Protocol

A Prospective Exploratory Single-Center Diagnostic Imaging Study Evaluating the Diagnostic Performance of 18F-labeled Fibroblast Activation Protein Inhibitor Positron Emission Tomography in Diffuse Gastric Cancer: Protocol for the FAPI-DGC Study

Yoshimasa Akashi[1], MD, PhD; Koichi Ogawa[2], MD, PhD; Yohei Owada[2], MD, PhD; Kentaro Hatano[3], PhD; Tadashi Hara[3], MD, PhD; Masaru Shimizu[4], MD, MPH, PhD; Yoshihiro Miyazaki[2], MD, PhD; Kinji Furuya[2], MD, PhD; Takahito Nakajima[3], MD, PhD; Tatsuya Oda[2], MD, PhD

[1]Faculty of Medicine, University of Tsukuba, Tsukuba, Ibaraki, Japan

[2]Department of Gastrointestinal and Hepato-Biliary-Pancreatic Surgery, Faculty of Medicine, University of Tsukuba, Tsukuba, Ibaraki, Japan

[3]Department of Radiology, Faculty of Medicine, University of Tsukuba, Tsukuba, Ibaraki, Japan

[4]Department of Clinical Research and Regional Innovation, Institute of Medicine, University of Tsukuba, Tsukuba, Ibaraki, Japan

Corresponding Author:
Yoshimasa Akashi, MD, PhD
Faculty of Medicine
University of Tsukuba
1-1-1 Tennodai
Tsukuba, Ibaraki, 305-8575
Japan
Phone: 81 29 853 3221
Fax: 81 29 853 3222
Email: yakashi@gwe.md.tsukuba.ac.jp

Abstract

Background: Accurate preoperative staging remains challenging in diffuse gastric cancer (DGC), which is characterized by poorly differentiated or signet ring cell histology, diffuse submucosal infiltration, stromal fibrosis, and a high propensity for peritoneal dissemination. Contrast-enhanced computed tomography (ceCT) may underestimate tumor depth, nodal involvement, and small-volume metastatic disease, whereas the diagnostic value of fluorodeoxyglucose (FDG)–positron emission tomography (PET) is limited in diffuse histological subtypes. Fibroblast activation protein inhibitor (FAPI)–PET targets cancer-associated fibroblasts and may provide additional biological information beyond conventional imaging.

Objective: The FAPI-DGC (Fibroblast Activation Protein Inhibitor Diffuse Gastric Cancer) study aims to evaluate the diagnostic performance, potential clinical value, and safety of adding fluorine-18 (^{18}F)–labeled FAPI positron emission tomography/computed tomography (PET/CT) to conventional preoperative staging in patients with DGC.

Methods: This prospective exploratory diagnostic imaging study will enroll 20 adults with biopsy-confirmed poorly differentiated adenocarcinoma or signet ring cell carcinoma who are scheduled to undergo curative gastrectomy or staging laparoscopy. All participants will undergo ^{18}F-labeled FAPI-74 PET/CT in addition to standard preoperative investigations, including ceCT. Preoperative tumor, node, and metastasis (TNM) staging based on conventional preoperative staging, including ceCT, and on staging incorporating FAPI-PET findings will be compared with postoperative pathological staging as the reference standard. The primary outcome is the exploratory assessment of preoperative staging accuracy. Secondary outcomes include detection rates of primary and metastatic lesions; correlations between FAPI uptake and histopathological features, including fibrosis and fibroblast activation protein expression; associations with serum tumor markers; and safety outcomes. Accuracy estimates with corresponding 95% CIs will be reported, and paired comparisons will be performed using appropriate exact statistical methods, where applicable.

Results: Research funding was approved in August 2025. Participant recruitment commenced on November 19, 2025. As of July 30, 2026, a total of 6 participants have been enrolled. Recruitment is planned to continue until March 2027, with study

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follow-up scheduled to be completed by June 2029. Data analysis will commence after completion of participant recruitment. The primary study results are expected to be published by the end of 2029.

Conclusions: This protocol describes a prospective exploratory diagnostic imaging study evaluating ^{18}F-FAPI-PET/CT for preoperative staging of DGC. Publication of this protocol will enhance transparency, establish an a priori record of the study methodology, and facilitate interpretation of subsequent study findings while informing the design of future confirmatory diagnostic imaging studies.

