scenario name

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

Version: 1.2

Version date: 2025.11.7

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

Study sponsor: Chen Donghe

7 November 2025

Revision History

edition	date	imprint
1.0	2025-8-26	first draft
1.1	2025-10-6	First Edition Revision
1.2	2025-11-7	Second Edition Revision

List of Multicenter Clinical Trial Sites

Research Principal Investigator and Principal Research Institution Information

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Join event list

Center number	Clinical Trial Institution Name
01	Zhejiang Provincial People's Hospital
02	Shulan (Hangzhou) Hospital
03	
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Researcher's Statement and Signature Page

This study is a prospective clinical trial, and the methodologies, equipment, and medications used have been widely applied 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 notified immediately, 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 when the study results are published.

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

Researcher's signature:

Date of signature:

scenario summary

Study name	Prospective clinical study of 18F-FAPI PET imaging in the diagnosis of lung cancer
Study protocol	This study adopted a prospective, multicenter research design. It aimed to evaluate the diagnostic research and exploration of 18F-FAPI PET/CT in lung cancer patients. A total of 120 subjects were planned to be enrolled from three centers nationwide (The First Affiliated Hospital of Zhejiang University School of Medicine, Zhejiang Provincial People's Hospital, and Shulan Hangzhou Hospital).
research design	perspective study
Number of research centers	3
sample capacity	120
indicatio	patients with suspected or confirmed lung cancer who have undergone 18F-FAPI PET/CT
purpose of research	The purpose of this study was to evaluate the diagnostic efficacy and prognostic value of 18F-FAPI PET/CT in lung cancer.
primary end point	Diagnostic efficacy of 18F-FAPI PET/CT in lung cancer (sensitivity, specificity, accuracy)
Selection criteria	(1) Patients suspected or diagnosed with lung cancer (2) 18F-FAPI PET/CT has been performed.
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 who cannot provide informed consent for the study; (4) Pregnant and lactating women.
study termination criteria	1. Achieve the research objectives; 2. Occurrence of severe adverse events
18F-FAPI Instructions	The Nuclear Medicine PET Center holds a Class IV Certificate for Radioactive Drugs, enabling independent production and development of radiopharmaceuticals for scientific research. 18F-FAPI is a routinely performed tracer in our hospital, with over 1,800 cases of 18F-FAPI PET/CT scans completed to date, primarily including pancreatic cancer, gastric cancer, colorectal cancer, and head and neck tumors.
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.

English abbreviation reference

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

1 Research Background

1.1 Current Status of Lung Cancer

Lung cancer is one of the most common malignant tumors worldwide, with its mortality rate ranking first among all cancers. According to the latest epidemiological data, the five-year survival rate of lung cancer is only 19.7%, indicating that the disease poses a serious threat to human health [1]. The incidence of lung cancer varies significantly across different regions, particularly in China, where both the incidence and mortality rates are higher than the global average. In some areas, such as certain coal mining regions in Yunnan, the incidence of lung cancer has significantly increased due to environmental pollution [2].

1.2 Research Progress of 18F-FAPI PET/CT in the Diagnosis of Lung Cancer

In recent years, 18F-FAPI PET/CT, as an emerging imaging technology, has demonstrated excellent sensitivity and specificity in the diagnosis of lung cancer. Studies have shown that 18F-FAPI PET/CT exhibits significant advantages in detecting lung adenocarcinoma (LAD). A prospective study revealed that 18F-FAPI PET/CT achieved a 100% detection rate for primary tumors. Moreover, in lesions within lymph nodes, pleura, bones, and other tissues, the maximum standard uptake value (SUVmax) of 18F-FAPI was generally higher than that of 18F-FDG. Additionally, 18F-FAPI PET/CT identified more lesions in the detection of lymph nodes, brain, and pleural lesions [3]. These findings indicate that 18F-FAPI PET/CT holds important clinical value in the early diagnosis and staging of lung cancer. Particularly in cases with low 18F-FDG affinity, 18F-FAPI PET/CT provides clearer imaging and higher SUVmax values [4]. Meanwhile, mediastinal and hilar lymph nodes still exhibit a high false-positive rate on 18F-FDG PET, whereas 18F-FAPI PET/CT enhances the specificity of lymph node diagnosis.

Furthermore, 18F-FAPI PET/CT has demonstrated high diagnostic efficacy in the staging evaluation of lung cancer patients. Studies have found that 18F-FAPI PET/CT achieves a diagnostic efficacy of 95.3% in T-stage classification, significantly superior to the 57.1% efficacy of 18F-FDG PET/CT [5]. This difference may be attributed to the specific binding of 18F-FAPI to fibroblast activation protein (FAP) in the tumor microenvironment, which enhances its sensitivity in tumor tissue recognition.

In comparative studies, 18F-FAPI PET/CT has also been found to be a viable alternative to 18F-FDG PET/CT in certain scenarios, particularly for tumors with low 18F-FDG affinity or cases with ambiguous imaging findings. Although 18F-FDG PET/CT remains the preferred imaging modality in specific situations, the potential of 18F-FAPI PET/CT as a complementary imaging approach should not be overlooked [4]. This complementarity offers novel insights into the comprehensive diagnosis of lung cancer, especially in the management of complex cases.

1.3 Current Challenges

1.3.1 The diagnostic efficacy of 18F-FAPI PET/CT in different lung cancer subtypes requires further validation

Although existing studies have demonstrated the significant efficacy of 18F-FAPI PET/CT in certain tumor types, its diagnostic performance across different lung cancer subtypes remains to be further validated. Significant biological and clinical differences exist among various lung cancer subtypes, particularly non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). Research indicates that the clinical validation of 18F-FAPI PET/CT for identifying lung cancer subtypes has not been sufficiently established. For instance, one study revealed that the sensitivity and specificity of 18F-FAPI PET/CT in detecting lung cancer differ from those of conventional 18F-FDG PET/CT, especially regarding tumor burden and metabolic activity across different subtypes [6]. Therefore, the specific diagnostic capabilities for various lung cancer subtypes still require validation through large-scale clinical trials.

1.3.2 Consistency of Imaging Evaluation Criteria in the Assessment of Treatment Efficacy for Lung Cancer

Currently, the most commonly used imaging evaluation standard is the Response Evaluation Criteria in Cancer (RECIST 1.1), which primarily relies on unidimensional measurements of tumor size. However, the limitation of RECIST 1.1 lies in its failure to adequately account for the biological characteristics of tumors and the complexity of treatment responses. For instance, the introduction of immunotherapy has made tumor response patterns more complex, potentially leading to temporary increases in tumor volume, which may be misinterpreted as disease progression under the traditional RECIST criteria. Consequently, 18F-FAPI PET/CT-based evaluation standards such as iRECIST have emerged to better reflect the efficacy of immunotherapy and account for the dynamic changes in tumor responses [7].

1.3.3 The Importance of 18F-FAPI PET/CT in Prognostic Prediction of Lung Cancer

There is a significant correlation between imaging features and tumor mutational burden (TMB), and imaging assessment can serve as an effective tool for predicting immune therapy response [26]. This combination not only improves the accuracy of efficacy prediction but also provides new insights for personalized treatment. However, as an emerging imaging technology, 18F-FAPI PET/CT still requires further research in predicting patient prognosis and treatment response.

Based on this, the present study adopted a prospective, multicenter research design to evaluate the diagnostic efficacy and prognostic value of 18F-FAPI PET/CT in lung cancer.

2 Objectives and Content of Clinical Research

2.1 Objectives of Clinical Research

The purpose of this study was to evaluate the diagnostic efficacy and prognostic value of 18F-FAPI PET/CT in lung cancer.

Primary endpoint: Diagnostic efficacy of 18F-FAPI PET/CT in lung cancer patients (sensitivity, specificity, accuracy)

secondary end points:

① Compare the diagnostic performance differences of 18F-FAPI PET/CT with CT, MR, and 18F-FDG PET imaging in clinical applications for lung cancer;

②Analysis of diagnostic differences in the subgroup of patients (pathological, genetic, etc.) using 18F-FAPI PET/CT;

③ Evaluation of 18F-FAPI PET/CT in predicting lung cancer prognosis.

2.1 Content of Clinical Studies

2.1.1 Evaluation of the Diagnostic Performance of 18F-FAPI PET/CT

This study aims to evaluate the sensitivity, specificity, and accuracy of 18F-FAPI PET/CT in lung cancer patients, providing a basis for clinical application. By performing 18F-FAPI PET/CT scans on lung cancer patients and collecting relevant data, the performance of this modality in early diagnosis, staging, and recurrence monitoring was analyzed. The goal is to provide a scientific basis for clinical decision-making in the diagnosis and treatment of lung cancer.

2.1.2 Comparative Study of 18F-FAPI PET/CT with Other Imaging Techniques (CT, MR, FDG PET/CT)

A comparative study of 18F-FAPI PET/CT versus conventional imaging modalities (CT or MR) or 18F-FDG PET/CT in lung cancer patients, evaluating the differences in tumor detection sensitivity, specificity, and accuracy among various imaging techniques. The study aims to clarify their advantages in clinical applications for lung cancer. The research will focus on analyzing the differences in tumor size, location, metastasis, and pathological characteristics among the imaging techniques, exploring the potential of 18F-FAPI PET/CT in improving diagnostic accuracy and early detection of lung cancer.

2.1.3 Diagnostic differences in the 18F-FAPI PET/CT analysis of lung cancer subgroups

Subgroup analysis was performed based on pathological type, stage, and molecular subtype, stratified by disease pathological type (adenocarcinoma/squamous cell carcinoma/small cell lung cancer), stage (early/advanced), and molecular subtype (EGFR mutation-positive, ALK-positive, ROS1-positive). The aim was to evaluate the differences in sensitivity and specificity of 18F-FAPI PET/CT across different patient populations. This study will help identify which specific types of lung cancer patients are more likely to benefit from 18F-FAPI PET/CT, thereby providing a basis for the development of individualized treatment plans.

2.1.4 Evaluation of 18F-FAPI PET/CT in Predicting Lung Cancer Prognosis

Based on TNM staging and PERCIST criteria, this study evaluates the post-treatment reassessment, efficacy prediction, and prognostic assessment (AUC comparison of PFS/OS) of 18F-FAPI PET/CT in lung cancer. The research will analyze the monitoring capability of 18F-FAPI PET/CT in assessing tumor response post-treatment

and its value in prognostic evaluation, aiming to provide clinicians with a more precise tool for assessing treatment efficacy. It tracks the time from diagnosis to specific events (e.g., CR, PR, SD, PD, recurrence, death) in lung cancer patients to identify influencing factors. Survival rates over time are plotted using Kaplan-Meier curves to visually compare survival differences across groups. Additionally, Cox proportional hazards model multivariate regression quantifies the contribution of factors such as age and pathological stage to survival risk, aiding clinical decision-making.

3 Mechanism of Action and Research Scope of 18F-FAPI PET/CT

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 modality for tumor diagnosis and therapeutic efficacy evaluation. However, 18F-FDG PET/CT exhibits relatively low sensitivity and specificity for tumors with low invasiveness, high differentiation, or mucinous tissue, while physiological uptake in organs such as the oropharynx and digestive tract often obscures tumor metabolism and uptake. Additionally, mediastinal and hilar lymph nodes still show a high rate of false positives on 18F-FDG PET, whereas 18F-FAPI PET/CT improves the specificity of lymph node diagnosis. Furthermore, compared to 68Ga-labeled tracers, 18F-labeled FAPI has better resolution potential due to its lower positron energy. Therefore, 18F-labeled FAPI holds significant clinical value and promising prospects.

4 Indications, Contraindications, and Precautions

4.1 Eligibility Criteria: Patients with suspected or confirmed lung cancer who have undergone 18F-FAPI PET/CT

4.2 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.

5 、 system design

5.1 Research Methods

This study adopted a prospective, multicenter research design. It aimed to evaluate the diagnostic research and exploration of 18F-FAPI PET/CT in lung cancer patients. A total of 120 subjects were planned to be enrolled from three centers nationwide (The First Affiliated Hospital of Zhejiang University School of Medicine, Zhejiang Provincial People's Hospital, and Shulan Hangzhou Hospital).

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 with suspected or confirmed lung cancer

(2) 18F-FAPI PET/CT has been performed.

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 subjects through the hospital's electronic medical record system. Subjects who do not meet the study requirements based on their personal conditions will not be approved to participate in the study.

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.

If a participant fails to respond to three telephone follow-ups, a registered mail letter must subsequently be sent to the participant. If the participant does not respond to the letter, the participant will be considered as having "lost to follow-up" for current study visits or telephone contacts. The investigator must record this information on the original data sheet. 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 patients who undergo examinations may participate in safety analysis as appropriate.

5.3.4 Selection Time

October 2025 to October 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 lung cancer patients (sensitivity, specificity, accuracy)

secondary end points:

① Compare the diagnostic performance differences of 18F-FAPI PET/CT with CT, MR, and 18F-FDG PET imaging in clinical applications for lung cancer;

②Analysis of diagnostic differences in the subgroup of patients (pathological, genetic, etc.) using 18F-FAPI PET/CT;

③ Evaluation of 18F-FAPI PET/CT in predicting lung cancer prognosis.

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 the study can proceed.

Prior to the commencement of the study, each investigator obtained written and dated approval/endorsement from the respective IEC for the study protocol (and any amendments), written informed consent, consent updates, and all other written information to be provided to the subjects. The written approval should be indicated, citing the final protocol version number and version date. The composition details of the IEC should be provided to the study sponsor for retention in the main study folder, including the names of the members and their roles within the committee (e.g., Chair, Expert, Founding Member).

During the study period, all documents requiring review should be submitted to the IEC by the study sponsor or investigator in accordance with national regulations.

Informed consent is a measure to protect participants. Prior to the study, investigators must provide detailed information about the clinical study to the participant or their guardian, 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.

history-taking

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.), along with the patient's follow-up medical records.

Image judgment criteria

The uptake of imaging agents in tissues or organs that normally do not take up such agents 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 distribution of the radioactive imaging agent in brain tissue. Compared to the liver, if the uptake is significantly increased in a lesion, it is considered positive, suggesting malignant tumors. Generally, moderate intestinal distribution and non-focal intestinal uptake are considered non-pathological.

Record the primary lesion location, number of metastatic lesions, SUVmax, and tumor volume, among other PET parameters.

7 Statistical Considerations

7.1 Total Sample Size

Assuming we obtained the sensitivity (Se) of 0.92, specificity (Se) of 0.96, and disease prevalence (P) of 0.05 from the literature [9-11], we set the allowable error (d) to 0.08, with a confidence level of 95% (Z=1.96). When estimating the sample size using sensitivity, the formula yields

N=(1.962*0.95*（1-0.95）/0.052=113

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

In addition, based on previous studies, the potential loss-to-follow-up rate for patients is estimated to be 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. This is a multicenter study, with 80 cases from our center (The First Affiliated Hospital of Zhejiang University School of Medicine), 20 cases from Zhejiang Provincial People's Hospital, and 20 cases from Shulan Hangzhou Hospital.

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. 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/CT diagnosis and pathological diagnosis was assessed using the kappa test. A p-value <0.05 was defined as statistically significant.

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 Negative / (True Negative + False Positive) × 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.

Bilateral test, $p<0.05$ defined as significant difference.

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

4) 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

Observational study duration: This study was an observational study, with patient mortality serving as the endpoint of follow-up.

10 Adverse Event Assessment and Reporting

10.1 Definition of Adverse Events

Adverse medical events (AMEs) in clinical trials during follow-up, including discomfort symptoms, signs or abnormal laboratory findings, and imaging abnormalities.

10.2 Major Adverse Events

New-onset clinical symptoms (e.g., fever), laboratory abnormalities (e.g., liver enzyme levels exceeding 3 times the upper limit), exacerbation of pre-existing conditions (e.g., worsening cardiac function classification), or imaging abnormalities (e.g., pneumothorax).

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 study period, all serious adverse events shall be immediately reported by the investigator to the attending physician or nurse-in-charge, and simultaneously submitted in writing to the clinical research management department of the affiliated clinical research institution, with written notification to the study sponsor. The clinical trial management department shall submit a written report to the relevant ethics committee and the provincial, autonomous region, or municipal food and drug administration and health and family planning authorities where the clinical research institution is located within 24 hours. For death events, the clinical research institution shall provide the ethics committee and the study sponsor with all required documentation. 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 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.

11.2 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.

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.

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. Qualified for 18F-FAPI PET/CT scanning.
2. All investigators hold GCP certificates.
3. 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 lung cancers

Plan ID:

Version: 1.2, November 7, 2025

Version number of the informed consent form: 1.2, November 7, 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：

Lung cancer is one of the most common malignant tumors worldwide, with its mortality rate ranking first among all cancers. According to the latest epidemiological data, the five-year survival rate of lung cancer is only 19.7%, indicating that the disease poses a serious threat to human health [1]. The incidence of lung cancer varies significantly across different regions, particularly in China, where both the incidence and mortality rates are higher than the global average. In some areas, such as certain coal mining regions in Yunnan, the incidence of lung cancer has significantly increased due to environmental pollution [2].

In recent years, 18F-FAPI PET/CT, as an emerging imaging technology, has demonstrated excellent sensitivity and specificity in the diagnosis of lung cancer. Studies have shown that 18F-FAPI PET/CT exhibits significant advantages in detecting lung adenocarcinoma (LAD). A prospective study revealed that 18F-FAPI PET/CT achieved a 100% detection rate for primary tumors. Moreover, in lesions within lymph nodes, pleura, bones, and other tissues, the maximum standard uptake value (SUVmax) of 18F-FAPI was generally higher than that of 18F-FDG. Additionally, 18F-FAPI PET/CT identified more lesions in the detection of lymph nodes, brain, and pleural lesions [3]. These findings indicate that 18F-FAPI PET/CT holds important clinical value in the early diagnosis and staging of lung cancer. Particularly in cases with low 18F-FDG affinity, 18F-FAPI PET/CT provides clearer imaging and higher SUVmax values [4]. Meanwhile, mediastinal and hilar lymph nodes still exhibit a high false-positive rate on 18F-FDG PET, whereas 18F-FAPI PET/CT enhances the specificity of lymph node diagnosis.

Furthermore, 18F-FAPI PET/CT has demonstrated high diagnostic efficacy in the staging evaluation of lung cancer patients. Studies have found that 18F-FAPI PET/CT achieves a diagnostic efficacy of 95.3% in T-stage classification, significantly superior to the 57.1% efficacy of 18F-FDG PET/CT [5]. This difference may be attributed to the specific binding of 18F-FAPI to fibroblast activation protein (FAP) in the tumor microenvironment, which enhances its sensitivity in tumor tissue recognition.

Although existing studies have demonstrated the significant efficacy of 18F-FAPI PET/CT in certain tumor types, its diagnostic performance across different lung cancer subtypes remains to be further validated. Significant biological and clinical differences exist among various lung cancer subtypes, particularly non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). Research indicates that the clinical validation of 18F-FAPI PET/CT for identifying lung cancer subtypes has not been sufficiently established. For instance, one study revealed that the sensitivity and specificity of 18F-FAPI PET/CT in detecting lung cancer differ from those of conventional 18F-FDG PET/CT, especially regarding tumor burden and metabolic activity across different subtypes [6]. Therefore, the specific diagnostic capabilities for various lung cancer subtypes still require validation through large-scale clinical trials.

Currently, the most commonly used imaging evaluation standard is the Response Evaluation Criteria in Cancer (RECIST 1.1), which primarily relies on unidimensional measurements of tumor size. However, the limitation of RECIST 1.1 lies in its failure to adequately account for the biological characteristics of tumors and the complexity of treatment responses. For instance, the introduction of immunotherapy has made tumor response patterns more complex, potentially leading to temporary increases in tumor volume, which may be misinterpreted as disease progression under the traditional RECIST criteria. Consequently, 18F-FAPI PET/CT-based evaluation standards such as iRECIST have emerged to better reflect the efficacy of immunotherapy and account for the dynamic changes in tumor responses [7].

In the treatment of lung cancer, the accuracy of imaging evaluation directly impacts the assessment of therapeutic efficacy. Taking 18F-FDG PET/CT as an example, this technology has demonstrated good sensitivity and specificity in evaluating treatment responses in patients with non-small cell lung cancer (NSCLC). Studies have found that 18F-FDG PET/CT can identify early post-treatment metabolic changes in tumors, thereby providing clinicians with timely feedback to adjust treatment regimens and improve patient survival rates [8]. Therefore, combining imaging evaluation with emerging biomarkers enables a more comprehensive assessment of treatment outcomes. Additionally, there is a significant correlation between imaging features and tumor mutation burden (TMB), making imaging evaluation an effective tool for predicting immune therapy responses [26]. This integration not only enhances the accuracy of efficacy prediction but also offers new insights for personalized treatment. However, as an emerging imaging technology, 18F-FAPI PET/CT still requires further research for predicting and evaluating patient prognosis and treatment responses.

purpose of research：

The purpose of this study was to evaluate the diagnostic efficacy and prognostic value of 18F-FAPI PET/CT in lung cancer patients.

Research process:

This study adopted a prospective, multicenter research design. It aimed to evaluate the diagnostic research and exploration of 18F-FAPI PET/CT in lung cancer patients. A total of 120 subjects were planned to be enrolled from three centers nationwide (The First Affiliated Hospital of Zhejiang University School of Medicine, Zhejiang Provincial People's Hospital, and Shulan Hangzhou Hospital).

（1） Indications: Patients with suspected or confirmed lung cancer who have undergone 18F-FAPI PET/CT.

（2） Primary endpoint: Diagnostic efficacy of 18F-FAPI PET/CT in lung cancer (sensitivity, specificity, accuracy)

（3） Selection criteria

I: Patients with clinical or imaging suspicion of lung cancer;

II: 18F-FAPI PET/CT scan has been performed.

（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. 18F-FAPI is a routinely performed tracer in our hospital, with over 1,800 cases

of 18F-FAPI PET/CT scans completed to date, primarily for pancreatic cancer, gastric cancer, colorectal cancer, and head and neck tumors.

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

（8） Study plan: A total of 120 eligible patients will be enrolled over a 3-year period, with pathological outcomes followed up and statistically analyzed.

（9） 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 value) were evaluated using the ROC curve. 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.

Specific projects in which patients participate:

1、Patients clinically suspected or confirmed with lung cancer are required to complete conventional imaging examinations (CT/MR or FDG PET) and undergo ^{18}F-FAPI PET/CT.

2、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.), as well as relevant laboratory tests and previous imaging findings (including plain radiography, ultrasound, CT, MRI, 18F-FDG PET/CT, PET/MR, etc.).

3、For follow-up coordination, you are required to regularly provide your clinical data (e.g., treatment plans, disease progression, etc.) as per the study requirements. This collaboration is essential for completing long-term follow-up, including monitoring the subject's condition, imaging findings, pathological results (such as tumor grading and Ki-67 index), and patient treatment outcomes, to collect prognostic information.

4、^{18}F-FAPI PET/CT and conventional imaging examinations (e.g., CT/MR) were completed prior to enrollment. After enrollment in this study, subjects were not required to undergo additional imaging or laboratory tests, only requiring follow-up without intervention to the clinical treatment plan.

Risks and Discomforts of Participation: This study is an observational study. During clinical follow-up, subjects may experience adverse medical events, including new-onset clinical symptoms (e.g., fever), laboratory abnormalities (e.g., liver enzyme levels exceeding 3 times the upper limit), exacerbation of pre-existing conditions (e.g., worsening of cardiac function classification), or imaging abnormalities (e.g., pneumothorax).
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.
The ^{18}F-FAPI PET/CT examination involves radioactive radiation. The physical half-life of the ^{18}F radionuclide is 108.5 minutes, and after 4-5 half-lives, the radiation is essentially completely metabolized in the body, with an effective dose of approximately 10-20 mSv, which complies with safety standards. Moreover, the radiation is rapidly metabolized, posing an extremely low risk to healthy adults. The equipment adheres to the "Radiation Protection Requirements for X-ray Computed Tomography" and complies with the principles of medical X-ray practice and protection.
The ^{18}F-FAPI contrast agent generally does not cause drug adverse events, but the following risks may occur: Mild allergic reactions such as rash and pruritus may occur with ^{18}F-FAPI, while severe adverse reactions such as shock are rare. However, no adverse reaction events related to ^{18}F-FAPI imaging scans have been reported in domestic or international literature to date.

Alternative treatment (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 the diagnosis of lung cancer. It is an observational study, with a particular focus on its role in the diagnostic efficacy of lung cancer and the assessment of prognostic prediction, aiming to provide a more effective diagnostic tool for clinical use. It does not involve 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 and other conventional imaging diagnostic methods are routinely performed in clinical practice. Application forms can be obtained for both outpatient and inpatient services, and these examinations are completed prior to enrollment. Therefore, the costs of pre-enrollment imaging examinations are borne by the participants themselves.

Compensation: None.

Compensation: During your participation in this clinical study, if you suffer any harm related to the study or experience serious adverse events, you may be entitled to corresponding compensation under the laws of China.

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 codes 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 Imaging in the Diagnosis and Treatment of Lung Cancer

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 consent 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 of signing are required.)

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: