RESEARCH PROTOCOL

Evaluation of Dual-Targeted 68Ga-FAPI-PSMA PET/CT for the Diagnosis and Staging of Solid Tumors

Protocol Number: 2023KT107-ZY02

Version: 3.0

Version Date: January 17, 2026

Last Approved: March 24, 2026

Funding Source: Institutional Research Fund [Anonymized]

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English translation prepared for submission use. Researcher names and direct identifying contact details have been anonymized at the user's request.

1. Study Background

1.1 Clinical Problem

Prostate cancer is the second most common cancer among men worldwide, with nearly 1.3 million patients annually, accounting for 13.5% of newly diagnosed cancers [1]. In recent years, the incidence in China has shown a rapid upward trend. In 2016, the number of new cases reached 120,000, ranking fifth among male malignant tumors and becoming the most common tumor of the male genitourinary system in China. It is expected that in the next decade, both the incidence and mortality of prostate cancer in China will further increase. By 2030, the number of new prostate cancer cases in China will reach 237,000 [2].

The mortality rate of prostate cancer in China is higher than that in Europe and the United States, mainly due to the lack of effective diagnostic and treatment guidance methods. "Early diagnosis and early treatment" is an important means to prolong the survival of cancer patients and reduce cancer mortality. Therefore, early precise diagnosis, clinical staging, and treatment guidance for prostate cancer are crucial for improving patient prognosis.

In the context of the "precision medicine" era, precise surgical resection based on early diagnosis of prostate cancer is the optimal treatment strategy. Existing imaging techniques such as preoperative biopsy, PSA testing, CT, magnetic resonance imaging, and positron emission tomography/computed tomography (PET/CT) play an important role in lesion evaluation. However, due to spatiotemporal differences and significant discrepancies between intraoperative anatomy and preoperative imaging, surgeons currently still rely mainly on experience, using palpation and visual inspection to identify and remove lesions during surgery. This can easily result in missed resection of small lesions and is one of the main causes of postoperative tumor recurrence.

How to accurately detect lesions at an early stage, identify lymph node metastasis, and define tumor boundaries, while completely removing tumors and preserving normal tissue structures as much as possible, thereby reducing recurrence and postoperative complications, remains a major challenge in clinical surgery.

At the same time, liver cancer, as one of the most common malignant tumors worldwide, also has a high incidence and mortality rate, ranking as the fifth most common cancer and the second leading cause of cancer-related death in China. Liver cancer has an insidious onset, with no obvious symptoms in the early stage, and most patients are diagnosed at middle or advanced stages, missing the optimal treatment opportunity. Similar to prostate cancer, surgical resection of liver cancer also faces major challenges in intraoperatively defining tumor boundaries in real time and identifying small lesions and satellite lesions, in order to ensure radical tumor resection while preserving functional liver tissue to the greatest extent.

1.2 PSMA as an Important Target for Clinical Diagnosis of Prostate Cancer

Prostate-specific membrane antigen (Prostate Specific Membrane Antigen, PSMA) possesses the functions of glutamate carboxypeptidase II (GCPII) and folate hydrolase 1 (FOLH1), and is capable of catalyzing the hydrolysis of N-acetylaspartylglutamate (NAAG) or other glutamate derivatives [3].

As a prostate cancer-specific membrane antigen, PSMA is overexpressed in nearly all prostate cancer samples (including high-grade malignant tumors, metastatic prostate

cancer, and castration-resistant prostate cancer), while it is only minimally expressed in normal tissues such as lacrimal glands, salivary glands, and proximal renal tubules.

Therefore, PSMA is an ideal biomarker for highly sensitive and highly specific imaging localization of metastatic prostate cancer lesions. Nuclear medicine PSMA-targeted probes with high specificity and favorable pharmacokinetic properties have important clinical significance in the diagnosis of prostate cancer. They can accurately assess the risk stratification of prostate cancer and also have potential for imaging in other tumors, with the prospect of becoming a new "century molecule" (potentially comparable to 18F-FDG).

