18}F-FDG uptake in patients who developed RE during chemoradiotherapy [25]. Therefore, we hypothesized that ^{18}F-FAPI-04 uptake might also have the potential to predict RE. This hypothesis was confirmed in the present study, and we also found radiation dose and T stage were correlated with RE. In contrast, Dzul et al. reported that the mean esophageal dose was the dosimetric parameter most correlated with grade 2 RE [26], and in their study, Mehmood et al. found that both V50 and V60 were predictors of the development of RE [25].

Furthermore, the present study also demonstrated that TBR_{blood} (during-RT) and ΔTBR_{blood} on ^{18}F-FAPI-04 PET/CT could predict RE well, especially grade 3 RE. Studies reported that about 18% of patients receiving CCRT will develop RE with severity of grade 3 or higher [27, 28]. The incidence of grade 3 RE in this study was 20% (6/30), which was consistent with previous reports. Grade 3 RE is commonly accompanied by many complications, such as ulcers, perforation, and even the formation of tracheoesophageal fistula [29, 30]. These complications can negatively affect patients' quality of life and have a significant adverse impact on long-term survival [31]. We observed a significant increase in the TBR_{blood} (during-RT) for patients who developed grade 3 RE compared with that in patients who developed RE of a lower grade 3. Similarly, Mehmood et al. reported significantly higher ^{18}F-FDG uptake in patients with grade 3 RE at weeks 2 and 7 of RT compared with uptake values in patients with RE lower than grade 3 [25]. These results indicate that a single FAPI PET examination during radiotherapy can screen high-risk patients for RE in advance, enabling early intervention and reducing the incidence of RE.

The acute effects of RT on the esophagus consist of symptoms of substemal burning along with pain on swallowing, which occur approximately 2 weeks after initiation of a conventional RT course (after administration of approximately 20 Gy), and higher grade RE typically occurs in the late course of RT [30, 32]. In the present study, the second ^{18}F-FAPI-04 PET/CT scan was conducted after patients had received a total RT dose of 40 Gy. Therefore, the imaging parameters evaluated in this study showed greater value for the prediction of any grade and grade 3 RE.

The main limitations of the present study include its single-center design and relatively small sample size. Further large-scale, multi-center clinical studies are needed to confirm our findings before their clinical application. Furthermore, in this study, primary tumor regions were excluded to reduce confounding changes on ^{18}F-FAPI-04 PET/CT associated with tumor response. This approach may have excluded the area receiving the highest radiation dose, but this may also have resulted in underestimation of the examined parameters. Our analysis of the maximum SUV of primary tumors may have helped to reduce the impact of this limitation. Lastly, ^{18}F-FAPI-04 PET/CT imaging was not performed at multiple time points after radiotherapy to find the earliest predicted time point for RE. Overall, further prospective trials are required to confirm the role of ^{18}F-FAPI-04 PET/CT

imaging for predicting RT toxicity prediction in patients with LA-ESCC.

Conclusion

^{18}F-FAPI-04 PET/CT can detect and predict RE in LA-ESCC patients treated with CCRT, especially when single FAPI detection of TBR_{blood} is given during the mid-stage of radiotherapy, and can specifically screen patients with RE, which has great potential value in guiding clinical treatment.

Abbreviations

CCRT	Concurrent chemoradiotherapy
FAPI	Fibroblast-activation protein inhibitor
FDG	Fluorodeoxyglucose
LA-ESCC	Locally advanced esophageal cancer
RE	Radiation esophagitis
RT	Radiotherapy
RTOG	Radiation therapy oncology group
TBR_{blood}	Target-to-background ratio

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12885-025-14236-3.

Supplementary Material 1

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Author contributions

Y. W. contributed to the study conception and design. Material preparation, data collection and analysis were performed by C. H., M. Z., Z. M., K.Q., J. J. Z.F., and J.Y. were responsible for reviewing all 18 F-FAPI PET/CT images. The first draft of the manuscript was written by X.H. and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data availability

Data generated or analyzed during the study are available from the corresponding author by request.

Declarations

Ethics approval and consent to participate

This study was an ongoing prospective clinical study that received ethical approval from the Ethics Committee of Shandong First Medical University Affiliated Cancer Hospital (institutional review board approval no. SDZLEC2021-112-02), and all of participants gave written and informed consent before the study. And this study adhered to the Declaration of Helsinki. This paper has been uploaded to Research Square as a preprint: https://www.researchsquare.com/article/rs-2410645/v1.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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