Trial Registration: Japan Registry of Clinical Trials jRCTs031250386; https://jrct.mhlw.go.jp/en-latest-detail/jRCTs031250386

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KEYWORDS

diffuse gastric cancer; fluorine-18–labeled fibroblast activation protein inhibitor positron emission tomography; 18F-FAPI-PET; imaging protocol; preoperative staging; exploratory study; prospective study

Introduction

Gastric cancer remains a major global health burden, particularly in East Asia, where it continues to be one of the leading causes of cancer-related mortality [1]. Among its histological subtypes, diffuse gastric cancer (DGC) represents a distinct clinicopathological entity characterized by poorly differentiated and signet ring cell histology, diffuse submucosal infiltration, extensive stromal fibrosis, and a high propensity for peritoneal dissemination [2,3]. In this subtype, precise assessment of tumor extent and metastatic spread is critical for selecting appropriate treatment strategies and avoiding unnecessary invasive procedures.

Current preoperative staging of gastric cancer relies primarily on a combination of upper gastrointestinal endoscopy; contrast-enhanced computed tomography (ceCT); and, in selected cases, staging laparoscopy [4]. According to both Japanese and international clinical practice guidelines, staging laparoscopy is recommended or considered for patients with advanced or locally advanced gastric cancer who are at increased risk of occult peritoneal metastasis [4,5]. However, ceCT has limited sensitivity for detecting early peritoneal metastases and accurately assessing tumor depth and nodal involvement, particularly in DGC [6]. Previous large-scale analyses have demonstrated suboptimal accuracy of ceCT-based T and N stages of tumor, node, and metastasis (TNM) staging, with a tendency toward underestimation in DGC [7]. In particular, small-volume peritoneal metastases frequently remain undetected on ceCT, and the sensitivity of ceCT for peritoneal dissemination is limited, often necessitating staging laparoscopy in patients at high risk of occult metastatic disease [8]. As a result, patients may undergo noncurative surgery or require additional invasive diagnostic procedures to clarify disease extent.

Positron emission tomography (PET) using fluorine-18 (^{18}F)–labeled fluorodeoxyglucose (FDG) may be incorporated into the initial staging workup of selected patients with potentially curable gastric cancer to detect unsuspected distant metastases, as recommended by recent National Comprehensive Cancer Network [9] and European Society for Medical Oncology [10] guidelines. Consistent with these recommendations, the prospective PLASTIC study demonstrated that FDG–positron emission tomography/computed tomography (PET/CT) can detect additional distant metastases beyond ceCT in selected patients with locally advanced gastric cancer [8]. However, FDG-PET has limited value for assessment of primary tumor extent (T stage) and regional lymph node involvement (N stage), particularly in DGC, and performs poorly in detecting occult peritoneal metastases. This reduced diagnostic performance is attributed to low glucose transporter expression, low tumor cellularity, abundant desmoplastic stroma, and a diffuse infiltrative growth pattern, all of which contribute to relatively low FDG uptake [11,12]. Consequently, current Japanese and international guidelines recommend only selective use of FDG-PET and do not recommend its routine use for staging of DGC [4,5,9,10]. These limitations highlight the need for imaging modalities that target tumor-associated stromal biology rather than tumor glucose metabolism.

Fibroblast activation protein (FAP) is a membrane-bound serine protease selectively overexpressed by cancer-associated fibroblasts, which constitute a major component of the tumor microenvironment in fibrotic malignancies [13]. DGC is characterized by abundant desmoplastic stroma [14], providing a biological rationale for FAP-targeted imaging. Immunohistochemical studies of gastric cancer have demonstrated substantial FAP expression in tumor-associated stroma, with FAP inhibitor (FAPI) uptake reported to correlate with stromal FAP expression [15]. FAPI-PET therefore enables visualization of stromal activity rather than tumor cell glucose metabolism and may be particularly advantageous in diffuse histological subtypes. Consistent with this biological rationale, previous clinical studies in gastric signet ring cell and mucinous carcinomas have demonstrated higher FAPI uptake and improved detection of primary tumors, lymph node metastases, and distant or peritoneal metastases compared with FDG-PET [16-19].

