scenario name

Prospective clinical study and exploration of ^{18}F-FAPI PET/CT imaging in cancers of unknown primary site

Version: 2.4

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Clinical Research Unit: The First Affiliated Hospital of Zhejiang University School of Medicine

Study sponsor: Chen Donghe

17 October 2025

Revision History

edition	date	imprint
1.0	2025-4-15	first draft
2.0	2025-6-2	Modify 1
2.1	2025-6-14	Change 2
2.2	2025-8-26	Modify 3
2.3	2025-10-5	Change 4
2.4	2025-10-17	Edit 5

List of Multicenter Clinical Trial Sites

Research Principal Investigator and Principal Research Institution Information

Study Principal Investigator	
Principal Research Unit	
address	
telephone	
portraiture	
postbox	

Join event list

Center number	Clinical Trial Institution Name
01	
02	
03	
04	
05	
06	
07	
08	
09	

Researcher's Statement and Signature Page

This study is a prospective clinical trial, and the methodologies, equipment, and medications employed have been widely adopted in clinical practice. A rigorous adverse event monitoring system will be established to meticulously record all adverse events and ensure timely and effective management. In the event of any serious or significant adverse event, regardless of its association with the study intervention or whether any intervention procedures have been performed, the study sponsor must be promptly notified, and a decision to terminate the study will be made based on the circumstances. The investigators guarantee strict confidentiality of participants 'personal data: all participant information and imaging will be labeled with numbers rather than names; identifiable information will not be disclosed to members outside the research team unless the participant consents; all study members and sponsors are required to adhere to confidentiality principles; all study records will be stored in locked filing cabinets for researchers' access only; during and after the study, government regulatory authorities or ethics committee members may conduct random checks on participants' personal data as per regulations; no personal information will be disclosed upon publication of the study results.

Researcher's signature

I have read and agreed to the protocol proposed in this document, and acknowledge the relevant content thereof. During the trial, I will strictly comply with the laws, regulations, and relevant rules of the People's Republic of China, fulfill my duties as a research participant, and adhere to confidentiality requirements.

Research institution: The First Affiliated Hospital of Zhejiang University School of Medicine

Name of investigator: Chen Donghe

Researcher Position: Associate Chief Physician in Nuclear Medicine

Researcher's signature:

Date of signature:

scenario summary

Study name	Prospective clinical study of 18F-FAPI PET/CT imaging in the application of cancer with unknown primary site
Study protocol	This study adopted a prospective, single-center research design. It aimed to evaluate the diagnostic research and exploration of 18F-FAPI PET/CT in patients with suspected primary tumors of unknown origin. A total of 120 subjects from one center (The First Affiliated Hospital of Zhejiang University School of Medicine) across the country were planned to be enrolled in this study.
research design	perspective study
Number of research centers	1
sample capacity	120
indicatio	patients with suspected or confirmed cancer of unknown primary origin
purpose of research	This study aims to evaluate the diagnostic efficacy, therapeutic assessment, prognostic analysis, and impact on clinical treatment decisions of 18F-FAPI PET/CT in patients with cancer of unknown primary.
primary end point	Diagnostic efficacy of 18F-FAPI PET/CT in patients with undetermined primary tumors (sensitivity, specificity, accuracy)
Selection criteria	(1) Patients in our hospital with clinical or imaging findings suggestive of cancer of unknown primary (2) Patients with previously diagnosed cancer of unknown primary origin suspected of recurrence or metastasis.
exclusion criteria	(1) Concurrent presence of other active malignant tumors or a history of other malignant tumors within the past 5 years; (2) Severe uncontrollable diseases or active infections; (3) Ineligible participants for informed consent. (4) Pregnant and lactating women.
study termination criteria	1. Achieve the research objectives; 2. Occurrence of serious adverse events
18F-Octreotide Description	The Nuclear Medicine PET Center holds a Class IV Certificate for Radioactive Drugs, enabling independent production and research of radiopharmaceuticals. Currently, our department has successfully prepared 18F-FAPI, with drug quality testing meeting national pharmacopoeia standards for radioactive drugs and having passed small animal safety testing.
Visit Plan	For patients under treatment and follow-up at this hospital, no in-person visits are required; relevant data can be obtained from the electronic medical record (EMR) system and imaging system of this hospital. For patients not receiving treatment at this hospital, a telephone follow-up protocol is implemented to obtain relevant pathological results.

research report	The study plans to enroll 120 eligible patients within 3 years, followed up their pathological results, and conduct statistical analysis.
statistical analysis	Statistical analysis was performed using SPSS 17.0. The diagnostic sensitivity, specificity, and negative/positive predictive values were calculated using a four-cell table. The area under the ROC curve and the optimal cutoff value (SUV optimal cutoff) were evaluated by ROC curve analysis. The consistency between 18F-FAPI PET diagnosis and pathological diagnosis was assessed using the kappa test. A p-value <0.05 was defined as statistically significant.
quality control	This study will establish a rigorous adverse event monitoring system to meticulously record all reported adverse events and ensure timely and effective management. Investigators will guarantee strict confidentiality of participants 'personal data: all subject information and imaging data will be labeled with numbers rather than names. During and after the study, government regulatory authorities or ethics committee members will be permitted to conduct random checks on participants' personal data in accordance with regulations. When the study results are published, no personal information will be disclosed.

English abbreviation reference

PET	Positron emission tomography
CT	Computed tomography
ROC	Receiver operating characteristic curve
FAPI	Fibroblast activation protein inhibitor

1 Research Background

Cancers of unknown primary site (CUPs) are a complex type of malignant tumor characterized by the inability to determine the location of the primary tumor despite standard clinical and pathological examinations. CUPs account for approximately 3-5% of all cancer cases, typically presenting with early metastasis and aggressive behavior, resulting in poor patient prognosis. Due to the lack of a definitive primary site, CUP patients often face limited treatment options, making effective diagnosis and treatment particularly crucial.

In the diagnostic process of CUPs, conventional imaging modalities such as CT and MRI often fail to accurately localize the primary tumor. In recent years, the development of positron emission tomography-computed tomography (PET/CT) has provided new possibilities for the detection of CUPs. Among these, 18F-FDG PET/CT has been widely applied in identifying primary tumors; however, in certain cases, its ability to distinguish small occult tumors from chronic inflammation is limited. In contrast, fibroblast activation protein inhibitor (FAPI) PET/CT, as an emerging imaging technique, has demonstrated promising potential in improving the accuracy of primary lesion localization.