Therefore, the development of molecular probes with specificity for prostate cancer will contribute to the precise diagnosis and treatment of prostate cancer. In recent years, specific small-molecule probes targeting PSMA have made major breakthroughs in the diagnosis, staging, prognosis, and recurrence monitoring of prostate cancer.

Large-scale data studies have shown that PSMA PET/CT has significant advantages over conventional imaging in detecting recurrent prostate cancer lesions [4], and has been recommended by NCCN and EAU guidelines for recurrence monitoring of prostate cancer.

1.3 Nuclear Medicine Diagnostic Probes Targeting PSMA

Molecular probes targeting PSMA were first developed based on antibody research (monoclonal antibodies such as 7E11 and J591), which have been applied in radionuclide imaging and targeted therapy studies [6, 7].

Early studies confirmed the feasibility of this approach; however, antibodies have limitations when used as routine clinical molecular imaging tools. These include long in vivo metabolic time, potential immune rejection, slow clearance from blood and non-target tissues, nonspecific uptake in organs, low tumor penetration, and prolonged retention of long half-life radionuclides in vivo, which may cause a certain degree of radiation damage to the body.

In contrast, small-molecule imaging agents have significant advantages in clinical translation: (1) rapid clearance of background signals from blood and tissues, allowing imaging to be completed within a short time (1-2 hours) using short half-life radionuclides (such as 11C, 13N, 68Ga, and 18F); (2) small molecules are generally not recognized or rejected by the immune system and are therefore safer; (3) diverse labeling methods; (4) chemical purification and quality control can be standardized, making them suitable for large-scale and low-cost applications.

The development of PSMA-targeted probes began with inhibitor research. Researchers have successively developed phosphonate-based ligands, urea-based ligands, and carbamate-based small-molecule inhibitors [8-14].

Among these, over the past 20 years, the most successful inhibitors used for imaging and therapy are those modified with zinc ion-binding groups that mimic the catalytic pocket of NAAG.

Among them, phosphoramidate and urea-based compounds have been widely studied for imaging applications. Urea-based inhibitors, which exhibit the highest affinity, relatively low molecular weight, and high clearance rate, are the most widely used in the diagnosis and treatment of prostate cancer.

In 2002, the Pomper laboratory at Johns Hopkins University School of Medicine first introduced urea-based small-molecule inhibitors into prostate cancer-specific nuclear medicine imaging research [15]. In 2012, they reported the clinical results of the

first-generation 18F imaging agent, confirming its feasibility and specificity [16].

Currently, PET imaging agents and radionuclide-targeted therapeutic agents used in clinical studies are mostly based on the glutamate-urea structure. Among them, widely reported PET imaging agents include 18F-DCFPyL, 68Ga-PSMA-11, 18F-PSMA-1007, 68Ga-PSMA-617, 68Ga-PSMA-I&T;, and Al18F-PSMA-BCH.

PSMA small-molecule imaging agents provide powerful imaging tools for precise staging of prostate cancer and accurate localization of biochemical recurrence lesions. As a result, PSMA has been referred to as a "star molecule," and its radionuclide-targeted diagnosis and therapy have created a multi-billion-dollar market worldwide.

During the principal investigator's postdoctoral research, in order to further improve the pharmacokinetic properties of PSMA nuclear medicine diagnostic probes, a class of small-molecule inhibitors based on the ODAP-PSMA structural scaffold was developed (see Figure 1). These compounds exhibit binding affinity to PSMA similar to that of glutamate-urea structures.

Based on this structure, further optimization led to the development of a novel nuclear medicine imaging probe, 68Ga-P137, which demonstrates excellent in vivo stability, metabolic performance, and specific targeting ability. In clinical studies, it has shown outstanding translational potential.

These research findings were published in the journals *Journal of Medicinal Chemistry* (IF 7.446) [17] and *European Journal of Nuclear Medicine and Molecular Imaging* (IF 9.236) [18].