To date, several clinical studies have evaluated FAPI-PET in gastric cancer, including cohorts enriched for diffuse and signet ring cell carcinomas, and a recent systematic review has demonstrated superior lesion detection compared with FDG-PET across upper-abdominal malignancies [16-20]. However, most published studies have primarily focused on lesion detectability or direct comparisons with FDG-PET, frequently using gallium-68–labeled tracers, and have generally been

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retrospective or heterogeneous in patient selection. Prospective clinical experience with ^{18}F-labeled FAPI tracers remains limited [21]. Although recent prospective studies using ^{18}F-labeled FAPI tracers have demonstrated favorable tumor-to-background contrast and a strong correlation between tracer uptake and stromal FAP expression, supporting their biological validity, these studies have largely been conducted in tumor types other than gastric cancer [22]. Accordingly, prospective data specifically evaluating the diagnostic performance of ^{18}F-labeled FAPI tracers for comprehensive preoperative staging in patients with DGC remain limited. Furthermore, the potential value of FAPI-PET for assessment of tumor extent, nodal involvement, and occult peritoneal metastases using pathological reference standards has not been systematically investigated in this patient population.

Building on the existing evidence, the present prospective exploratory study (FAPI-DGC [Fibroblast Activation Protein Inhibitor Diffuse Gastric Cancer] study) aims to evaluate the diagnostic performance, potential clinical value, and safety of incorporating ^{18}F-labeled FAPI-PET into standard preoperative staging in DGC.

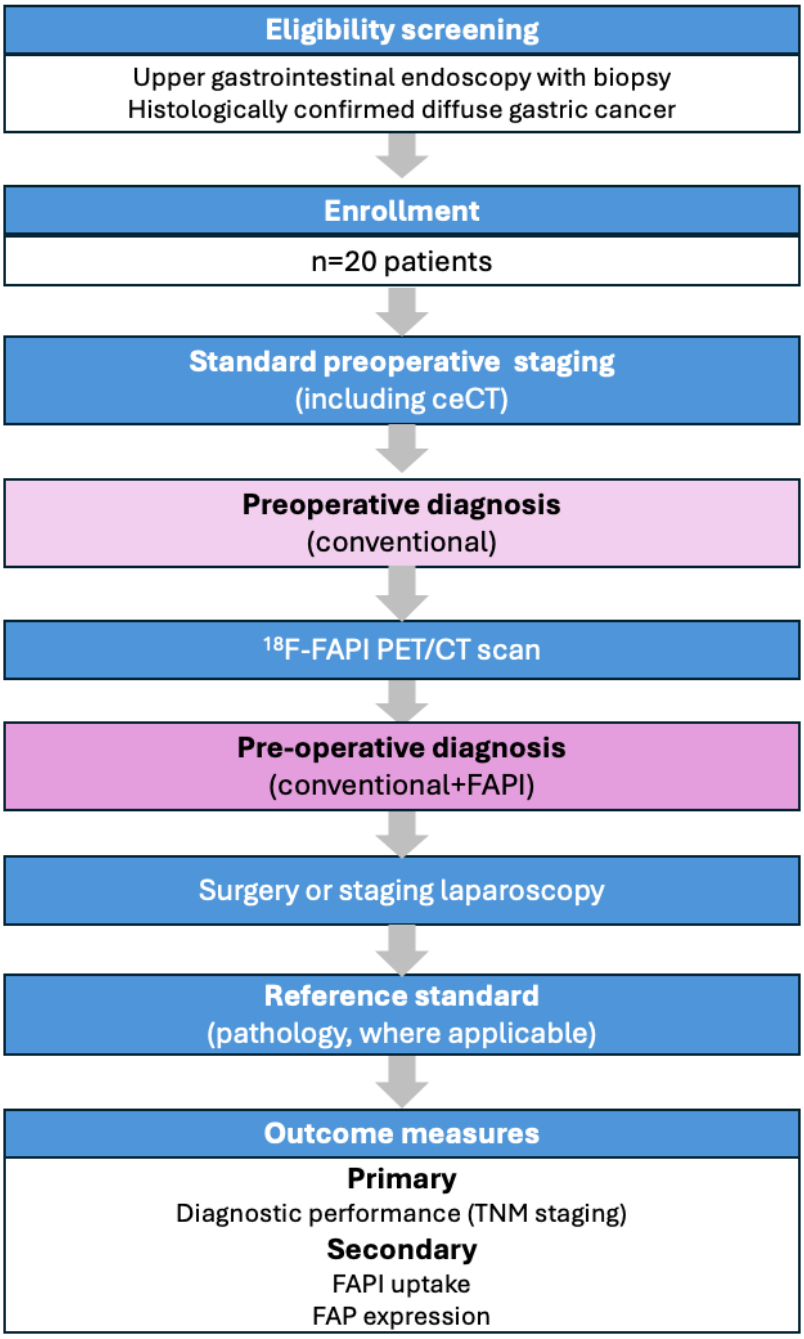
Methods

Study Aims and Design

This study is a prospective exploratory single-center diagnostic imaging study designed to evaluate the diagnostic performance, potential clinical value, and safety of ^{18}F-labeled FAPI-PET for preoperative staging of DGC (Figure 1). The study has been prospectively registered in the Japan Registry of Clinical Trials (jRCTs031250386). Participants are recruited at Tsukuba University Hospital, while ^{18}F-labeled FAPI-74 PET/CT imaging is performed at the Advanced Imaging Centre Tsukuba. The study is designed as an adjunctive imaging study in which ^{18}F-labeled FAPI-PET findings are added to standard preoperative assessments without altering routine clinical care.

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Figure 1. Study workflow of the Fibroblast Activation Protein Inhibitor Diffuse Gastric Cancer (FAPI-DGC) study. Eligible patients with histologically confirmed diffuse gastric cancer undergo routine preoperative staging, including contrast-enhanced computed tomography (ceCT), followed by study-specific fluorine-18 (^{18}F)–labeled fibroblast activation protein inhibitor (FAPI) positron emission tomography/computed tomography (PET/CT). Conventional preoperative staging and fibroblast activation protein inhibitor (FAPI)–assisted staging are compared with the reference standard to evaluate diagnostic performance and secondary outcomes. FAP: fibroblast activation protein; TNM: tumor, node, and metastasis.



Participants

Eligible participants are adult patients (aged ≥18 years) with histologically confirmed gastric cancer who are scheduled to undergo curative surgical resection or staging laparoscopy. Eligibility criteria are summarized in Textbox 1.

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Textbox 1. Eligibility criteria.

Inclusion criteria

- Aged ≥18 years
- Histological diagnosis of gastric cancer based on endoscopic biopsy
- Presence of diffuse gastric cancer (poorly differentiated adenocarcinoma [por, por1, and por2] or signet ring cell carcinoma) in preoperative biopsy specimens; patients with mixed histology are eligible if any diffuse-type component is identified
- Planned curative gastrectomy or staging laparoscopy
- Ability to provide written informed consent

Exclusion criteria

- Previous gastrectomy
- Severe renal dysfunction (blood urea nitrogen ≥25 mg/dL or serum creatinine ≥2.0 mg/dL)
- Pregnancy, breastfeeding, or intention to become pregnant during the study period
- Known phenylketonuria
- Any other condition that the investigators deem to make the participant unsuitable for study participation

Sample Size Rationale

The planned sample size of 20 participants was pragmatically determined based on the exploratory nature of this pilot imaging study, tracer availability, and institutional case volume. No formal hypothesis-driven sample size calculation was performed because the primary objective is to obtain preliminary estimates of diagnostic accuracy and to generate data for planning future confirmatory studies. With a sample size of 20 participants, diagnostic accuracy estimates are expected to have relatively wide 95% CIs, reflecting the exploratory nature of the study. The resulting precision will be explicitly reported to facilitate interpretation of the findings and to inform the design and sample size estimation of subsequent studies.

Imaging Procedures

The FAPI-74 precursor is obtained from SOFIE iTheranostics. ^{18}F is produced at the Advanced Imaging Centre Tsukuba using an Eclipse HP cyclotron (Siemens) by proton irradiation of oxygen-18 (^{18}O)–enriched water. The radionuclide is recovered as aluminum-^{18}F (Al^{18}F), and ^{18}F-labeled FAPI-74 is synthesized using an automated synthesis module (MPS-200; Sumitomo Heavy Industries). The product is purified using an Oasis HLB Plus Light Cartridge (Waters), sterile filtered, and prepared for intravenous administration. Production and quality control are performed under the Good Manufacturing Practice system established at the Advanced Imaging Centre Tsukuba. The radiolabeling approach is based on previously reported methods for ^{18}F-Al^{18}F–labeled FAPI-74 [23].