FAPI PET/CT can more accurately identify malignant tumors by targeting fibroblast-activating protein (FAP). In one study, this technology successfully detected 51% of primary lesions in patients with unknown primary cancers of the head and neck, compared to only 25% detected by 18F-FDG PET/CT. Additionally, 18F-FAPI PET/CT demonstrated higher positive predictive value and accuracy, making it of significant value in altering treatment strategies.

This project aims to conduct a prospective study on 18F-FAPI PET/CT in patients with cancer of unknown primary, providing these patients with a more sensitive and reliable diagnostic tool, which is expected to improve their prognosis. Meanwhile, the application of this technology in different types of cancer still requires further research to verify its long-term efficacy and potential advantages.

2 Objectives and Content of Clinical Research

2.1 Purpose of Clinical Research

This study aims to evaluate the diagnostic efficacy, therapeutic assessment, and prognostic prediction of 18F-FAPI PET/CT in patients with cancer of unknown primary.

Primary endpoint: Diagnostic efficacy of 18F-FAPI PET/CT in patients with undetermined primary tumor (sensitivity, specificity, accuracy).

secondary end points:

① The diagnostic performance of 18F-FAPI PET/CT compared with CT, MR and 18F-FDG PET in the clinical application of cancer with unknown primary site was compared.

② Assess the heterogeneity of sensitivity and specificity of 18F-FAPI PET/CT for different system sites (neck/thorax/abdomen).

③ Study on efficacy evaluation and prognostic prediction of 18F-FAPI PET/CT in patients with primary tumors of unknown origin.

2.2 Content of Clinical Studies

Diagnostic efficacy of 18F-FAPI PET/CT in patients with undetermined primary tumor (sensitivity, specificity, accuracy)

Collect clinical characteristics of patients with undetermined primary tumors, including age, gender, medical history, and relevant imaging findings. Analyze the imaging manifestations of 18F-FAPI PET/CT in patients with undetermined primary tumors and conduct comparative analysis with pathological results to clarify the correlation between the results of 18F-FAPI PET/CT in detecting primary tumors, lymph node metastases, or distant metastases (positive/negative) and the pathological gold standard diagnosis (positive/negative). A 18F-FAPI-positive lesion is defined as a site with 18F-FAPI uptake higher than the adjacent background uptake. Evaluate the sensitivity, specificity, and accuracy of 18F-FAPI PET/CT in identifying primary tumors and detecting metastases in patients with undetermined primary tumors to determine the practical clinical value of this imaging technique.

②Comparison of diagnostic performance differences between 18F-FAPI PET/CT and CT, MR, and 18F-FDG PET imaging in the clinical application for cancers with unknown primary sites

CT or MR are routine imaging examinations for patients upon admission, particularly for the evaluation of head and neck or gastrointestinal tumors. However, CT or MR provide only local morphological imaging, while PET/CT, which offers systemic functional fusion anatomy, can compensate for their limitations. Therefore, a subset of patients undergo conventional 18F-FDG PET/CT imaging prior to admission under clinical evaluation. For patients with suspected CUPs, the ability to identify the primary lesion site through specific imaging agents combined with systemic functional fusion anatomy is of significant clinical importance for treatment planning. This study does not mandate that subjects undergo CT, MR, or 18F-FDG PET/CT imaging. If a patient has already completed the aforementioned examinations prior to 18F-FAPI PET/CT scanning, the 18F-FAPI PET/CT will be performed one week after the completion of those examinations to avoid delays in diagnosis and treatment.

A comparative study of 18F-FAPI PET/CT imaging results and PET parameter records, including primary lesions, lymph node metastases, or distant metastases (positive/negative), with conventional imaging (CT or MR) or 18F-FDG PET/CT in patients with undetermined primary lesions, evaluates the differences in sensitivity, specificity, and accuracy of each imaging modality in tumor detection of primary and metastatic lesions. The study also assesses the accuracy of TNM staging, with pathological results or clinical follow-up as the gold standard. Through systematic analysis of the advantages and disadvantages of various imaging techniques, this research provides a basis for clinical selection of appropriate imaging modalities, promoting early diagnosis and treatment of undetermined primary lesions.

③ Evaluation of the heterogeneity in sensitivity and specificity of 18F-FAPI PET/CT for different system sites (neck/thorax/abdomen)

Based on existing clinical guideline evidence, the sensitivity and specificity of different imaging techniques for diagnosing primary tumors of unknown origin vary significantly depending on the anatomical location and structural characteristics of the disease. According to the anatomical site, the sensitivity, specificity, and accuracy of 18F-FAPI PET/CT in evaluating the T stage, N stage, and M stage of primary tumors of unknown origin in different regions and systems (e.g., head and neck, chest, and abdomen) were analyzed separately based on the pathological gold standard diagnosis (positive/negative) to determine the clinical value of these imaging techniques in various systems and organs.

Study on Efficacy Evaluation and Prognostic Prediction of 18F-FAPI PET/CT in Patients with Primary Tumors of Unknown Origin

Based on the tumor TNM staging and PERCIST efficacy evaluation criteria, the therapeutic efficacy of 18F-FAPI PET/CT in the treatment of cancers with unknown primary sites was assessed.

Evaluation of Solid Tumor Response (RECIST 1.1 Criteria Combined with Functional Imaging)

Metabolic parameters

- • Complete metabolic resolution (CMR): Complete disappearance of lesion ^{18}F-FDG uptake after treatment (SUVmax of target lesion reduced to liver baseline level).
- • Partial metabolic relief (PMR): SUVmax reduction>30% (inflammatory interference must be excluded).
- • Metastatic progression (MPD): SUVmax increase>30% or new metastatic lesions (≥1cm with SUVmax>2.5).

Collect baseline PET parameters (lesion SUVmax, lesion SUVmean, MTV, LTV, bone marrow SUVmax, etc.), and plot the survival rate trend over time using Kaplan-Meier curves based on efficacy evaluation, pathological response, and clinical follow-up data (PFS/OS) to visually compare survival differences among groups. Employ Cox proportional hazards model for multivariate regression to quantify the contribution of age, pathological stage, and other factors in predicting disease progression, recurrence, and mortality risk, thereby supporting clinical decision-making.

3 Characteristics, composition, working principles, mechanisms of action, and research scope of the imaging agent

3.1 Characteristics of Contrast Agents:

The drug has passed the testing standards of the 2015 edition of the "China Pharmacopoeia" and the biosafety experiment. The drug quality control is conducted in accordance with the "Radioactive Drug Control Method" in Part IV of the 2015 edition of the "China Pharmacopoeia":

(1) Clarity: The injection should be a colorless, transparent, sterile, pyrogen-free, stable solution of water and ethanol (15%).

(2) pH value: The pH value should be maintained within a specified range (using pH test strips or pH meter for measurement).

(3) Specific activity: The specific activity must be no less than 37×10^3 MBq/mol (calculated using an activity meter).

(4) Radioisotope purity: Using an appropriate gamma spectrometer, only two peaks (0.511MeV and 1.02 MeV) can be detected (calculated by activity meter).

(5) Radiochemical purity: The radiochemical purity must exceed 95% (determined by TLC or HPLC).

(6) Chemical purity: The chemical purity must exceed 95% (as determined by HPLC analysis).

(7) Bacteriological examination: Aseptic and free of pyrogen.

(8) Bacterial endotoxins: The detected endotoxin levels are within the normal range.

(9) Acetonitrile content below 0.01%.

(10) The K222 content is below 50 ng/mL.

3.3 Working Principle, Mechanism of Action, and Research Scope

18F (97% β+, T1/2=109.7 minutes) is currently the most widely used radionuclide in PET/CT due to its chemical, physical, and nuclear properties, making it an ideal choice for peptide-based imaging. 18F-FDG is the most commonly used PET tracer in oncology, serving as the preferred option for tumor diagnosis and evaluation of treatment efficacy. However, 18F-FDG PET/CT exhibits relatively low sensitivity and specificity for tumors with low invasiveness, high differentiation, or mucinous tissues, while also showing significant physiological uptake in organs such as the oropharynx and digestive tract, which often masks tumor metabolism and uptake. Additionally, compared to 68Ga-labeled tracers, 18F-labeled FAPI has lower positron energy and thus offers better resolution potential. Consequently, 18F-labeled FAPI holds significant clinical value and promising prospects.

4 Indications, Contraindications, and Precautions

4.1 Indications: Patients with suspected or confirmed cancer of unknown primary

4.2 Contraindications:

(1) Concurrent presence of other active malignant tumors or a history of other malignant tumors within the past 5 years;

(2) Severe uncontrollable diseases or active infections;

(3) Ineligible participants for informed consent.

(4) Pregnant and lactating women.

5. Overall Design

5.1 Research Methods

This study adopted a prospective, single-center research design. It aimed to evaluate the diagnostic research and exploration of 18F-FAPI PET/CT in patients with cancer of unknown primary. A total of 120 subjects from one center (The First Affiliated Hospital of Zhejiang University School of Medicine) across the country were planned to be enrolled in this study.

5.2 Measures to Reduce or Avoid Bias

5.2.1 Blinding

No blinding.

5.2.2 Clinical Indicator Assessment

The gold standard is the pathological result of biopsy or surgery.

5.3 Subject Selection

5.3.1 Eligibility Criteria for Subjects

(1) Patients in our hospital with clinical or imaging findings suggestive of cancer of unknown primary

(2) Patients with previously diagnosed cancer of unknown primary origin suspected of recurrence or metastasis.

5.3.2 Exclusion Criteria for Subjects

(1) Concurrent presence of other active malignant tumors or a history of other malignant tumors within the past 5 years;

(2) Severe uncontrollable diseases or active infections;

(3) Ineligible participants for informed consent.

(4) Pregnant and lactating women.

5.3.3 Criteria and Procedures for Subject Withdrawal from the Study

Clinical trial personnel will collect medical history and verify the inclusion/exclusion criteria of participants through the hospital's electronic medical record system. If a participant's personal conditions do not meet the study requirements, they will not be approved to participate. Participants who experience hypoglycemic reactions, tremors, pain, severe abdominal pain, or other reasons that prevent them from cooperating with the examination may withdraw from the study at any time.

5.3.3 Subject Loss to Follow-up

Lost to follow-up: Participants did not complete the specified follow-up period but did not 'formally' withdraw from the clinical trial.

The primary subjects are those who underwent puncture or surgery at external hospitals. If the subjects are unable to return for follow-up visits or cannot be contacted by phone, at least three separate telephone attempts should be made to obtain necessary information. All attempts must be documented in the original records. If the subject does not respond to three telephone follow-ups, a registered mail letter must subsequently be sent to the subject. If the subject does not respond to the letter, the subject is considered to have been "lost to follow-up" for the current study visit or telephone contact. The investigator must record this information in the original records. The investigator must report this information to the relevant ethics committee in accordance with the procedures of their institution.

For cases with lost-to-follow-up, the reasons should be explained, and their e-CRF forms should be retained for review. No diagnostic efficacy statistical analysis will be performed, but the examinations will be conducted, and participation in safety analysis may be considered based on circumstances.

5.3.4 Selection Time

July 2025 to July 2028, for 3 years.

5.3.5 Number of Subjects Required for Clinical Studies

120 cases

5.4 Study Endpoints

Primary endpoint: Diagnostic efficacy of 18F-FAPI PET/CT in patients with undetermined primary tumor (sensitivity, specificity, accuracy).

secondary end points:

③ The diagnostic performance of 18F-FAPI PET/CT compared with CT, MR and 18F-FDG PET in the clinical application of cancer with unknown primary site was compared.

④ Assess the heterogeneity of sensitivity and specificity of 18F-FAPI PET/CT for different system sites (neck/thorax/abdomen).

③ Study on efficacy evaluation and prognostic prediction of 18F-FAPI PET/CT in patients with primary tumors of unknown origin.

6 Research Procedures and Operational Standards

6.1 Ethical Principles and Informed Consent

Clinical studies shall commence only after the relevant materials have been approved by the ethics committee. During the implementation of the study, any revision to the protocol (excluding administrative aspects) must be re-approved by the ethics committee before proceeding with the study.

Prior to the initiation of the study, each investigator obtained written and dated approval/endorsement from the respective independent ethics committee for the study protocol (and any amendments), written informed consent, consent updates, and all other written information to be provided to the subjects. The approval was expressed in writing, citing the final protocol version number and version date.

During the study period, all documents requiring review should be submitted to the independent ethics committee by the study sponsor or investigator. Informed consent from participants is a measure to protect subjects. Prior to the study, the investigator must provide the participant or their guardian with a detailed explanation of the clinical study, ensuring full understanding and obtaining informed consent. The clinical study may only commence after the informed consent form has been signed.

6.2 Subject Screening

Participants will sign an informed consent form prior to enrollment in this study. Investigators will explain the nature, purpose, and risks of the study and provide the participants with an informed consent form. Participants will be given sufficient time to consider the significance of the study before deciding whether to participate. Any

modifications to the informed consent form must be notified and approved by the ethics committee prior to participant enrollment.

First, participants must undergo an informed consent process and sign an informed consent form. Subsequently, eligible subjects are screened from the target population according to the pre-established inclusion and exclusion criteria of this study, after which they may be considered for inclusion in the research.

Baseline data collection included general examinations, medical history, and laboratory tests conducted at the same hospital or external hospitals within one week prior to the signing of the informed consent form. Adverse events and concomitant medications were collected after the signing of the informed consent form.

6.3 Medical History Collection

Conduct a detailed inquiry into the patient's medical history to clarify symptoms, signs, and prior medical history (e.g., tumor history, surgical history, biopsy history, radiotherapy history, chemotherapy history, family history, allergy history, etc.), relevant laboratory tests, previous imaging findings (including plain radiography, ultrasound, CT, MRI, as well as 18F-FDG PET/CT, PET/MR, etc.), and recent pathological results (including tumor grading and Ki-67 index, etc.).

6.4 Patient Preparation and Precautions

①Pregnant women should avoid examinations unless the benefits outweigh the radiation risks to both the mother and fetus. ②Patients require adequate hydration to ensure rapid excretion of the contrast agent, thereby reducing systemic radiation dose and improving imaging quality. For patients without contraindications, they should be instructed to drink plenty of water before the examination and again after the contrast agent injection. Patients should be advised to empty their bladder prior to imaging. For patients with urinary incontinence, prior consultation with the clinician is recommended to consider indwelling catheters or urine bags. ③An intravenous access must be established before injection, and medication can be administered via a catheter to prevent contrast agent leakage. ④Patients do not need to fast and may take antihypertensive or hypoglycemic medications.

6.5 Radioactive Drugs

The recommended intravenous dose of 18F-FAPI is 3.7 MBq/kg body weight (0.1 mCi/kg body weight), with a typical range of 3.7-4.44MBq (0.1-0.12 mCi). For obese patients, the dose may be increased as appropriate. Additionally, the radiopharmaceutical should not be administered concomitantly with parenteral nutrition solutions.

6.6 Image Acquisition

The positioning of the patient's arms during positional scanning depends on the examination purpose. For a full-body examination, both arms should be placed at the sides of the body.

If thoracic or abdominal cavity scanning is required, the patient should be instructed to place both hands on the head.

CT Scanning Protocol CT scans are used for attenuation correction and lesion localization, while diagnostic CT scans can clarify the relationship between lesions and adjacent tissues or organs. The CT scanning protocol depends on the indication for the examination and whether it can provide additional diagnostic information. With more diagnostic information and the resulting...

The increase in radiation dose from external sources needs to be weighed against the need to meet the low-dose principle.

The optimal image quality for PET acquisition is generally obtained 45 to 60 minutes after the contrast agent injection. A whole-body scan (from the head to the mid-femur) is typically performed, but localized acquisition may also be conducted based on clinical needs. The acquisition time per patient bed can be adjusted according to the injection dose, attenuation time, and body mass index.

The number and detector vary.

During examinations, excessive activity of contrast agents in the urinary system may degrade image quality

and interfere with the detection of adjacent organs, particularly those in the pelvic region.
Preoperative instructions: Advise the patient to increase fluid intake to achieve adequate hydration. Diuretics and catheterization may be employed when necessary to reduce the radioactivity of urinary bladder contents.

Image processing is carried out by the built-in system for iterative reconstruction. If the equipment conditions permit, time flight technique can be used to obtain data and reconstruction.
The optimal parameters of image processing and reconstruction depend on the patient and the detector.

6.7 Image Judgment Criteria

Nuclear medicine physicians should be familiar with the normal biological distribution and abnormal distribution patterns of 18F-FAPI in the human body. The uptake of the imaging agent in tissues or organs that normally do not take it can be considered pathological. Typically, 18F-FAPI is rapidly cleared from the bloodstream. Taking 18F-FAPI as an example, radioactive distribution can be observed in the salivary glands, thyroid, liver, biliary tract, gallbladder, pancreas, adrenal glands, kidneys, intestines, collecting system, and bladder, with almost complete excretion through the biliary tract. There is minimal radioactive imaging agent distribution in brain tissue. Compared to the liver, if a lesion shows significantly increased uptake, it is considered positive, suggesting malignant tumors. Generally, moderate intestinal distribution and non-focal intestinal uptake are considered non-pathological.

5.8 Report Writing

Objective The purpose of 8F-FAPI imaging report is to answer the clinical questions of the applicant and to clarify the adaptability, necessity and diagnostic efficacy of the examination.

Check process:

Registration and appointment ── Pre-examination preparation (no fasting required) ── Medical history inquiry and documentation, informed consent ── Signing of informed consent form ── 8F-FAPI drug injection ── Waiting period before scanning (approximately 1 hour) ── Scanning (approximately 20-30 minutes)

7 Statistical Considerations

7.1 Total Sample Size

Assuming we find in the literature that the sensitivity (Se) is 0.92, the specificity (S) is 0.88, the disease prevalence (P) is 0.05, we set the allowable error (d) to 0.08, the confidence level is 95% (Z=1.96): When we estimate the sample size using sensitivity, the formula yields

N=(1.962*0.92* （1-0.85） /0.052=113

The sample size was estimated to be 113 cases according to theoretical calculation.

Furthermore, based on previous studies, the potential loss-to-follow-up rate for patients is estimated at 5%-10%. This study anticipates a 10% loss-to-follow-up rate during the clinical trial, with a calculated total sample size of 120 cases.

7.2 Significance Level and Power of Clinical Studies

The significance level α was set at 0.05; the confidence level was 0.95.