Figure 1. Discovery of ODAP-PSMA small-molecule inhibitors. A) Structure of PSMA protein and structure-activity relationship of catalytic function. B) Three types of interactions between molecular probes and PSMA protein. C) Discovery and validation of ODAP-structured inhibitors.

1.4 Advantages of the Second Targeting Moiety FAP

Fibroblast activation protein (FAP) is a type II transmembrane glycoprotein composed of 760 amino acids and belongs to the dipeptidyl peptidase family. It is highly expressed in cancer-associated fibroblasts (CAFs), which account for approximately 90% of the tumor volume in epithelial-derived tumors.

Given that FAP is overexpressed in the stroma of more than 90% of epithelial tumors, it is also highly expressed in CAFs of various solid tumors, including prostate cancer, liver cancer, ovarian cancer, and endometrial cancer. This makes FAP a potential broad-spectrum target for the diagnosis and treatment of multiple solid tumors, including prostate cancer, liver cancer, ovarian cancer, and endometrial cancer.

Based on this, the construction of a dual-target molecular probe targeting both FAP and PSMA has certain research significance and clinical application value in improving the sensitivity of early detection of primary and metastatic lesions in multiple solid tumors, including prostate cancer, liver cancer, ovarian cancer, and endometrial cancer.

1.5 Existing Conditions

On the basis of PSMA-targeted molecular probes, this research group successfully introduced a FAP-targeted molecular probe and constructed a dual-target molecular probe labeled with 68Ga, namely 68Ga-FAPI-PSMA.

68Ga-FAPI-PSMA can be conveniently prepared by a one-step labeling method, with a radiochemical purity greater than 95%. The prepared PET probe meets quality control requirements and is suitable for clinical trial conditions. In addition, preclinical in vitro

and in vivo evaluations of the probe have been completed. Relevant research results have been published in *Molecular Pharmaceutics* (Mol Pharm. 2023 Feb 6;20(2):1415-1425).

Stability studies of 68Ga-FAPI-PSMA demonstrated that the in vitro radiochemical purity at 4 hours is approximately 95%, and the in vivo radiochemical purity at 1 hour is approximately 90%. The in vitro and in vivo stability results are shown in Figure 2, indicating that 68Ga-FAPI-PSMA has good stability both in vitro and in vivo.

Figure 2. In vitro and in vivo stability of 68Ga-FAPI-PSMA.

PSMA-positive 22RV1 tumor-bearing mouse models were used. A total of 7.4 MBq of 68Ga-FAPI-PSMA and 68Ga-PSMA-617 were injected via tail vein, respectively. One hour after injection, micro-PET/CT imaging was performed, and the maximum standardized uptake value (SUVmax) of the tumors was measured.

Micro-PET/CT imaging results of tumor-bearing mice showed that at 1 hour, the uptake value of 68Ga-FAPI-PSMA in tumors was (SUVmax = 1.32), which was higher than that of 68Ga-PSMA-617 (SUVmax = 0.25).

The experimental results indicate that 68Ga-FAPI-PSMA has higher PSMA-targeting binding ability compared with 68Ga-PSMA-617. The results are shown in Figure 3.

Figure 3. Uptake of 68Ga-FAPI-PSMA and 68Ga-PSMA-617 in prostate cancer tumor-bearing mice.

Similarly, comparative imaging of the two probes was also performed in hepatocellular carcinoma model mice (HepG2), as shown in Figure 4. Likewise, the tumor uptake of 68Ga-FAPI-PSMA was significantly higher than that of 68Ga-PSMA-617.

In addition, 68Ga-FAPI-PSMA was able to specifically identify tumors in tumor-bearing mouse models of colon cancer, ovarian cancer, and breast cancer.

Figure 4. Uptake of 68Ga-FAPI-PSMA and 68Ga-PSMA-617 in hepatocellular carcinoma tumor-bearing mice.

Figure 5. Imaging of 68Ga-FAPI-PSMA in tumor-bearing mice with colon cancer, ovarian cancer, and breast cancer.

The biodistribution results of 68Ga-FAPI-PSMA in normal KM mice showed that 68Ga-FAPI-PSMA is rapidly cleared by the kidneys, with very low uptake in most normal organs such as the heart, liver, spleen, and brain.

At 30 minutes post-injection, the highest uptake was observed in the small intestine (22.22 ± 6.94 %ID/g), followed by bone (11.41 ± 1.45 %ID/g), large intestine (6.74 ± 1.31 %ID/g), and muscle (3.46 ± 0.62 %ID/g).

During the biodistribution study, no significant changes in vital signs or behavior were observed in all mice. The biodistribution results are shown in Figure 4.

Figure 4. Biodistribution of 68Ga-FAPI-PSMA in KM mice.

1.6 Application Prospects

Based on the structural framework of PSMA-targeted probes, by introducing the second targeting moiety fibroblast activation protein (FAP), while maintaining the specific targeting of PSMA in prostate cancer, the advantages of FAP expression in the tumor microenvironment can be utilized to improve the accuracy and sensitivity of early detection of primary and metastatic lesions in prostate cancer and hepatocellular carcinoma.

This provides important clinical application value for early diagnosis, precise lesion localization, prognosis evaluation, and intraoperative navigation in clinical patients.

2. Preparation of 68Ga-FAPI-PSMA

2.1 Radiolabeling Route of 68Ga-FAPI-PSMA

68Ga-FAPI-PSMA is prepared through a one-step radiochemical reaction.

2.2 Radiolabeling Procedure of 68Ga-FAPI-PSMA

The preparation of 68Ga-FAPI-PSMA can be divided into the following steps:

1. Turn on the incubator and set the temperature to 95°C;

2. Add 240 μL of 1.0 M NaAc solution into a 10 mL vacuum vial (V1);

3. Elute the 68Ga-68Ge generator with 4 mL of 0.05 M HCl into the above vacuum vial (V1);

4. Add 4 μL of 5 mg/mL FAPI-PSMA into vial V1, mix thoroughly, and react at 95°C for 10 min;

5. Activate the Sep-C18 Light column using 5 mL ethanol and 10 mL water for injection, respectively, and remove air with 10 mL air flow for later use;

6. After cooling to room temperature, add 3 mL of water for injection to dilute, then load onto the activated Sep-C18 column. Wash with 5 mL water for injection to remove free 68Ga ions;

7. Elute the product into product vial V2 using 0.6 mL of 80% ethanol solution;

8. Dilute with normal saline to 5 mL and filter through a 0.22 μm sterile filter membrane to obtain the final product.

2.3 Quality Standards of 68Ga-FAPI-PSMA Preparation

According to the *Chinese Pharmacopoeia (2015 Edition)*, the quality standards of 68Ga-FAPI-PSMA preparation are established as follows:

1) **Appearance:** This product should be a colorless, clear solution without visible particulate matter. Inspection method: visual inspection.

2) **Identification:** Take an appropriate amount of this product and determine according to the half-life determination method (Appendix XIII, Chinese Pharmacopoeia 2015 Edition). The measured half-life should meet the specified requirements.

3) **pH Value:** The pH value should be between 5.0 and 8.0 (Appendix XIII, Chinese Pharmacopoeia 2015 Edition). Determined using standard pH test paper.

4) **Radiochemical Purity:** Take an appropriate amount of this product and determine according to high-performance liquid chromatography (HPLC) (Appendix V D, Chinese Pharmacopoeia 2015 Edition), under the same chromatographic conditions as the identification test. The radiochemical peak area of 68Ga-FAPI-PSMA should be no less than 95% of the total radioactive peak area.

5) **Radioactivity Concentration:** Take an appropriate amount of this product and determine according to the radioactivity (concentration) determination method (Appendix XIII, Chinese Pharmacopoeia 2015 Edition). At the time indicated on the label, the radioactivity concentration should be no less than 370 MBq/mL.

6) **Residual Solvent:** Determine according to the third method of residual solvent determination (Appendix VIII P, Chinese Pharmacopoeia 2015 Edition): accurately measure an appropriate amount of ethanol and dilute quantitatively with normal saline to prepare a reference solution with a concentration of 10%. Take an appropriate

amount of this product as the test solution. Use a capillary column with nitroterephthalic acid-modified polyethylene glycol as the stationary phase. Programmed temperature conditions: initial temperature 40°C, maintained for 5 minutes; increase at 40°C per minute to 200°C, maintained for 5 minutes. FID detector temperature: 250°C. Injection port temperature: 200°C. Direct injection method is used. Nitrogen is used as carrier gas with a flow rate of 1 mL/min. Record the chromatogram. The ethanol content should be no more than 10%, calculated by the external standard method using peak area.

7) **Bacterial Endotoxin:** Take an appropriate amount of this product, dilute at least 30 times with water for bacterial endotoxin testing, and test according to the law (Appendix XI E, Chinese Pharmacopoeia 2015 Edition). The endotoxin content should be less than 15 EU per mL.

8) **Sterility:** Take an appropriate amount of this product and test according to the law (Appendix XI H, direct inoculation method, Chinese Pharmacopoeia 2015 Edition). It should meet the specified requirements.

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3. Study Objectives and Significance

3.1 Study Objective

To compare the diagnostic performance of three imaging agents, 68Ga-FAPI-PSMA, 68Ga-PSMA-617, and 68Ga-FAPI-04, in the differentiation of malignancy, staging, and metastasis in various solid tumors including prostate cancer, liver cancer, ovarian cancer, and endometrial cancer. To evaluate the role of 68Ga-FAPI-PSMA in early diagnosis, tumor localization and staging, therapeutic efficacy monitoring, and prognostic assessment of solid tumors.

3.2 Significance

The 68Ga-FAPI-PSMA probe developed in this project, based on the advantages of the nuclear medicine platform, will promote the establishment of production registration standards for this radiopharmaceutical and obtain a 68Ga-FAPI-PSMA imaging agent that meets clinical research standards.

By exploring the value of the 68Ga-FAPI-PSMA probe in early diagnosis, tumor metastasis, and prognosis evaluation in various solid tumors including prostate cancer, liver cancer, ovarian cancer, and endometrial cancer, this project has important clinical value in early diagnosis and precise diagnosis and treatment guidance for these patients. It also has significant social significance in improving clinical benefits for patients with prostate cancer and hepatocellular carcinoma.

4. Implementation Plan

4.1 Study Design

Single-center, open-label, self-controlled study.

4.2 Study Endpoints

Primary Endpoint: The standardized uptake value (SUV) of target lesions or suspected tumor lesions of 68Ga-FAPI-PSMA in patients with various solid tumors (including prostate cancer, liver cancer, ovarian cancer, and endometrial cancer) within each time window.

Secondary Endpoints: (1) The ratio (SUVR) of the standardized uptake value of 68Ga-FAPI-PSMA in target lesions or suspected tumor lesions to that in corresponding normal tissues within each time window; (2) to explore the temporal pattern of biological distribution of 68Ga-FAPI-PSMA in vivo; (3) to evaluate and compare the application value of 68Ga-FAPI-PSMA in detecting metastatic lesions in the human body.

4.3 Study Population

Patients with various solid tumors (including prostate cancer, liver cancer, ovarian cancer, and endometrial cancer) or suspected tumors.

4.3.1 Inclusion Criteria

1) Age 18-75 years, male, ECOG score 0 or 1 (see Appendix 1);

2) Patients scheduled to undergo pathological biopsy or tumor surgery within the past 2 months, including those with prostate cancer, liver cancer, ovarian cancer, endometrial cancer, or suspected tumors;

3) Expected survival ≥12 weeks;

4) Hematologic and liver/renal function meeting the following criteria: WBC ≥4.0×10⁹/L or neutrophils ≥1.5×10⁹/L, PLT ≥100×10⁹/L, Hb ≥90 g/L; PT or APTT ≤1.5 ULN; T-Bil ≤1.5×ULN, ALT/AST ≤2.5×ULN or ≤5×ULN (for patients with liver metastasis), ALP ≤2.5×ULN (≤4.5×ULN if bone or liver metastasis), BUN ≤1.5×ULN, SCr ≤1.5×ULN;

5) At least one measurable target lesion according to RECIST 1.1;

6) Male participants must agree to use contraception during the study and for 6 months after completion;

7) Able to understand and voluntarily sign the informed consent form, with good compliance.

4.3.2 Exclusion Criteria

1) Severe hepatic or renal dysfunction;

2) Inability to lie supine for 30 minutes;

3) Refusal to participate in the clinical study;

4) Claustrophobia or other psychiatric disorders;

5) Other conditions deemed unsuitable for participation by the investigator.

4.3.3 Sample Size and Dosage

A total of 20 participants are planned to be enrolled. Based on previous literature, the expected baseline tumor uptake of 68Ga-FAPI-PSMA in this study predicts that the area under the ROC curve (AUC) for predicting major pathological response (MPR) can reach 0.86.

Study hypothesis: baseline tumor uptake of 68Ga-FAPI-PSMA can effectively predict MPR in prostate cancer patients after neoadjuvant immunotherapy (AUC > 0.5). Sample size was calculated using PASS (15.0.5) software. Parameters: $\alpha = 0.05$, $\beta = 0.2$, power = 0.8, expected AUC = 0.86, null AUC = 0.5, dropout rate = 10%. Calculated sample size: 20 participants.

Each participant will receive a single intravenous injection of 68Ga-FAPI-PSMA and 68Ga-PSMA-617 or 68Ga-FAPI-04, followed by PET/CT imaging within the specified time window. The administered radioactive dose is approximately 0.1-0.15 mCi/kg.

4.4 Study Procedures

Relevant examinations including routine blood tests, urine tests, blood biochemistry, electrocardiogram, imaging examinations, vital signs, and physical examinations within 2 weeks prior to enrollment will be collected as baseline assessments to evaluate whether the participant meets the inclusion criteria.

Participants will first undergo 68Ga-PSMA-617 or 68Ga-FAPI-04 imaging, followed by 68Ga-FAPI-PSMA imaging. The interval between the two examinations will be less than 1 week. Within 2 months after completion of the two examinations, investigators will conduct 2-3 follow-up visits through the hospital medical record system or telephone to collect participants' laboratory results, pathological results, and comprehensive diagnostic results from other imaging examinations.

Imaging Procedures

68Ga-PSMA-617 Examination: The prepared and quality-controlled 68Ga-PSMA-617 (0.1-0.15 mCi/kg) will be intravenously injected into the participant. After resting quietly for 1 hour, PET/CT imaging of the head and torso will be performed using the following systems: Philips Gemini TF16, Siemens Biograph mCT flow PET/CT, and United Imaging Total-body PET/CT uEXPLORER. The scanning range is from the top of the head to the upper one-third of the thigh. Delayed imaging at 2-4 hours may be performed if necessary. The participant will be in the supine position with calm breathing. Data will be reconstructed using the OSEM method to obtain coronal, sagittal, and transverse PET images and PET/CT fusion images.

68Ga-FAPI-04 Examination: The prepared and quality-controlled 68Ga-FAPI-04 (0.1-0.15 mCi/kg) will be intravenously injected into the participant. After resting quietly for 1 hour, PET/CT imaging will be performed under the same conditions, scanning range, and reconstruction method as described above.

68Ga-FAPI-PSMA Examination: Within 1 day to 7 days after completion of the 68Ga-PSMA-617 examination, 68Ga-FAPI-PSMA imaging will be performed. The prepared and quality-controlled 68Ga-FAPI-PSMA (0.1-0.15 mCi/kg) will be intravenously injected into the participant. After resting quietly for 1 hour, PET/CT imaging will be performed using the same equipment, scanning range, and reconstruction method as above.

All three PET/CT examinations (68Ga-PSMA-617, 68Ga-FAPI-04, and 68Ga-FAPI-PSMA) for the same participant will be conducted using the same scanning equipment, parameters, and reconstruction algorithms.

Image Interpretation

Two sets of PET/CT images will be jointly interpreted by two nuclear medicine physicians with many years of diagnostic experience. A diagnosis will only be made when the interpretations of two or more physicians are consistent. All imaging data will be archived for subsequent statistical analysis.

Follow-up

Within 2 months after completion of 68Ga-FAPI-PSMA PET/CT imaging, clinical follow-up (2-3 times) will be conducted to collect laboratory test results (tumor markers), pathological results (including pathological subtype and tumor HER2 expression status, etc.), and imaging results (CT, MRI, PET, etc.).

Data Statistical Analysis

Descriptive statistical analysis will be performed for SUV and SUVR of each tumor lesion. Descriptive statistics include mean, standard deviation, coefficient of variation, minimum value, and maximum value. The temporal variation characteristics of SUV and SUVR will be analyzed. Scatter plots of SUV distribution among participants will be generated.

Comparison of SUV and SUVR values between 68Ga-FAPI-PSMA PET/CT imaging and 68Ga-PSMA-617 or 68Ga-FAPI-04 PET/CT imaging: paired t-test will be used for comparison of means between two groups; Pearson chi-square test will be used for comparison between groups. A P value < 0.05 will be considered statistically significant. Positive lesions detected by 68Ga-FAPI-PSMA PET/CT imaging will be statistically analyzed and correlated with corresponding tumor tissue immunohistochemistry results.

Study Workflow for Participants

Intravenous injection of imaging agent 68Ga-PSMA-617 or 68Ga-FAPI-04 → PET/CT imaging of head and torso at 1 hour post-injection → optional delayed imaging at 2-4 hours → first image reconstruction and post-processing → intravenous injection of imaging agent 68Ga-FAPI-PSMA → PET/CT imaging of head and torso at 1 hour post-injection → optional delayed imaging at 2-4 hours → second image reconstruction and post-processing → interpretation by at least two experienced physicians → case follow-up (within 2 months after examination, collection of laboratory results, pathological results, and comprehensive imaging diagnostic results).

5. Risk/Benefit Assessment

5.1 Benefits

If the participant agrees to participate in this study, the participant may obtain direct medical benefit, but may also not benefit. It is expected that the information obtained from this study will provide guidance for future patients with similar conditions.

5.2 Risks

1) **Safety of 68Ga-FAPI-PSMA:** In this study, each intravenous injection may occasionally cause pain at the injection site or mild allergic reactions (such as erythema or swelling), which do not require special treatment and do not cause systemic risks.

2) **Radiation Exposure:** Participants in this study will receive a certain level of radiation. The radiation dose of each examination is approximately equivalent to that of a contrast-enhanced abdominal and pelvic CT scan.

3) **Special Population Protection:** For minors and elderly individuals, it is recommended to drink more water and urinate frequently on the day of examination to facilitate rapid excretion of the imaging agent. No special protective measures are required for other participants.

4) **Unknown Risks:** There may be currently unforeseeable risks and adverse reactions.

6. Research Costs

Participants will be exempted from the cost of one PET/CT scan using 68Ga-PSMA-617 or 68Ga-FAPI-04. The drug cost and examination cost of 68Ga-FAPI-PSMA imaging will be covered by the research project. Participants will not bear any study-related costs.

7. Confidentiality of Data

All medical data of enrolled participants may be reviewed by relevant personnel of the sponsoring institution, regulatory authorities, or independent ethics committees to verify the appropriateness of study conduct. Signing the informed consent form indicates that the participant agrees to such review.

8. Other Matters

None.

9. Investigator Information

9.1 Principal Investigator

Name: [Anonymized]
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Email: [Anonymized]

9.2 Study Team Members

All study team member names and direct identifying contact details have been anonymized in this submission version.

Project roles retained from the source document include: project guidance, image processing, drug preparation and quality control, radiolabeling, and precursor synthesis.