All enrolled participants undergo ^{18}F-labeled FAPI-74 PET/CT in addition to standard preoperative investigations. A fixed activity of 185 MBq (5 mCi), rather than a weight-adjusted dose, is administered intravenously, with a maximum chemical dose of 40 µg. The approved protocol does not specify a separate minimum or maximum acceptable activity range. Participants are instructed to fast for at least 6 hours before tracer administration; water without sugar is permitted. PET/CT imaging is performed using a Biograph VISION PET/CT scanner (Siemens) at the Advanced Imaging Centre Tsukuba. Images are acquired at an early phase (10-20 minutes after injection), an intermediate phase (approximately 60 minutes), and a delayed phase (2-3 hours). Depending on logistical constraints and participant consent, 2 or 3 imaging time points may be obtained. Low-dose computed tomography (CT) is performed for attenuation correction and anatomical localization, followed by PET acquisition from the head to the midthigh using continuous-bed-motion acquisition. PET images are reconstructed using ordered-subset expectation maximization with point-spread-function and time-of-flight corrections.

Imaging Interpretation

PET/CT images will be independently reviewed by at least 1 board-certified radiologist. FAPI uptake in primary and metastatic lesions will be visually assessed using a 5-point scale with reference to the Lugano classification [24]. When abnormal uptake is identified, metabolic parameters, including the maximum standardized uptake value and metabolic tumor volume, will also be recorded.

Reference Standard

Postoperative histopathological findings serve as the reference standard for assessment of the primary tumor (T stage) and regional lymph node involvement (N stage) in patients undergoing curative gastrectomy. Peritoneal metastases identified at staging laparoscopy and confirmed histopathologically are regarded as pathological M1 disease. Because pathological confirmation of M0 disease is not feasible in patients undergoing curative resection, M0 status is determined according to the final routine clinical assessment based on conventional preoperative staging, consistent with standard clinical practice.

Preoperative Staging Assessment

Preoperative tumor staging is performed in 2 sequential steps. First, conventional preoperative staging, including ceCT, is determined based on routine clinical assessments, including upper gastrointestinal endoscopy, ceCT, and other imaging

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modalities as clinically indicated. Although ceCT is not specified as an eligibility criterion, all enrolled patients undergo routine preoperative ceCT before ^{18}F-labeled FAPI-PET as part of standard clinical care.

After this staging has been finalized and recorded, the multidisciplinary evaluation committee reviews the FAPI-PET findings together with the radiologist's interpretation and determines the FAPI-assisted preoperative staging.

Outcome Measures

Primary Outcome

The primary outcome is the exploratory assessment of preoperative staging accuracy (TNM categories) using conventional preoperative staging, including ceCT, and preoperative staging incorporating ^{18}F-labeled FAPI-PET findings, with postoperative pathological staging serving as the reference standard.

Secondary Outcomes

The secondary outcomes are as follows: detection rate of primary gastric cancer lesions by ^{18}F-labeled FAPI-PET; detection rate of metastatic lesions, including lymph node and peritoneal metastases; accuracy of tumor extent assessment based on anatomical tumor distribution; correlation between FAPI uptake parameters and histopathological findings, including fibrosis and FAP expression in resected specimens; associations between FAPI uptake and serum tumor markers (carcinoembryonic antigen, carbohydrate antigen 19-9, and carbohydrate antigen 125); comparison of tracer uptake between early and delayed imaging phases; and safety outcomes, including the incidence and severity of adverse events.

Statistical Analysis

The distribution and summary statistics of baseline characteristics will be calculated for each analytical population. For nominal variables, frequencies and proportions will be reported. For continuous variables, summary statistics including mean, SD, median, and range will be calculated.

The accuracy of preoperative staging will be evaluated by comparing ceCT-based imaging alone with imaging incorporating FAPI-PET findings in the same patients. Diagnostic accuracy estimates will be presented with corresponding 95% CIs. Differences in staging accuracy between the 2 approaches will be assessed using the McNemar test, and exact paired methods will be used where appropriate. Secondary outcomes will be summarized using descriptive statistics.

Safety Assessment

All adverse events occurring from tracer administration until surgery will be recorded and graded according to the Common Terminology Criteria for Adverse Events (version 6.0) [25]. Events deemed unrelated to the study procedures will be documented but excluded from safety analyses.

Ethical Considerations

This study has been approved by the Tsukuba University Clinical Research Review Board (TCRB25-016) and is conducted in accordance with the Clinical Trials Act of Japan and the principles of the Declaration of Helsinki. Written informed consent is obtained from all participants prior to enrollment. Participants are informed of the purpose of the study, the procedures involved, potential risks related to radiation exposure and tracer administration, and their right to withdraw consent at any time without prejudice to their clinical care.

The study protocol has been prospectively registered in the Japan Registry of Clinical Trials (jRCTs031250386) prior to participant enrollment. Study results will be disseminated through publication in peer-reviewed scientific journals and presentation at national and international academic conferences. No identifiable personal information will be disclosed.

Study-specific ^{18}F-labeled FAPI-PET/CT is scheduled within the routine preoperative workup and is not intended to delay treatment. Conventional preoperative staging is completed before review of the FAPI-PET findings to minimize incorporation bias. Clinically significant incidental findings are communicated promptly to the treating physician. On the basis of previous dosimetry studies, the additional effective radiation dose associated with study participation is estimated to be approximately 3 to 4 mSv [26]. This additional radiation exposure was considered acceptable in relation to the exploratory objectives of the study and is explained during the informed consent process.

Patient and Public Involvement

Patients and the public were not involved in the design, conduct, reporting, or dissemination plans of this research. Study results will be shared with participants upon request after completion of the trial.

Results

Research funding was approved in August 2025. Participant recruitment commenced on November 19, 2025. As of July 30, 2026, a total of 6 participants have been enrolled. Recruitment is planned to continue until March 2027, with study follow-up scheduled to be completed by June 2029. No data analysis has been performed as of July 30, 2026, because participant recruitment is not yet complete. Data analysis is planned to commence after completion of participant recruitment. The primary study results are expected to be published by the end of 2029.

Discussion

This study is designed to evaluate whether the addition of ^{18}F-labeled FAPI-PET/CT to conventional ceCT-based preoperative imaging can improve the diagnostic assessment of DGC and to provide preliminary estimates of its diagnostic performance. By prospectively comparing conventional preoperative staging, including ceCT, with staging incorporating FAPI-PET against pathological reference standards, the study is expected to provide evidence regarding the potential added value of FAPI-PET in this clinically challenging subtype.

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DGC, including signet ring cell carcinoma, poses substantial diagnostic challenges due to its diffuse growth pattern, extensive stromal fibrosis, and high incidence of occult peritoneal dissemination. Accurate preoperative staging is essential for appropriate treatment selection, yet existing imaging modalities frequently underestimate disease extent in this subtype [7]. The present prospective exploratory study is designed to address this unmet clinical need by evaluating the diagnostic performance and potential clinical utility of ^{18}F-labeled FAPI-PET as an adjunct to standard preoperative staging.

The biological rationale for FAPI-PET imaging lies in its ability to visualize FAP-expressing cancer-associated fibroblasts within the tumor stroma. Pathological studies have demonstrated prominent desmoplastic stroma and activated stromal fibroblasts in gastric cancer, including signet ring cell and diffuse-type carcinomas [27,28]. More recent molecular and pathological analyses have also identified an FAP-expressing fibroblast population in DGC [29]. These findings provide a biological rationale for FAP-targeted imaging in this histological subtype. By targeting the tumor microenvironment rather than tumor cell glucose metabolism, FAPI-PET may complement conventional imaging of FDG-PET, particularly in tumors with low FDG uptake [30]. In addition, ^{18}F-labeled tracers offer practical advantages over gallium-68–labeled compounds, including wider availability and suitability for delayed-phase imaging [21].

Previous studies have reported higher FAPI uptake and improved detection of primary gastric tumors and metastatic lesions compared with FDG-PET, including in cohorts containing signet ring cell and other diffuse-type carcinomas [16-21]. However, many previous studies were retrospective, included heterogeneous patient populations, focused primarily on lesion detectability or direct comparison with FDG-PET, and predominantly evaluated gallium-68–labeled tracers. The present study builds on this evidence by prospectively evaluating an ^{18}F-labeled FAPI tracer for comprehensive TNM staging in a clinically defined cohort of patients with DGC, using predefined imaging assessments and pathological reference standards where applicable. We hypothesize that incorporating FAPI-PET findings may improve staging assessment compared with conventional ceCT-based imaging alone; however, given the exploratory design and sample size, the study is intended to provide preliminary estimates rather than establish diagnostic superiority.

Several features strengthen the study design. This is a prospective, hospital-based study with protocol registration before participant enrollment and predefined imaging and staging procedures. In addition, enrollment is limited to patients who are candidates for gastrectomy or staging laparoscopy, permitting histopathological verification of the primary tumor and regional lymph nodes in resected cases and of peritoneal metastases when identified and sampled during staging laparoscopy. The assessment of FAPI uptake in relation to fibrosis and FAP expression may also help clarify the pathological basis of the imaging findings. The final diagnostic accuracy results will be reported in accordance with the STARD (Standards for Reporting of Diagnostic Accuracy Studies) recommendations, where applicable.

Several limitations should be acknowledged. The limited sample size and the exploratory nature of the study may restrict the precision and generalizability of the diagnostic performance estimates. Pathological verification is not available for every staging component; in particular, pathological confirmation of M0 status is generally not feasible and is therefore based on the final clinical assessment. Furthermore, although the hospital-based, single-center design supports consistent recruitment and study procedures, it may limit external generalizability. The study is not powered to establish definitive diagnostic superiority or to support changes in routine clinical practice. Nevertheless, the prospective design and detailed imaging and pathological assessments are expected to provide valuable preliminary data for planning future adequately powered, multicenter diagnostic accuracy studies.

In summary, this protocol describes a prospective exploratory study evaluating ^{18}F-labeled FAPI-PET for preoperative staging of DGC. The study is expected to provide preliminary evidence regarding the diagnostic performance and potential clinical value of FAPI-PET while informing the design of future multicenter diagnostic accuracy studies. Publication of this protocol will enhance methodological transparency and facilitate interpretation of the final study results.

Funding

This study was supported by the Grant for Implementation of Advanced Medicine from Tsukuba University Hospital. The funder had no role in the study design; collection, analysis, or interpretation of data; the writing of the manuscripts; or the decision to submit the study results for publication.

Generative AI Use

An AI-based language model, ChatGPT (OpenAI), was used to assist in drafting and editing the initial manuscript based on the approved study protocol. The authors reviewed, revised, and approved all content and take full responsibility for the accuracy, integrity, and originality of the manuscript.

Authors' Contributions

YA formulated the research plan with advice from YM and Tsukuba Clinical Research and Development Organization and drafted the study protocol manuscript. YA, KO, and YO, as attending physicians, are responsible for patient recruitment, obtaining

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informed consent, and conducting preoperative diagnosis. KH is responsible for tracer preparation and quality assurance. TH and TN, as radiologists, are responsible for evaluating fibroblast activation protein inhibitor (FAPI)–positron emission tomography (PET) uptake. MS is responsible for statistical analysis. KF is responsible for study monitoring, and TO provides overall supervision. All authors critically reviewed and approved the final version of the study protocol.

Conflicts of Interest

None declared.

Multimedia Appendix 1

SPIRIT checklist.
[PDF File (Adobe PDF File), 140 KB-Multimedia Appendix 1]

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Abbreviations

^{18}F: fluorine-18
All^{18}F: aluminum–fluorine-18
ceCT: contrast-enhanced computed tomography
CT: computed tomography
DGC: diffuse gastric cancer
FAP: fibroblast activation protein
FAPI: fibroblast activation protein inhibitor
FAPI-DGC: Fibroblast Activation Protein Inhibitor Diffuse Gastric Cancer
FDG: fluorodeoxyglucose
PET: positron emission tomography
PET/CT: positron emission tomography/computed tomography
STARD: Standards for Reporting of Diagnostic Accuracy Studies
TNM: tumor, node, and metastasis

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