7.3 Statistical Methods

Statistical analysis was performed using SPSS 17.0.

① Diagnostic performance evaluation, four-grid table index calculation:

Sensitivity = True positives / (True positives + False negatives) × 100%

Specificity = True negatives / (True negatives + False positives) × 100%

Positive predictive value = true positive / (true positive + false positive)

Negative predictive value = true negative / (true negative + false negative)

②ROC curve analysis:

Calculate the area under the curve (AUC) and evaluate diagnostic performance (AUC>0.9 indicates excellent, 0.8-0.9 indicates good, 0.7-0.8 indicates moderate).

Determine the optimal cutoff for SUV using the maximum Youden index.

③ consistency check

The consistency between 18F-FAPI PET/CT and pathological diagnosis was evaluated using the Kappa coefficient.

Kappa>0.8: Excellent consistency;

0.6-0.8: High consistency;

<0.6: Consistency should be interpreted with caution.

For two-tailed test, a p-value <0.05 was considered statistically significant.

④ survival analysis

Kaplan-Meier method:

Collect baseline PET parameters (lesion SUVmax, lesion SUVmean, MTV, LTV, bone marrow SUVmax, etc.), and plot PFS/OS curves according to treatment response (CR/PR vs. SD/PD), pathological response (e.g., MPR status), or PET parameter grouping (e.g., high/low SUVmax). Compare the significance of survival differences between groups using the Log-rank test (p<0.05).

Cox proportional hazards model:

Univariate analysis: Screening of clinical variables associated with PFS/OS (age, stage, SUVmax, MTV, etc.).

Multivariate analysis: Significant univariate variables (p<0.1) were included, with quantified hazard ratios (HR) and 95% confidence intervals.

Verify the proportional hazards assumption (Schoenfeld residual test).

8 Data Recording and Management

8.1 Investigator Data Records

1) For all eligible participants who have signed the informed consent form, their relevant data and laboratory test results must be meticulously and thoroughly documented.

2) All imaging data were interpreted by two attending physicians with over 5 years of experience in nuclear medicine, and the chief physician provided the final consensus interpretation for any questionable cases.

3) Adopt a prospective design to ensure standardized data collection (e.g., all preoperative imaging data of subjects are acquired under uniform equipment conditions).

4) Standardization processing (e.g., N4 bias field correction) is performed during the storage of original DICOM files to reduce the impact of image heterogeneity.

5) Original data records, signed by the investigator and dated.

6) Confirm that all adverse events have been documented, and that serious adverse events have been reported and recorded in accordance with relevant procedures in a timely manner.

9 Expected Research Progress

Study recruitment period: 36 months

Observation period: This study is a diagnostic trial, with the follow-up endpoint defined as the completion of 18F-FAPI PET/CT examination and the receipt of pathological results.

10 Adverse Event Assessment and Reporting

10.1 Definition of Adverse Events

Any adverse medical event unrelated to the examination and the use of the contrast agent that occurs during or after the medical imaging in a clinical trial, including symptoms, signs, or abnormal laboratory findings.

10.2 Major Adverse Events

The 18F-FAPI imaging agent generally does not cause adverse drug reactions, but the following risks may occur: mild allergic reactions such as rash and pruritus may occasionally occur, while severe adverse reactions such as shock are rare. Currently, no adverse events related to the 18F-FAPI imaging agent have been reported in domestic or international literature. In 2021, our center conducted 18F-FAPI PET scans ethically, with over 1,800 cases scanned to date, involving gastric cancer, esophageal cancer, pancreatic cancer, colorectal cancer, and hepatocellular carcinoma. The safety profile is favorable, with no adverse reactions observed.

Radiation safety: The risk model is based on the Linear No-Threshold (LNT) hypothesis, which posits that any dose of radiation may cause damage, and the risk increases with cumulative dose. Repeated medical imaging examinations (particularly those involving ionizing radiation, such as CT, PET/CT, and X-ray) may lead to cumulative radiation dose and potentially increase health risks. For high-risk populations (e.g., emergency patients, chronic disease patients, etc.), a rigorous risk assessment is required to weigh diagnostic benefits against radiation risks. According to the As Low As Reasonably Achievable (ALARA) principle,

dose-modulating techniques, optimized scanning protocols, avoidance of unnecessary examinations, reduction of repeat examinations, and optimized dose management should be implemented [6-8].

10.3 Documentation of General Adverse Events

All directly observed and subject-reported adverse events should be documented on the electronic case report form.

Researchers should avoid colloquial expressions and use standardized medical terminology to record adverse events, which should at least include:

- Start and end dates
- order of severity
- causality
- Measures taken
- Outcome of Adverse Events

10.4 Recording and Reporting of Serious Adverse Events

During the examination, all serious adverse events, regardless of their correlation with the contrast agent used in the study, must be immediately recorded on-site, including the time of occurrence, symptoms and signs, changes in vital parameters, as well as the name and dose of the radiopharmaceutical. The investigator should promptly administer appropriate treatment measures to the subject. In cases of contrast agent allergy, intramuscular injection of epinephrine (0.3 mg, concentration 1:1000) plus high-flow oxygen therapy should be administered. Simultaneously, a written report must be submitted to the clinical research management department of the affiliated clinical research institution, and the study sponsor must be notified in writing. The clinical trial management department must submit a written report to the relevant ethics committee and the provincial, autonomous region, or municipal food and drug administration and health authorities where the clinical research institution is located within 24 hours. For death events, the clinical research institution must provide all required documentation to the ethics committee and the study sponsor. Contact information is as follows:

Contact	contacts	contact number	portraiture
The First Affiliated Hospital of Zhejiang University School of Medicine	Chen Donghe	13777452235	0571-87236432

10.5 Management and Follow-up of Adverse Events

10.5.1 Management of Adverse Events

In the event of any adverse event during the study, the investigator should first assess its nature and implement necessary therapeutic measures to ensure the maximum protection of the subject's rights and interests.

10.5.2 Follow-up of Adverse Events

Investigators should conduct follow-up investigations for all adverse events (including serious adverse events) and perform regular follow-ups based on the condition until the adverse event reaches its final outcome, documenting the follow-up process and the outcome of the adverse event.

11. Quality Control and Quality Assurance

11.1 Laboratory Quality Control

18F-FAPI will customize specifications according to the quality standards of the 2015 edition of the "China Pharmacopoeia", testing the pH value, specific activity, radiochemical purity, radionuclide purity, and chemical purity of each batch of drugs, conducting regular batch-endotoxin testing and bacterial culture. The test report must include all items (including date, test items, test results, and their normal value ranges), and relevant personnel should sign.

11.2 Researcher Qualifications

Researchers participating in clinical studies must possess professional expertise, qualifications, and capabilities in clinical research, and pass qualification reviews. The personnel requirements should be relatively fixed.

11.3 Pre-study Researcher Training

The research team is responsible for conducting pre-study training to ensure that clinical researchers fully understand the overall study context, protocol, and related aspects.

11.4 Quality Assurance

Quality assurance is defined as planned and systematic activities established to ensure that studies, data generation, documentation, and reporting are conducted in accordance with the Good Clinical Practice for Radioactive Drugs (GCP-RD) and relevant regulatory requirements.

12 Personal Data and Data Protection

All data obtained in clinical studies are protected under data protection regulations. Investigators are prohibited from disclosing the names and other personal information of subjects (excluding date of birth/age and gender).

Similarly, data storage for statistical evaluation must be conducted under the subject's study ID. Only the investigator can identify the subject's name 或其他 personal details through the study ID.

If the name of a subject needs to be identified for medical reasons during the study, all relevant personnel are obligated to maintain confidentiality.

If you save and process personal data, you should pay attention to the requirements of data protection laws.

13 Confidentiality

All participants in this clinical study should treat the purpose, content, and results of this study as confidential.

14 Data Preservation

Investigators shall properly preserve the original records, including all subjects' records, along with all relevant supporting materials, namely hospital medical records, all signed original informed consent forms, and related documentation. Investigators shall retain clinical study materials for a period of ten years after the conclusion of the clinical study.

15 Research Summary and Termination

The lead unit is responsible for completing the clinical study summary report, confirming the content of the summary report, and signing and stamping it before submitting the summary to the center. The study sponsor shall,

in accordance with regulatory requirements, recover or archive all items, documents, and raw data, after which the clinical study shall be terminated.

16 Final Report and Disclosure Principles

The investigators should agree on the final study report.

The research findings may be published as scientific literature. The results may also be submitted to regulatory authorities.

17 Responsibilities of Each Party

17.1 Responsibilities of the Clinical Study Principal Investigator

（1） Conduct standardized training for all participants to familiarize them with the study protocol, unify the operational procedures, and standardize the recording methods and evaluation criteria.

（2） Ensure that the entire clinical research process is strictly conducted in accordance with the operational procedures.

（3） Strictly review the entered data to ensure the completeness, authenticity, and reliability of the electronic medical record report form. Ensure the traceability of the data.

17.2 Responsibilities of Medical Institutions Undertaking Clinical Research

(1) Provide the subject with a truthful explanation of the 18F-FAPI PET/CT scanning procedure and potential adverse reactions. Prior to the initiation of the clinical study, the subject must be given sufficient time to consider participation in the study.

(2) Accurately record adverse events and analyze their causes; adverse events and serious adverse events shall be reported within 24 hours of occurrence;

(3) When adverse events occur, clinical investigators shall promptly make clinical judgments and take measures to protect the interests of subjects; if necessary, the ethics committee has the authority to immediately terminate the clinical study.

(4) In case of discontinuation of clinical research, the subjects and the ethics committee shall be notified;

(5) Complete the clinical research report and be responsible for its accuracy and reliability;

(6) Obligation to maintain confidentiality regarding the materials provided by the research applicant.

18 Qualifications of Research Centers and Investigators

All investigators and research centers participating in this study must meet the following requirements prior to obtaining eligibility for this study:

1. Class IV Certificate for Radioactive Drugs;
2. Be equipped with professional technical personnel commensurate with the production of radioactive pharmaceuticals, possess facilities for safety, protection, and treatment of exhaust gases, waste, and wastewater, and establish a stringent quality management system;
3. While developing a new drug process route, it is essential to investigate the drug's physicochemical properties, purity (including radionuclide purity), testing methods, pharmacology, toxicology, animal pharmacokinetics, radioactivity, dosage, dosage form, and stability.
4. All investigators hold GCP certificates.
5. All investigators underwent standardized training prior to the study to familiarize themselves with the relevant injection doses, procedural protocols, scanning parameters, pharmacokinetic distribution characteristics, and lesion interpretation.

References：

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Informed Consent Form for Clinical Research Projects

Study Title: Prospective clinical study and exploration of ^{18}F-FAPI PET/CT imaging in cancers of unknown primary site

Plan ID:

Version: 2.4, October 17,2025

Version number of the informed consent form: 2.4, October 17,2025

Research institution: The First Affiliated Hospital of Zhejiang University School of Medicine

Principal Investigator: Chen Donghe

Subject Name: Subject Name Abbreviation: Subject Name: Subject Name Abbreviation:

Subject address:

Subject phone number:

We hereby invite you to participate in a clinical study. This informed consent form provides you with information to assist in your decision regarding participation in this clinical study. Please take the time to carefully review the following content. If you have any unclear questions or terms, you may discuss them with the relevant physician.

Your participation in this study is entirely voluntary. This study has been reviewed and approved by the Hospital Clinical Research Ethics Committee—IIT Ethics Review Panel.

Research Background：

Cancers of unknown primary site (CUPs) are a complex type of malignant tumor characterized by the inability to determine the location of the primary tumor despite standard clinical and pathological examinations. CUPs account for approximately 3-5% of all cancer cases, typically presenting with early metastasis and aggressive behavior, resulting in poor patient prognosis. Due to the lack of a definitive primary site, CUP patients often face limited treatment options, making effective diagnosis and treatment particularly crucial.

In the diagnostic process of CUPs, conventional imaging modalities such as CT and MRI often fail to accurately localize the primary tumor. In recent years, the development of positron emission tomography-computed tomography (PET/CT) has provided new possibilities for the detection of CUPs. Among these, 18F-FDG PET/CT has been widely applied in identifying primary tumors; however, in certain cases, its ability to distinguish small occult tumors from chronic inflammation is limited. In contrast, fibroblast activation protein inhibitor (FAPI) PET/CT, as an emerging imaging technique, has demonstrated promising potential in improving the accuracy of primary lesion localization.

FAPI PET/CT can more accurately identify malignant tumors by targeting fibroblast-activating protein (FAP). In one study, this technology successfully detected 51% of primary lesions in patients with unknown primary cancers of the head and neck, compared to only 25% detected by 18F-FDG PET/CT. Additionally, 18F-FAPI PET/CT demonstrated higher positive predictive value and accuracy, making it of significant value in altering treatment strategies.

This project aims to conduct a prospective study on 18F-FAPI PET/CT in patients with cancer of unknown primary, providing these patients with a more sensitive and reliable diagnostic tool, which is expected to improve their prognosis. Meanwhile, the application of this technology in different types of cancer still requires further research to verify its long-term efficacy and potential advantages.

purpose of research：

This study aims to evaluate the diagnostic efficacy, therapeutic assessment, prognostic analysis, and impact on clinical treatment decisions of 18F-FAPI PET/CT in patients with cancer of unknown primary.

Research process:

1. Patient Recruitment and Follow-up

This study adopted a prospective, single-center research design. It aimed to evaluate the diagnostic research and exploration of 18F-FAPI PET/CT in patients with cancer of unknown primary. A total of 120 subjects from one center (The First Affiliated Hospital of Zhejiang University School of Medicine) across the country were planned to be enrolled in this study.

（1） Indications: Patients with suspected cancer of unknown primary.

（2） Primary endpoint: Diagnostic efficacy of 18F-FAPI PET/CT in patients with undetermined primary tumor (sensitivity, specificity, accuracy)

（3） Selection criteria

I: Patients in our hospital with clinical or imaging findings suggestive of cancer of unknown primary;

II: Patients with previously diagnosed cancer of unknown primary origin suspected of recurrence or metastasis.

（4） exclusion criteria

I: Severe, uncontrollable disease or active infection;

II: Concurrent presence of other active malignant tumors or a history of other malignant tumors within the past 5 years;

III: Ineligible participants for informed consent.

IV: Pregnant and Lactating Women

（5） Study termination criteria: achievement of study objectives; occurrence of serious adverse events

（6） 18F-FAPI Description: The Nuclear Medicine PET Center holds a Class IV Certificate for Radioactive Drugs, enabling independent production and development of radioactive research medications. Currently, our department has successfully prepared 18F-FAPI, with drug quality testing meeting national pharmacopoeia standards for radioactive drugs and having passed small animal safety testing.

（7） Visit Schedule: For patients under follow-up treatment in this hospital, no in-person visits are required; relevant data can be obtained from the electronic medical record (EMR) system and imaging system of this hospital. For patients not receiving treatment in this hospital, telephone follow-up is implemented to obtain relevant pathological results.

2. Research Process and Operational Standards

(1) Medical history collection

Conduct a detailed inquiry into the patient's medical history to clarify symptoms, signs, and prior medical history (including tumor history, surgical history, biopsy history, radiotherapy history, chemotherapy history, family history, allergy history, previous imaging findings (such as plain X-ray, ultrasound, CT, MRI, 18F-FDG PET/CT, PET/MR, etc.), and recent pathological results (including tumor grading and Ki-67 index)).

(2) Patient Preparation and Precautions

①Pregnant women should avoid examinations unless the benefits outweigh the radiation risks to both the mother and fetus. ②Patients require adequate hydration to ensure rapid excretion of the contrast agent, thereby reducing systemic radiation dose and improving imaging quality. For patients without contraindications, they should be instructed to drink plenty of water before the examination and again after the contrast agent injection. Patients should be advised to empty their bladder prior to imaging. For patients with urinary incontinence, prior consultation with the clinician is recommended to consider indwelling catheters or urine bags. ③An intravenous access must be established before injection, and medication can be administered via a catheter to prevent contrast agent leakage. ④Patients do not need to fast and may take antihypertensive or hypoglycemic medications.

(3) Radioactive drugs

The recommended intravenous dose of 18F-FAPI is 3.7 MBq/kg body weight (0.1 mCi/kg body weight), with a typical range of 3.7-4.44MBq (0.1-0.12 mCi). For obese patients, the dose may be increased as appropriate. Additionally, the radiopharmaceutical should not be administered concomitantly with parenteral nutrition solutions.

(4) Image acquisition

The positioning of the patient's arms during positional scanning depends on the examination purpose. For a full-body examination, both arms should be placed at the sides of the body. If thoracic or abdominal scanning is required, the patient should be instructed to place both hands on the head.

CT Scanning Protocol CT scans are used for attenuation correction and lesion localization, while diagnostic CT scans can clarify the relationship between lesions and adjacent tissues or organs.

The CT scanning protocol depends on the indication for the examination and whether it can provide additional diagnostic information. With more diagnostic information and the resulting...

The increase in radiation dose from external sources needs to be weighed against the need to meet the low-dose principle.

The optimal image quality for PET acquisition is generally obtained 45 to 60 minutes after the contrast agent injection. A whole-body scan (from the head to the mid-femur) is typically performed, but localized acquisition may also be conducted based on clinical needs. The acquisition time per patient bed may vary depending on factors such as injection dose, attenuation time, body mass index (BMI), and detector type.

During the examination, excessive activity of the imaging agent in the urinary system may reduce image quality and interfere with the detection of adjacent organs, particularly pelvic organs. Patients are advised to drink plenty of water prior to the examination to achieve adequate hydration. Diuretics and catheterization may be employed when necessary to reduce the radiological activity of bladder urine.

Image processing utilizes the built-in system for iterative reconstruction. If equipment conditions permit, time-of-flight (TOF) technology may be additionally employed to acquire data and perform reconstruction. The optimal parameters for image processing and reconstruction depend on factors such as the patient and the detector.

(5) Inspection process:

Registration and appointment ── Pre-examination preparation (no fasting required) ── Medical history inquiry and documentation, informed consent ── Signing of informed consent form ── Injection of 18F-FAPI radiopharmaceutical ── Waiting period before scanning (approximately 1 hour) ── Scanning (approximately 20-30 minutes)

Risks and Discomforts of Participating in the Study:

CT or MR are routine imaging examinations for patients upon admission, particularly for the evaluation of head and neck or gastrointestinal tumors. However, CT or MR provide only local morphological imaging, while PET/CT, which offers systemic functional and integrated anatomical imaging, can compensate for their limitations. Therefore, some patients undergo routine 18F-FDG

PET/CT imaging prior to admission under clinical evaluation. For patients with suspected CUPs, the identification of the primary lesion site through specific imaging agents combined with systemic functional and integrated anatomical imaging can significantly aid in treatment planning. In this study, both CT or 18F-FDG PET/CT imaging and 18F-FAPI PET/CT scanning involve radiation exposure. Based on the risk model and the linear no-threshold (LNT) hypothesis, any radiation dose may cause damage, and the risk increases with cumulative dose. Repeated medical imaging examinations may lead to radiation dose accumulation and potentially increase health risks. For high-risk populations (e.g., emergency patients, chronic disease patients), strict risk assessment is required, and the diagnostic benefits must be weighed against radiation risks. Following the As Low As Reasonably Achievable (ALARA) principle, dose-modulated techniques, optimized scanning protocols, and avoidance of unnecessary examinations are employed. To avoid delaying patient care, 18F-FAPI PET/CT should be performed one week after routine imaging examinations. PET imaging scans are generally not hazardous. The equipment used in this clinical study complies with the 'Radiation Protection Requirements for X-ray Computed Tomography' and adheres to the principles of medical X-ray practice and protection.

The 18F-FAPI imaging agent generally does not cause adverse drug reactions, but the following risks may occur: 18F-FAPI may induce mild allergic reactions such as rash and pruritus, while severe adverse reactions like shock are rare. However, no adverse reaction events related to 18F-FAPI imaging scans have been reported in domestic or international literature to date. In response to potential adverse events, this clinical study has established corresponding SOP emergency procedures for adverse event management. If you experience any discomfort during the examination, please promptly inform the clinical researcher, and we will provide timely intervention. Our center initiated 18F-FAPI PET studies in 2021 with ethical approval, and to date, over 1,800 scans have been performed, involving gastric cancer, esophageal cancer, pancreatic cancer, colorectal cancer, and hepatocellular carcinoma. The safety profile is favorable, with no adverse reactions observed.

Alternative therapies (Are there any other medical options available to me besides participating in this study or not participating in it?): This study aims to evaluate the application value of 18F-FAPI PET/CT in patients with cancer of unknown primary, with a particular focus on its role in primary tumor localization, treatment decision-making, and prognosis assessment, in order to provide a more effective diagnostic tool for clinical practice, without involving specific treatment modalities or protocols.

Benefits of participating in the study:

If you agree to participate in this study, you may potentially gain direct medical benefits in the localization and characterization of tumor lesions; however, you may also not benefit, but this could be beneficial for similar patients. We hope that the information obtained from your participation in this study will be instructive for patients with the same condition in the future.

Costs associated with participating in the study: 18F-FAPI PET/CT examination is free of charge

Compensation: A report with images and text, along with a DVD disc, will be compiled from PET color film and 15-20 sheets of 8x12 inch Hiti high-quality photo paper.

Compensation: According to China's Good Clinical Practice (GCP) and the Ethical Review Measures for Biomedical Research Involving Human Subjects, the rights and interests of participants in clinical research are protected as follows: For physical injuries directly caused by research interventions or procedures (such as adverse drug reactions or examination complications), the medical institution where the researcher is located shall bear the treatment costs and provide reasonable compensation. The scope of compensation includes: treatment expenses, lost income, transportation subsidies, and other direct economic losses (based on Article 1219 of the Civil Code regarding medical liability). Exclusions from compensation: Non-research-related damages (such as disease progression or side effects of non-specified concomitant medications) are not covered. Predictable known adverse reactions (such as post-chemotherapy hair loss) that were explicitly informed in the informed consent form and signed by the participant do not trigger compensation.

Right to Refuse Participation or Withdrawal from the Study: You may choose not to participate in this study or have the right to withdraw at any stage of the trial without any reason, and your medical treatment and benefits will not be affected by this decision. Once you decide to participate in this study, please sign this informed consent form to indicate your agreement. Prior to enrollment, a physician will conduct a screening to confirm whether you are a suitable candidate.

Privacy and confidentiality:

During the study period, your personal information such as name and gender will be replaced with pseudonyms or numbers and strictly confidential. Only the relevant physicians will be aware of your data, and your privacy rights will be well protected. Study conclusion

The results may be published in a journal, but no personal information will be disclosed. If you agree to participate in this study, all your medical records will be reviewed by relevant personnel from the

research institution initiating this study, relevant authoritative agencies, or an independent ethics committee to assess the study's implementation.

Is it appropriate? If you have signed the informed consent form, it means you agree to allow the aforementioned personnel to review your information. How to obtain assistance in the study:

You may access relevant information and updates on this study at any time. For inquiries related to this research, please contact Chen Donghe at 87236432. Contact details for the Clinical Research Ethics Committee—IIT Ethics Review Panel: No.79 Qingchun Road, Shangcheng District, Hangzhou, Zhejiang Province, 0571-87233418.

Informed Consent Signature-Consent Page

If you fully understand the content of this research project and agree to participate in this study, you will sign this informed consent form in duplicate, with one copy retained by the investigator and one by the participant or their authorized representative.

Clinical Research Project Title: Prospective Clinical Study on the Application of 18F-FAPI PET/CT Imaging in Cancer with Unknown Primary Lesion

Signed by the subject or their legal representative:

Agree to the statement:

1、 I confirm that I have read and understood the informed consent form for this study, and that the potential issues and solutions during the research process have been explained to me, with the opportunity to raise my own questions.

2、 I have been made aware that participation in the study is voluntary and that my refusal to participate in the study will not compromise any of my legitimate interests.

3、 I have been informed that the physicians participating in this study, the person in charge of this work at the First Affiliated Hospital of Zhejiang University, and the medical

ethics committee have the authority to review the study records and case materials. I agree that the aforementioned personnel may directly access my study records and understand that such information will be treated confidentially.

4、 I agree to participate in this study

Subject signature:_____ date：

Contact information for participants:

(Note: If the subject is incapacitated or has limited capacity, the guardian's signature and date must be included.)

Guardian's signature:_____date：

Guardian contact information:_____Guardian and subject relationship:

(Note: If the subject is unable to read the informed consent form, an independent witness must be present to confirm that the investigator has informed the subject of all the contents of the informed consent form. The witness must sign and date the document.)

Independent Witness Signature:_____date：

Contact information for independent witnesses:

Researcher's signature:_____date：

Contact information for researchers: