Head to head comparison of ^{68}Ga-FAPI PET/CT with ^{18}F-FDG PET/CT in primary and metastatic lesions of gastric tumor: A systematic review and meta-analysis

Cailiang Gao MD,
Huiting Liu MD,
Lirong Zhou MD,
Wei Huang MD,
Xue Liu MD

Department of Nuclear Medicine, Chongqing University Three Gorges Hospital, Wanzhou, 404100, Chongqing, China.

Keywords: Gastric tumor - ^{68}Ga-FAPI - ^{18}F-FDG - Meta-analysis - PET/CT - Fibroblast activation protein

Corresponding authors:
Xue Liu MD,
Department of Nuclear Medicine, Chongqing University Three Gorges Hospital, Wanzhou, 404100, Chongqing, China.
thyroid@126.com

Received:
27 September 2023
Accepted revised:
21 March 2024

Abstract

Objective: Our study aims to head to head compare the application of gallium-68-fibroblast activation protein inhibitor (^{68}Ga-FAPI) positron emission tomography/computed tomography (PET/CT) and fluorine-18-fluorodeoxyglucose (^{18}F-FDG) PET/CT in primary and metastatic lesions of gastric tumor to determine the superior diagnostic tool. **Materials and Methods:** A systematic search, up to March 31, 2023, across PubMed, Embase, and Cochrane Library databases utilized a data-specific Boolean logic strategy. Sensitivity (SEN) and specificity (SPE) evaluations of ^{68}Ga-FAPI and ^{18}F-FDG PET/CT in gastric cancer lesions were conducted. The quality of the studies was assessed using QUADAS-2, and publication bias was examined through Begg and Egger tests. **Results:** Analysis involved 141 gastric tumor patients and 2753 metastatic lesions in five studies, with overall satisfactory study quality and no apparent publication bias. Patient-level data showed a combined SEN of 0.95 (95% CI: 0.90-0.98) for ^{68}Ga-FAPI and 0.84 (95% CI: 0.77-0.89) for ^{18}F-FDG. At the lesion level, combined SENs were 0.91 (95% CI: 0.84-0.96) for ^{68}Ga-FAPI and 0.72 (95% CI: 0.63-0.80) for ^{18}F-FDG. The pooled SEN for detecting lymph node metastases was 0.78 (95% CI: 0.74-0.82) for ^{68}Ga-FAPI and 0.35 (95% CI: 0.30-0.39) for ^{18}F-FDG, with pooled SPE values of 0.99 (95% CI: 0.98-0.99) and 0.97 (95% CI: 0.96-0.98), respectively. For detecting distant metastases, pooled SEN values were 0.97 (95% CI: 0.96-0.98) and 0.69 (95% CI: 0.66-0.72) for ^{68}Ga-FAPI and ^{18}F-FDG, with pooled SPE values of 0.86 (95% CI: 0.82-0.89) and 0.64 (95% CI: 0.59-0.68), respectively. **Conclusion:** This meta-analysis concluded that ^{68}Ga-FAPI PET/CT was significantly more sensitive than ^{18}F-FDG PET/CT in assessing primary gastric tumors, lymph nodes, and distant metastases, but the difference in the specificity of lymph node metastasis was not significant.

Hell J Nucl Med 2024; 27(1): 35-45 *Epub ahead of print: 18 April 2024* *Published online: 30 April 2024*

Introduction

Gastric cancer, starting in the stomach, ranks as the fifth most frequently occurring cancer globally and as the third top cause of cancer-related mortality [1]. The treatment of gastric cancer is stage-specific, involving surgical procedures, chemotherapy, radiation therapy, immunotherapy, and targeted therapy [2]. In patients with stage IA or IB cancer, the 5-year survival rate following surgical resection ranges from 60% to 80% [1]. Positron emission tomography (PET) is a medical imaging technique that utilizes a radiotracer to visualize metabolic processes within the body, while PET/computed tomography (CT) combines the strengths of PET and CT scans [3]. Fluorine-18-fluorodeoxyglucose (^{18}F-FDG) PET/CT is commonly utilized for the diagnosis and staging of gastric cancer [4]. However, this modality has limited sensitivity for detecting gastric cancer, particularly in early stages and low metabolic activity cancers [5]. False-positive results may arise from physiological uptake in the gastric wall and gastritis, and the intensity of uptake cannot predict survival outcomes [6, 7]. Therefore, there is a need for more sensitive PET probes for accurate diagnosis and staging of gastric cancer [8].

Many tumors harbor cancer-associated fibroblasts that exhibit high levels of fibroblast activation protein (FAP) [9]. FAP inhibitors (FAPI) can target and visualize these tumors by binding to FAP, a protein overexpressed in certain tumors. Gallium-68-FAPI (^{68}Ga-FAPI) and other radiolabeled FAPI probes have demonstrated efficacy in various cancers such as lung, breast, prostate, sarcoma, and head and neck cancer [10, 11]. In contrast to ^{18}F-FDG PET/CT, which focuses on tumor cell glucose metabolism, radiolabeled FAPI imaging can reveal cancer-associated fibroblasts and extracellular fibrosis within the tumor stroma [8].

Recent studies have underscored the utility and superiority of ^{68}Ga-FAPI PET over ^{18}F-FDG PET in gastric cancers, spanning from initial staging to recurrence detection [12-15]. Qin et al. (2022) [8] reported that ^{68}Ga-FAPI PET outperformed ^{18}F-FDG PET in primary tumor detection (100.00% [14/14] vs. 71.43% [10/14]; P=0.03) with higher tracer uptake

levels (P<0.05). Watabe et al. (2023) [16] observed greater accumulation of FAPI-PET in primary sites and metastatic lesions compared to ^{18}F-FDG PET, particularly in detecting peritoneal carcinomatosis. Furthermore, ^{68}Ga-FAPI PET displayed notable efficacy in gastric signet ring cell carcinoma, where uptake levels are typically low in this subtype using ^{18}F-FDG PET [12]. Despite the promising findings, the high heterogeneity in results is attributed to varying sample sizes, quality disparities, and geographical influences. Therefore, conducting a rigorous meta-analysis is essential to reconcile discrepancies, enhance effect estimates, and provide robust evidence for evidence-based medicine.

A meta-analysis by Wang et al. (2023) [17] compared the use of ^{68}Ga-FAPI-04 PETmagnetic resonance imaging (MRI)/CT with ^{18}F-FDG PET MRI/CT in gastric cancer and found that ^{68}Ga-FAPI-04 PET MRI/CT was superior in detecting primary tumors, lymph node metastases, and peritoneal metastases. Another meta-analysis [18] evaluated the application of ^{68}Ga-FAPI PET/CT or PET/MR in digestive system tumors, revealing the high accuracy and sensitivity of ^{68}Ga-FAPI PET in diagnosing and evaluating such tumors. However, both meta-analyses included a mix of PET/MRI and PET/CT equipment, leading to significant statistical methodological and clinical heterogeneity in their results. Moreover, they did not assess publication bias within the studies. Caution is advised when interpreting the outcomes of these meta-analyses due to the diverse nature of the included studies.

Our study aims to directly compare the effectiveness of ^{68}Ga-FAPI PET/CT and ^{18}F-FDG PET/CT in primary and metastatic lesions of gastric cancer to determine the superior diagnostic tool.

Materials and Methods

The meta-analysis complied with the guidelines specified in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. This study was registered in the PROSPERO database with the registration number CRD42023395260.

Data sources and search strategy

We conducted a comprehensive search across multiple databases, including PubMed, EMBASE, Web of Science, and the Cochrane Library, for diagnostic studies related to "FAPI-PET", "FDG-PET", and "gastric cancer" published from the earliest indexing date through 31st March 2023. The search utilized a database-specific Boolean logic approach incorporating keywords such as FAP, FAPI, fibroblasts, cancer-associated fibroblasts, CAF, PET, PET/CT, PET-CT, FDG, fluorodeoxyglucose, positron emission tomography, gastric cancer, stomach cancer, stomach tumor, and gastric tumor. To ensure completeness, we hand-searched the reference lists of the identified publications. Two independent reviewers(CLG and HTL), conducted the search process.

Inclusion and exclusion criteria

The analysis included articles that were published and met the following criteria:

1) ^{68}GA-FAPI PET/CT and ^{18}F-FDG PET/CT were evaluated simultaneously as diagnostic methods for gastric tumor (primary tumor, lymph node and distant metastasis).
2) The lesions were confirmed by histopathology or combined clinical/imaging follow-up.
3) Sufficient data were provided to calculate the number of positive cases with respect to the primary gastric tumor, or true-positive, false-positive, false-negative, and true-negative cases of non-primary tumors (lymph nodes or distant metastases).

The exclusion criteria were as follows:

1) Those who were evaluated for gastric tumors utilized only one imaging agent (FAPI or FDG);
2) PET/MRI was employed;
3) The study subjects included stomach, duodenal, or colo,rectal tumors;
4) Overlapping papers;
5) Review articles, animal experiments, editorials or letters, comments, and conference proceedings;
6) A lack of access to the full text;
7) A sample size of fewer than 10 patients or lesions.

Quality assessment

The methodological quality of each eligible article was appraised by two independent reviewers (CLG and HTL). Any discrepancies were resolved through consultation or by involving a third reviewer. The modified Quality Assessment of Diagnostic Accuracy Studies version 2 (QUADAS-2), as recommended by the Cochrane Collaboration guidelines [19], was used for evaluation. Each item was classified as having a "high", "low", or "unclear" risk of bias.

Data extraction

Data extraction was carried out on literature that met the predetermined criteria. Each study's data included the first author's name, publication year, country of origin, study design (prospective or retrospective), study center type (single-center or multi-center), gastric cancer subtype, diagnostic criteria used, purpose of imaging, interpretation of images, patient age and gender distribution, sample size, range of PET/CT scans, type of imaging agent used, injection activity, time interval between ^{68}Ga-FAPI and ^{18}F-FDG scans, maximum standardized uptake value (SUVmax) of primary lesions, tumor-to-background ratio (TBR), and type of image analysis (qualitative, quantitative, or semi-quantitative). Sensitivity (SEN), specificity (SPE), and accuracy were recorded or calculated for each patient and/or lesion. Subgroup analyses were performed by collecting these data when analyzing primary and non-primary (metastatic) tumors. Unpublished literature was not sought through author contact.

Statistical analysis

This study collected data from all eligible studies and employed descriptive statistics and frequency tables to summarize the data. Subgroup analyses were conducted on primary and non-primary tumors, and diagnostic pooled assessments of ^{68}Ga-FAPI PET/CT and ^{18}F-FDG PET/CT were performed within these subgroups. The utility of ^{68}Ga-FAPI PET/CT and ^{18}F-FDG PET/CT in primary tumors, encompassing primary staging

and recurrence on a patient-level basis, was evaluated. For non-primary tumors, assessments were undertaken lesion by lesion, covering metastases in lymph nodes, adrenal glands, peritoneum, liver, bones, and other sites. The primary aim of this study was to assess the effectiveness of ^{68}Ga-FAPI PET/CT and ^{18}F-FDG PET/CT in detecting gastric tumors by calculating combined measures such as sensitivity, specificity, and the area under the curve (AUC). Cochran's Q homogeneity tests and I^2 were employed to evaluate data consistency, with $I^2 \leq 50\%$ set as the acceptable level of heterogeneity. Subgroup analyses or sensitivity analyses would be conducted in case of high heterogeneity, followed by pooling the results using a random effects model. Additionally, Begg and Egger tests were carried out to evaluate publication bias. Statistical significance was evaluated with two-tailed tests, using a significance threshold of $P<0.05$. All statistical analyses were performed using Stata version 16.0 software (StataCorp LP, College Station, TX, USA), Review Manager software (Cochrane Collaboration, version 5.3.5, London, United Kingdom), and MetaDiSc 1.4 (Clinical Biostatistics team of the Ramón y Cajal Hospital in Madrid, Spain).

Results

Literature search and study selection

A comprehensive systematic search was conducted across three key databases: PubMed/MEDLINE, Embase, and the Cochrane Library, resulting in the retrieval of 86 relevant articles. To ensure data quality, 42 duplicate articles were excluded. The titles and abstracts of the remaining papers were scrutinized based on specific inclusion and exclusion criteria, leading to the exclusion of 27 articles. This process left us with a final selection of 17 papers for full-text assessment. Following a thorough review of these 17 articles, five met the criteria and were selected for inclusion in the meta-analysis. For a detailed visualization of the literature screening process, refer to Figure 1.

Characteristics of the included studies

The studies examined in this review were published between 2022 and 2023. Of these, four studies [12-14, 20] were undertaken in China, while one study [15] was conducted in Turkey. These studies involved 141 patients with gastric tumors and 2753 metastatic lesions, all of which were classified as adenocarcinomas, with 78 cases showing signet ring cell features. Among these studies, three [13-15] were prospective in design, while the rest were retrospective. Additionally, one study [12] gathered data from multiple centers, whereas the others were single-center studies. The age range of patients spanned from 24 to 85 years. Further details of the characteristics of the five studies included in the meta-analysis can be found in Table 1.

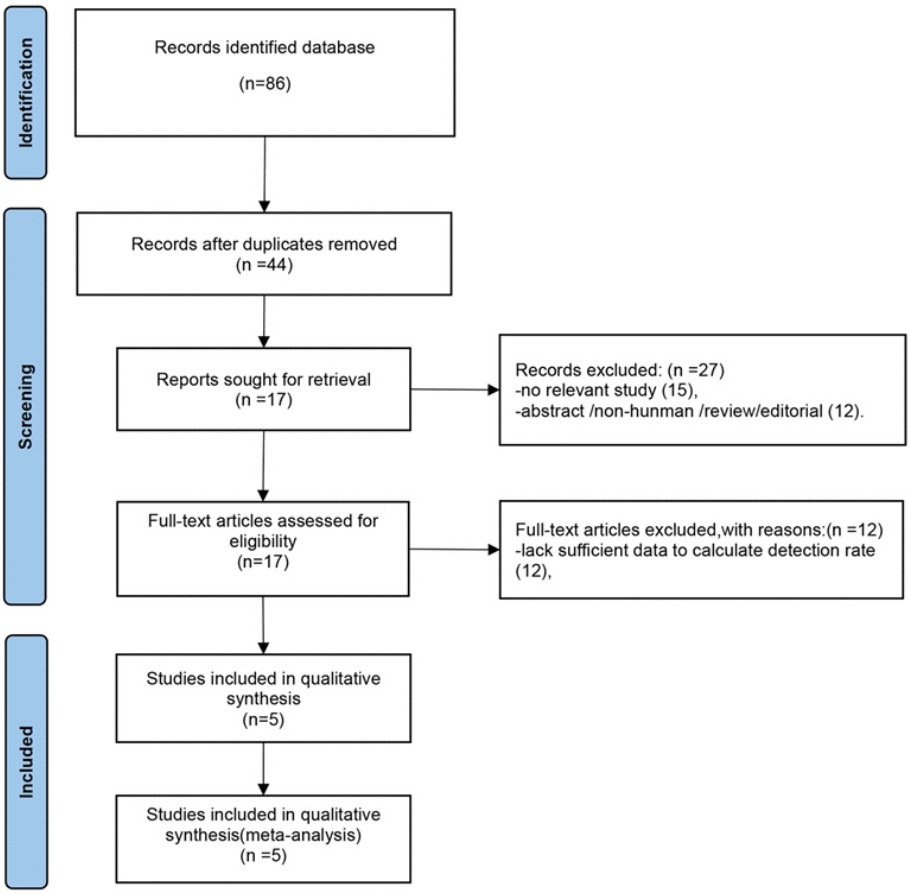

Figure 1. Flowchart of the search for eligible studies on ^{68}Ga-FAPI and ^{18}F-FDG PET/CT in patients of gastric cancer. Five articles were finally selected for this meta-analysis.

Table 1. Basic study and patient characteristics.

Author	Year	Country	Gender (male/female)	Patient/lesion (n)	Age（years）	Study center	Study design	Diagnostic criteria	Histological type (n)	Imaging analyses
Chen et al. [12]	2023	China	16/18	22/739	Median 51 (IQR:25-85)	Multicenter	Retrospective	HP, imaging follow-up	GSRCC 34 (100%)	Q+V
Lin et al. [13]	2022	China	40/16	45/762	Median 63.8 (range: 28-85)	Single-center	Prospective	HP, laboratory tests and imaging follow-up	Containing SRCC 17 (37.8%), Without SRCC 28 (62.6%)	Q+V
Miao et al. [14]	2022	China	44/18	62/362	Median 64 (range: 24-75)	Single-center	Prospective	HP, laparoscopic exploration,imaging follow-up	PCC 27 (43.5%), non-PCC 35 (56.5%)	Q+V
Zhang et al. [20]	2022	China	12/13	19/368	Mean 56±12 (range: 35-79)	Single-center	Retrospective	HP, imaging follow-up	WDAc 2 (8%), MDAc 2 (8%), PDAc 11 (44%), PDAc with partial SRCC 4 (16%), PDAc with partial MAc and SRCC 1 (4%), UDAc 5 (20%)	Q+V
Gündoğan et al. [15]	2022	Turkey	12/9	15/217	Median 61 (range: 40-81)	Single-center	Prospective	HP	GAc 21 (100%)	Q+V

IQR, Interquartile range; HP, Histopathology; n, number; GSRCC, Gastric signet-ring-cell carcinoma; PCC,poorly cohesive carcinoma (including signet ring cell carcinoma); WDAc, Well-differentiated adenocarcinoma; MDAc, Moderately differentiated adenocarcinoma; PDAc, Poorly differentiated adenocarcinoma; MAc, Mucinous adenocarcinoma; UDAc, Unknown differentiated adenocarcinoma; GAc, Gastric adenocarcinoma;V, visual analysis; Q, quantitative analysis.

Technical aspects

Table 2 summarizes the techniques of ^{68}Ga-FAPI PET/CT and ^{18}F-FDG PET/CT as reported in five articles focusing on the diagnosis and evaluation of gastric cancer. While both PET/CT and PET/MRI imaging modalities were employed in the study by Chen et al. (2023) [12], our study specifically utilized PET/CT scanners for imaging all subjects, with ^{68}Ga-FAPI-04 and ^{18}F-FDG serving as the imaging agents. The time interval between injection of the imaging agents and scanning across all studies ranged from 35 to 71 minutes.

Regarding scan ranges, four studies [13-15, 20] primarily covered PET/CT scans from the head to the upper middle thigh. Additionally, the interval duration between scans involving the two imaging agents was detailed in four studies [12-15]. Specifically, three studies [12, 13, 15] completed the scans within a week, while another study [14] finished the process in nine days.

All studies conducted semi-quantitative image analyses, where three studies [12, 13, 15] utilized both SUVmax and TBR for image interpretation. Furthermore, a comparison of SUVmax values between ^{68}Ga-FAPI PET/CT and ^{18}F-FDG PET/CT imaging agents was performed in all studies, indicating that the ^{68}Ga-FAPI-SUVmax values of primary tumors surpassed the ^{18}F-FDG-SUVmax values.

Risk of bias and applicability

In evaluating the quality of the included studies, QUADAS-2 was utilized, as depicted in Figure 2. Our assessment revealed that none of the studies exhibited low quality, with an overall satisfactory quality assessment. Consequently, the risk of bias and concerns regarding applicability were determined to be relatively low for the studies scrutinized in our meta-analysis.

Quantitative analysis (meta-analysis)

Based on primary tumor performance analysis

Patient-level data from four studies [13-15, 20] were utilized to evaluate the SEN of ^{68}Ga-FAPI PET/CT and ^{18}F-FDG PET/CT in primary gastric tumors, resulting in combined SEN values of 0.95 (95% CI: 0.90-0.98; I2=64.4%, P=0.04) and 0.84 (95% CI: 0.77-0.89; I^2=78.8%, P=0.00) respectively (Figure 3A, B). At the lesion-level, the combined SENs from four additional studies [12, 13, 15, 20] were 0.91 (95% CI: 0.84-0.96; I^2=70.8%, P=0.02) for ^{68}Ga-FAPI and 0.72 (95% CI: 0.63-0.80; I^2=93.5%, P=0.00) for ^{18}F-FDG (Figure 3C, D). Limited primary tumor data availability hindered the pooling of effect sizes for specificity, thereby limiting the meta-analysis to sensitivity assessment only. Nevertheless, the consolidated sensitivity estimates offer valuable insights into the overall performance of the diagnostic tests, facilitating informed clinical decision-making.

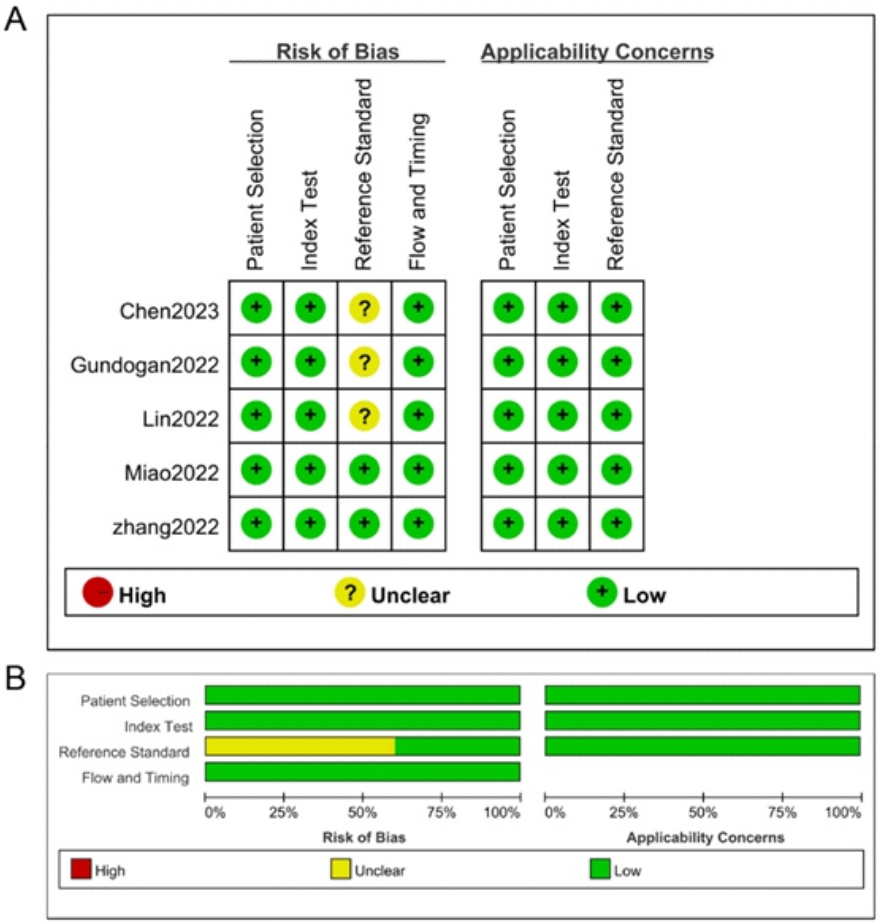

Figure 2. Risk of bias and applicability concerns the summary (A) and graph (B) of the studies included in the systematic review according to the QUADAS-2 tool. Overall quality of the included studies was deemed satisfactory.

Table 2. *Technical aspects of ^{68}Ga-FAPI and ^{18}F-FDG in the included studies.*

Author	PET/CT scanner	^{68}Ga-FAPI-04 (Activity)	^{18}F-FDG (Activity)	Time interval between the two scans	Scanning time	Scanning scope	PTSUVmax		PT TBR	
							^{68}Ga-FAPI	^{18}F-FDG	^{68}Ga-FAPI	^{18}F-FDG
Chen et al. [12]	NG	Median 194.3 (133.2-281.2) MBq	Median 281.2 (203.5-358.9) MBq	2 days (1-7 days)	One hour	NG	Median 5.2 (0.7–20.3)	Median 2.2 (1.0-6.9)	Median 7.6 (0.9-21.4)	Median 1.3 (0.6-3.1)
Lin et al. [13]	SyngoMultiModality Workplace, Siemens	111-185MBq	3.7MBq/kg	Less than 1 week	35-71 min	From the head to the upper thighs	Mean 10.3 ± 3.8	Mean 8.1 ± 4.9	Mean 11.6 ± 5.4	Mean 5.8 ± 3.6
Miao et al. [14]	Biograph Vision 450, Siemens	1.85-2.96MBq/kg	3.7-4.44MBq/kg	Within 9 days	30-60 min	From the vertex to midthigh	Median 18.81 (IQR: 12.66, 23.18)	Median 10.44 (IQR: 5.97, 16.09)	NG	NG
Zhang et al. [20]	uMI780, United Imaging Healthcare	1.85MBq/kg	3.7MBq/kg	NG	60 min	From the vertex to midthigh	Mean 10.28 (IQR: 4.98, 13.38)	Mean 3.20 (IQR: 2.51, 4.85)	NG	NG
Gündoğan et al.[15]	Discovery IQ 4 ring 20 cm axial FOV,GE Healthcare	2MBq/kg	3.5-5.5MBq/kg	Maximum 1 week	One hour	From the vertex to midthigh	Median 11.0 (0.8-25.1)	Median 6.1 (2.2-24.6)	Median 8.8 (2.4-27.0)	Median 5.1 (2.4-33.7)

PT, primary tumour; IQR, Interquartile range; SUV-max, maximum standardized uptake value; TBR, tumor-to-background ratio; GE, General Electric Company; NG, Not given.

Based on non-primary tumor (lymph node and distant metastasis) performance analysis

Due to the absence of patient-level data, only data at the metastatic lesion level could be combined, leading to limitations in capturing potential variations in diagnostic performance among patients. The pooled SEN of ^{68}Ga-FAPI PET/CT and ^{18}F-FDG PET/CT in non-primary tumors were 0.91 (95% CI: 0.90-0.93; I^2=98.4%, P=0.00) and 0.57 (95% CI: 0.54-0.60; I^2=92.4%, P=0.00), with pooled SPE of 0.95 (95% CI: 0.94-0.96; I^2=94.7%, P=0.00) and 0.86 (95% CI: 0.84-0.88; I^2=97.3%, P=0.00), respectively, alongside AUC values of 0.98 and 0.62, respectively. To mitigate inter-study heterogeneity, subgroup analyses were conducted for lymph node and distant metastasis, yielding pooled SEN for detecting lymph node metastases of 0.78 (95% CI: 0.74-0.82) and 0.35 (95% CI: 0.30-0.39) with ^{68}Ga-FAPI PET/CT and ^{18}F-FDG PET/CT, and pooled SPE of 0.99 (95% CI: 0.98-0.99) and 0.97 (95% CI: 0.96-0.98), respectively (Figure 4A, B, C, D). The AUC values were 0.98 and 0.49, respectively.

For the detection of distant metastases, the combined SEN were 0.97 (95% CI: 0.96-0.98) for ^{68}Ga-FAPI PET/CT and 0.69 (95% CI: 0.66-0.72) for ^{18}F-FDG PET/CT, with corresponding SPE of 0.86 (95% CI: 0.82-0.89) and 0.64 (95% CI: 0.59-0.68), as depicted in Figure 5A, B, C, D. The area under the curve (AUC) values were 0.89 and 0.82, respectively.

Publication bias

Utilizing funnel plots, we visually assessed the potential publication bias in the included studies. The funnel plots, constructed for primary tumors, lymph node metastases, and distant metastases, based on the sensitivity of ^{68}Ga-FAPI PET/CT and ^{18}F-FDG PET/CT, exhibited predominantly symmetrical patterns, suggesting an absence of publication bias across the combined studies.

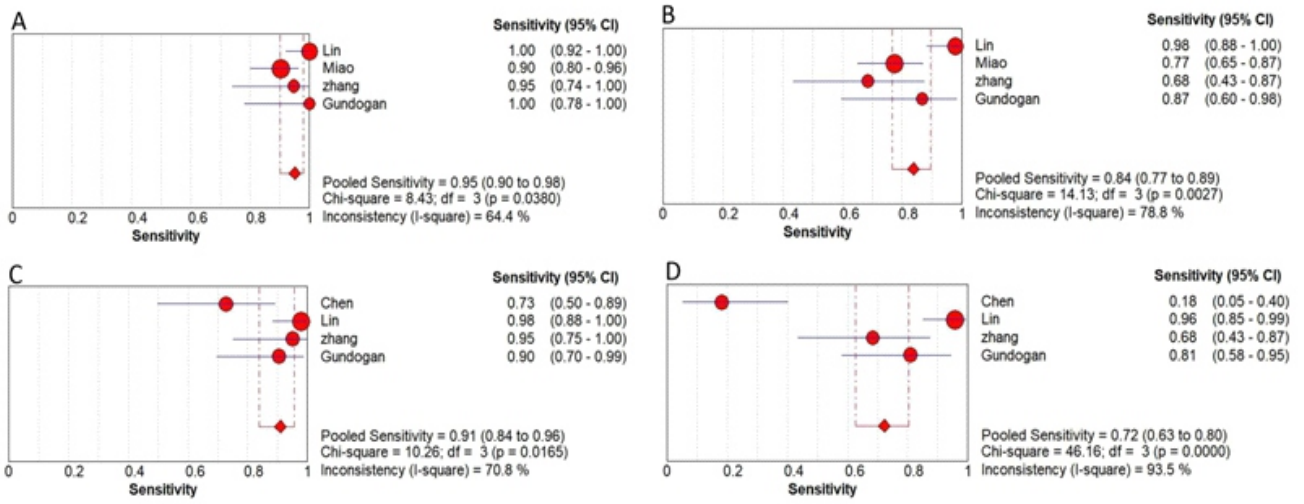

Figure 3. Forest plot of primary gastric tumors. Based on patient-level data, the pooled SEN of ^{68}Ga-FAPI (A) and ^{18}F-FDG (B). Based on lesion-level data, the pooled SEN of ^{68}Ga-FAPI (C) and ^{18}F-FDG (D).

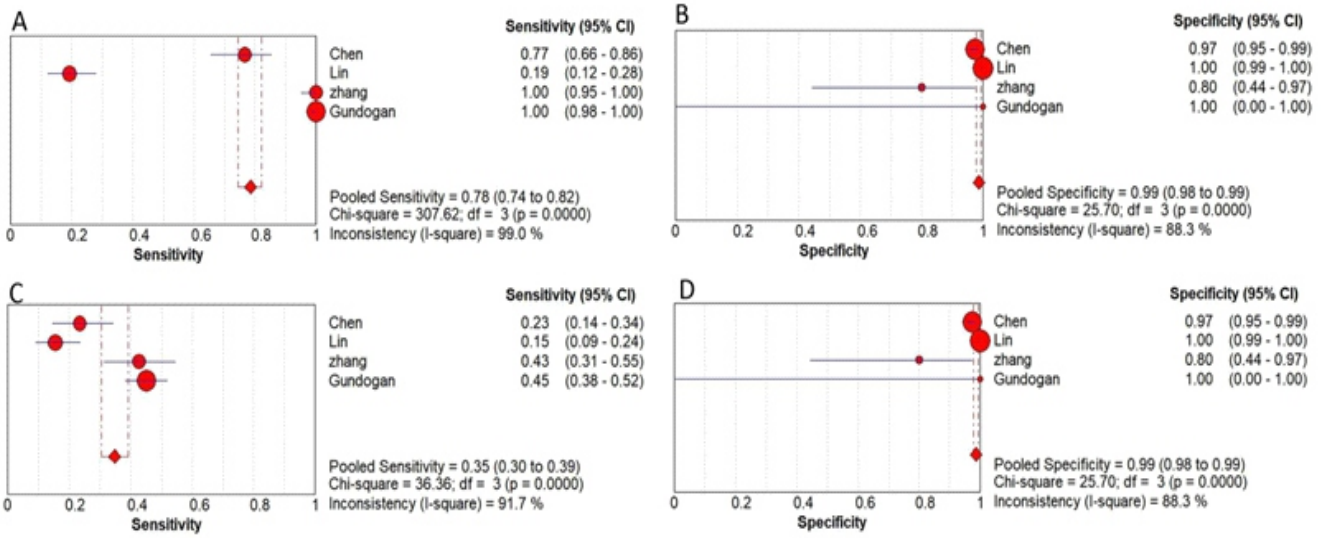

Figure 4. Forest plot of the lymph node metastases. The pooled SEN for ^{68}Ga-FAPI (A) and ^{18}F-FDG (B), the pooled SPE for ^{68}Ga-FAPI (C) and ^{18}F-FDG (D).

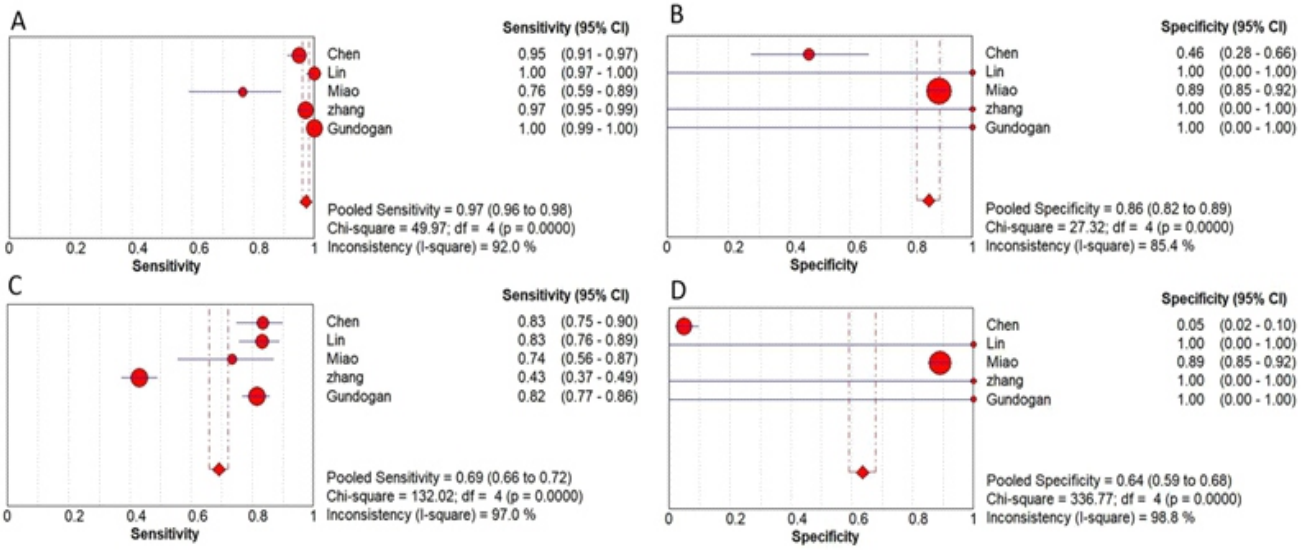

Figure 5. Forest plot of the distant metastases. The pooled SEN for ^{68}Ga-FAPI (A) and ^{18}F-FDG (B), the pooled SPE for ^{68}Ga-FAPI (C) and ^{18}F-FDG (D).

Discussion

Gastric cancer represents a highly invasive and biologically heterogeneous tumor entity often diagnosed at advanced stages [1]. This highlights the critical need for imaging modalities with heightened sensitivity and specificity to precisely assess tumor location and extent, enabling early detection and guiding effective treatment strategies. Gallium-68-FAPI PET/CT, an innovative molecular targeted imaging modality targeting tumor cell surface-specific proteins, offers superior specificity in visualizing tumor cells, surpassing conventional metabolic PET/CT approaches [10]. Our meta-analysis reveals that ^{68}Ga-FAPI PET/CT exhibits increased sensitivity in detecting primary gastric tumors compared to ^{18}F-FDG PET/CT (0.95 vs. 0.84), aligning with existing literature [10, 21], underscoring its diagnostic accuracy across diverse cancers. Notably, the absence of patient-level data in some studies may constrain the generalizability of our findings. Concerning metastatic lesions, our analysis demonstrates that ^{68}Ga-FAPI PET/CT outperforms ^{18}F-FDG PET/CT in both sensitivity and specificity for non-primary tumors detection (SEN: 0.91 vs. 0.57, SPE: 0.95 vs. 0.86), suggesting its heightened relevance in gastric cancer detection and staging, particularly in identifying distant metastases. The study further indicates that ^{68}Ga-FAPI PET/CT has higher combined sensitivity and quite similar specificity to ^{18}F-FDG PET/CT in detecting lymph node metastases, a crucial consideration impacting treatment decisions and prognostic outcomes.

Our meta-analysis findings suggest that ^{68}Ga-FAPI PET/CT outperforms ^{18}F-FDG PET/CT in diagnosing primary gastric tumors, particularly in the detection of primary lesions. These results support the notion that ^{68}Ga-FAPI PET/CT stands as a more dependable method for identifying primary gastric tumors, offering enhanced precision in lesion localization and diagnosis of lesion extent. The variance in sensitivity between these techniques may stem from their distinct targeting of varied biological traits. While ^{18}F-FDG and ^{68}Ga-FAPI employ differing tumor imaging mechanisms, each yielding disparate performance in tumor identification [22]. As tumor cells undergo heightened metabolism via increased glucose uptake, leading to elevated lactate production, FDG scanning serves as a prevalent technique in tumor imaging [23]. Conversely, ^{68}Ga-FAPI utilizes positron emission dosimetry to target fibroblast activation protein on tumor cell surfaces, diverging from the glucose metabolic detection of tumor cells [24]. Being prominently expressed in tissue fibrosis and tumor proliferation processes, fibroblast activation protein exhibits significantly elevated levels in gastric cancer cells relative to normal tissues or benign lesions like gastric ulcers [25]. Hence, ^{68}Ga-FAPI PET/CT holds potential for heightened sensitivity and specificity in tumor detection, especially in cases showcasing pronounced morphological diversity.

A meta-analysis by Huang et al. (2023) [18] suggested that ^{68}Ga-FAPI PET/MR or PET/CT exhibited a sensitivity of 95% for detecting gastrointestinal tract lesions. A previous study [21] on the use of ^{68}Ga-FAPI and ^{18}F-FDG PET/CT in abdominal and pelvic malignant tumors found that the detection rates for primary gastric cancer were 99% with ^{68}Ga-FAPI and 97% with ^{18}F-FDG, respectively, slightly higher than our findings. This difference may be attributed to the inclusion of both true positives and false positives in their positive cases. The depth of invasion and tumor size are key factors influencing ^{68}Ga-FAPI-04 uptake in gastric cancer [14]. In addition, ^{68}Ga-FAPI shows low sensitivity for detecting early-stage gastric cancer [14]. Considering conditions such as inflammation and fibrosis can lead to increased uptake in ^{68}Ga-FAPI PET/CT scans, a detailed understanding of the patient's medical history is essential for interpreting imaging results [12]. In the context of pathology, ^{68}Ga-FAPI PET/CT shows significantly higher uptake rates in infiltrating adenocarcinoma SRCC and mucinous carcinoma compared to ^{18}F-FDG PET/CT, a phenomenon possibly associated with GLUT-1 ex-

pression levels [13]. The improved diagnostic precision of ^{68}Ga-FAPI in primary gastric tumors over ^{18}F-FDG PET/CT can be attributed to its higher SUVmax, TBR, and impressive image contrast capabilities [12, 13]. This is due to the selective binding of ^{68}Ga-FAPI to FAP on tumor cell surfaces, allowing for precise identification of tumor cells within tissues and resulting in heightened SUVmax values [26]. Additionally, the rapid distribution and clearance of ^{68}Ga-FAPI in non-tumor tissues contribute to reduced uptake in these areas, thereby enhancing the TBR and image contrast, which facilitates clearer visualization of the tumor [27]. Furthermore, FAPI demonstrates less variability in SUVmax uptake between different tumors compared to ^{18}F-FDG imaging, potentially because FAPI targets a specific set of proteins with consistent expression levels, whereas ^{18}F-FDG uptake is influenced by variable glucose metabolism across tumor stages, treatments, and drug resistances [26].

Accurate evaluation of lymph node metastasis is crucial for predicting the prognosis of patients with gastric cancer and aiding in treatment decision-making. In this study, we evaluated the effectiveness of two imaging agents in detecting lymph node metastasis in gastric cancer, finding that ^{68}Ga-FAPI demonstrated superior overall detection capability for metastatic lesions in the lymph nodes associated with gastric cancer compared to ^{18}F-FDG. This conclusion was based on assessments of sensitivity, specificity, diagnostic odds ratio, and ROC analysis. Specifically, the sensitivity of ^{68}Ga-FAPI in diagnosing lymph node metastatic lesions was notably higher at 0.78 compared to 0.35 for ^{18}F-FDG. Chen et al. (2023) [12] examined 77 confirmed cases of lymph node metastasis and reported that ^{68}Ga-FAPI detected 77% (59/77) of the lymph node lesions, while ^{18}F-FDG only detected 23% (18/77). The increased detection rate with ^{68}Ga-FAPI may be attributed to its higher uptake and TBR in metastatic lymph nodes [12], consistent with findings from previous studies [28, 29]. However, Miao et al. (2023) [14] observed that the sensitivity of ^{68}Ga-FAPI was not significantly higher than that of ^{18}F-FDG, with both demonstrating relatively low sensitivity rates (63.6% vs. 54.5%, P>0.05). Some studies [14] have suggested several reasons for the low sensitivity of ^{68}Ga-FAPI in detecting regional lymph nodes in gastric cancer. Firstly, postoperative lymph node dissection for pathological detection may lead to false-negative results, particularly in regional lymph nodes. Secondly, patients included in regional lymph node analysis may be in earlier disease stages, resulting in small and obscure metastatic lymph nodes. Additionally, the uptake of small lymph nodes near the stomach may be masked by the radioactive volume effect of primary gastric tumors and gastric motion. It has also been proposed that the limited performance of ^{68}Ga-FAPI in detecting lymph node metastasis could be influenced by the biological characteristics of the tumor and the level of lymph node cell enrichment [30]. Furthermore, our study indicated that both imaging agents exhibited comparable specificity in detecting lymph node metastasis (^{68}Ga-FAPI: 0.99 vs. ^{18}F-FDG: 0.97), leading us to believe that both have similar abilities to rule out the presence of lymph node metastasis.

The potential sites of distant metastases in gastric cancer encompass the liver, adrenal glands, bones, peritoneum, ovaries, and infrequent sites [12, 13]. Previous research [31] has highlighted the efficacy of ^{18}F-FDG PET in detecting liver, lung, and bone metastases, exhibiting a sensitivity of 95.2% and a specificity of 100%. Nevertheless, our meta-analysis reveals that ^{68}Ga-FAPI demonstrates notably higher sensitivity (0.97 vs. 0.69) and specificity (0.86 vs. 0.64) in identifying metastatic lesions of gastric cancer compared to ^{18}F-FDG. Specifically, ^{68}Ga-FAPI failed to identify all metastatic lesions, as evidenced by Miao et al. (2023) [14] reporting the detection of three liver metastases by ^{18}F-FDG PET/CT that were missed by ^{68}Ga-FAPI-04 PET/CT, while one liver metastasis detected by ^{68}Ga-FAPI PET/CT was misdiagnosed as a false positive. Similarly, Zhang et al. (2022) [32] noted that ^{18}F-FDG PET identified more pancreatic cancer liver metastases than ^{68}Ga-FAPI-04 (P<0.00). Peritoneal dissemination commonly occurs as a mode of distant metastasis in gastric cancer. Notably, Gallium-68-FAPI-04 exhibits minimal physiological uptake in the intestine, resulting in reduced background uptake within the peritoneal cavity. This characteristic enhances the sensitivity and diagnostic superiority of ^{68}Ga-FAPI-04 over ^{18}F-FDG PET/CT in detecting peritoneal implants [14]. Furthermore, larger tumor lesions with supporting stroma exceeding 2mm may contain a stromal volume larger than the tumor cells themselves [33]. Therefore, in cases where there is abundant FAP expression in the stroma, ^{68}Ga-FAPI-04 PET may exhibit higher sensitivity than ^{18}F-FDG PET [14]. Nevertheless, it is important to note that ^{68}Ga-FAPI PET shows lower specificity than ^{18}F-FDG PET in detecting bone and visceral metastases due to the presence of more false-positive lesions on ^{68}Ga-FAPI PET images [12]. Chen et al. (2023) [12] also suggested that conditions such as bone marrow fibrosis, arthritis, granulomas, uterine fibroids, pneumonia, and esophagitis can exhibit ^{68}Ga-FAPI uptake leading to false-positive results. Therefore, meticulous interpretation of ^{68}Ga-FAPI PET/CT images is necessary to prevent misdiagnosis, emphasizing the importance of considering additional imaging findings and clinical data, not solely relying on the uptake levels of ^{68}Ga-FAPI [12, 18].

Heterogeneity among studies poses a potential source of bias in meta-analysis, stemming from variations in patient characteristics, methodological approaches, and overall study quality [34]. Our analysis revealed heterogeneity in the sensitivity of ^{68}Ga-FAPI and ^{18}F-FDG in evaluating gastric primary tumors. Subgroup analyses were performed based on lesion and patient characteristics, but heterogeneity persisted. Further subgroup analyses were conducted by differentiating non-primary lesions into lymph nodes and distant metastases, revealing continued heterogeneity possibly attributed to differences in radioactive dosage, scan timing, imaging instrumentation, and study populations. To account for this heterogeneity, random-effects models were utilized for effect size amalgamation. Additionally, the histological type of gastric cancer may influence result heterogeneity, with varying pathological types affecting the response to FAPI-PET/CT. Addressing publication bias, a common concern in meta-analyses given the preference for publishing positive results [35], we employed funnel plots in our assessment. Symmetrical funnel plots were observed for both primary tumor staging and non-primary tumor metastasis, suggesting an absence of publication bias.

In contrast, while Wang et al. (2023) [17] also examined the

diagnostic capabilities for gastric cancer, their inclusion of subjects undergoing PET/MRI and PET/CT imaging introduced increased heterogeneity among studies. Our study featured stringent inclusion and exclusion criteria, comprehensive outcome indicators, and all five included studies utilized both imaging agents concurrently. Notably, evaluation extended beyond primary tumor staging to include lymph nodes and distant metastases for ^{68}Ga-FAPI and ^{18}F-FDG PET/CT. Quality assessment utilizing the QUADAS-2 tool revealed no studies of low quality and an overall satisfactory level of study quality. However, several limitations were identified in our meta-analysis. Primarily, the limited number of published articles in this area led to the inclusion of only five studies, potentially introducing bias. Moreover, significant discrepancies in sample size and study design across the included studies may impact result reliability. Lastly, persistent heterogeneity among studies, as evidenced by the lack of improvement post subgroup analyses, may influence the accuracy of combined results.

In conclusion, our meta-analysis revealed that ^{68}Ga-FAPI PET/CT exhibited significantly higher sensitivity compared to ^{18}F-FDG PET/CT in evaluating primary gastric tumors, lymph nodes, and distant metastases. However, no significant difference was found in the specificity of detecting lymph node metastases.

The authors declare that they have no conflicts of interest.

Funding

This study was supported by 2022 Hospital-level Scientific Research Project of Chongqing University Three Gorges Hospital (2022YJKYXM-021).

Bibliography

1. Sexton RE, Al Hallak MN, Diab M et al. Gastric cancer: a comprehensive review of current and future treatment strategies. *Cancer Metastasis Rev* 2020; 39(4): 1179-203.
2. Joshi SS, Badgwell BD. Current treatment and recent progress in gastric cancer. *CA Cancer J Clin* 2021; 71(3): 264-79.
3. Mayerhoefer ME, Prosch H, Beer L et al. PET/MRI versus PET/CT in oncology: a prospective single-center study of 330 examinations focusing on implications for patient management and cost considerations. *Eur J Nucl Med Mol Imaging* 2020; 47(1): 51-60.
4. Dębiec K, Wydmański J, d'Amico A et al. The application of ^{18}F-FDG-PET/CT in gastric cancer staging and factors affecting its sensitivity. *Hell J Nucl Med* 2021; 24(1): 66-74.
5. Filik M, Kir KM, Aksel B et al. The Role of ^{18}F-FDG PET/CT in the Primary Staging of Gastric Cancer. *Mol Imaging Radionucl Ther* 2015; 24(1): 15-20.
6. Kitajima K, Nakajo M, Kaida H et al. Present and future roles of ^{18}F-FDG-PET/CT imaging in the management of gastrointestinal cancer: an update. *Nagoya J Med Sci* 2017; 79(4): 527-43.
7. Stahl A, Ott K, Weber WA et al. ^{18}F-FDG PET imaging of locally advanced gastric carcinomas: correlation with endoscopic and histopathological findings. *Eur J Nucl Med Mol Imaging* 2003; 30(2): 288-95.
8. Qin C, Shao F, Gai Y et al. ^{68}Ga-DOTA-FAPI-04 PET/MR in the Evaluation of Gastric Carcinomas: Comparison with ^{18}F-FDG PET/CT. *J Nucl Med* 2022; 63(1): 81-8.
9. Chen R, Yang X, Yu X et al. The feasibility of ultra-early and fast total-body ^{68}Ga-FAPI-04 PET/CT scan. *Eur J Nucl Med Mol Imaging* 2023; 50(3): 661-6.
10. Kratochwil C, Flechsig P, Lindner T et al. ^{68}Ga-FAPI PET/CT: Tracer Uptake in 28 Different Kinds of Cancer. *J Nucl Med* 2019; 60(6): 801-5.
11. Giesel FL, Kratochwil C, Lindner T et al. ^{68}Ga-FAPI PET/CT: Biodistribution and Preliminary Dosimetry Estimate of 2 DOTA-Containing FAP-Targeting Agents in Patients with Various Cancers. *J Nucl Med* 2019; 60(3): 386-92.
12. Chen H, Pang Y, Li J et al. Comparison of ^{68}Ga-FAPI and ^{18}F-FDG uptake in patients with gastric signet-ring-cell carcinoma: a multicenter retrospective study. *Eur Radiol* 2023; 33(2): 1329-41.
13. Lin R, Lin Z, Chen Z et al. ^{68}Ga-DOTA-FAPI-04 PET/CT in the evaluation of gastric cancer: comparison with ^{18}F-FDG PET/CT. *Eur J Nucl Med Mol Imaging* 2022; 49(8): 2960-71.
14. Miao Y, Feng R, Guo R et al. Utility of ^{68}Ga-FAPI-04 and ^{18}F-FDG dual-tracer PET/CT in the initial evaluation of gastric cancer. *Eur Radiol* 2023; 33(6): 4355-66.
15. Gündoğan C, Kömek H, Can C et al. Comparison of ^{18}F-FDG PET/CT and ^{68}Ga-FAPI-04 PET/CT in the staging and restaging of gastric adenocarcinoma. *Nucl Med Commun* 2022; 43(1): 64-72.
16. Watabe T, Giesel FL. Fibroblast Activation Protein Inhibitor PET/CT in Gastric Cancer. *PET Clin* 2023; 18(3): 337-44.
17. Wang Y, Luo W, Li Y. ^{68}Ga-FAPI-04 PET MRI/CT in the evaluation of gastric carcinomas compared with ^{18}F-FDG PET MRI/CT: a meta-analysis. *Eur J Med Res* 2023; 28(1): 34.
18. Huang D, Wu J, Zhong H et al. ^{68}Ga-FAPI PET for the evaluation of digestive system tumors: systematic review and meta-analysis. *Eur J Nucl Med Mol Imaging* 2023; 50(3): 908-20.
19. Whiting PF, Rutjes AW, Westwood ME et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Ann Intern Med* 2011; 155(8): 529-36.
20. Zhang S, Wang W, Xu T et al. Comparison of Diagnostic Efficacy of ^{68}Ga-FAPI-04 and ^{18}F-FDG PET/CT for Staging and Restaging of Gastric Cancer. *Front Oncol* 2022; 12: 925100.
21. Liu X, Liu H, Gao C et al. Comparison of ^{68}Ga-FAPI and ^{18}F-FDG PET/CT for the diagnosis of primary and metastatic lesions in abdominal and pelvic malignancies: A systematic review and meta-analysis. *Front Oncol* 2023; 13: 1093861.
22. Satpati D, Sharma R, Sarma HD et al. Comparative evaluation of ^{68}Ga-labeled NODAGA, DOTAGA, and HBED-CC-conjugated cNGR peptide chelates as tumor-targeted molecular imaging probes. *Chem Biol Drug Des* 2018; 91(3): 781-8.
23. Fadaka A, Ajiboye B, Ojo O et al. Biology of glucose metabolization in cancer cells. *J Oncological Sciences* 2017; 3(2): 45-51.
24. Giesel FL, Kratochwil C, Lindner T et al. ^{68}Ga-FAPI PET/CT: Biodistribution and Preliminary Dosimetry Estimate of 2 DOTA-Containing FAP-Targeting Agents in Patients with Various Cancers. *J Nucl Med* 2019; 60(3): 386-92.
25. Mori Y, Dendl K, Cardinale J et al. FAPI PET: Fibroblast Activation Protein Inhibitor Use in Oncologic and Nononcologic Disease. *Radiology* 2023; 306(2): e220749.
26. Mona CE, Benz MR, Hikmat F et al. Correlation of ^{68}Ga-FAPI-46 PET Biodistribution with FAP Expression by Immunohistochemistry in Patients with Solid Cancers: Interim Analysis of a Prospective Translational Exploratory Study. *J Nucl Med* 2022; 63(7): 1021-6.
27. Meyer C, Dahlbom M, Lindner T et al. Radiation Dosimetry and Biodistribution of ^{68}Ga-FAPI-46 PET Imaging in Cancer Patients. *J Nucl Med* 2020; 61(8): 1171-7.
28. Pang Y, Zhao L, Luo Z et al. Comparison of ^{68}Ga-FAPI and ^{18}F-FDG Uptake in Gastric, Duodenal, and Colorectal Cancers. *Radiology* 2021; 298(2): 393-402.
29. Kuten J, Levine C, Shamni O et al. Head-to-head comparison of ^{68}Ga-FAPI-04 and ^{18}F-FDG PET/CT in evaluating the extent of disease in gastric adenocarcinoma. *Eur J Nucl Med Mol Imaging* 2022; 49(2): 743-50.
30. Sollini M, Kirienko M, Gelardi F et al. State-of-the-art of FAPI-PET imaging: a systematic review and meta-analysis. *Eur J Nucl Med Mol Imaging* 2021; 48(13): 4396-414.
31. Chung HW, Lee EJ, Cho YH et al. High ^{18}F-FDG uptake in PET/CT predicts worse prognosis in patients with metastatic gastric adenocarcinoma. *J Cancer Res Clin Oncol* 2010; 136(12): 1929-35.
32. Zhang Z, Jia G, Pan G et al. Comparison of the diagnostic efficacy of ^{68}Ga-FAPI-04 PET/MR and ^{18}F-FDG PET/CT in patients with pancreatic cancer. *Eur J Nucl Med Mol Imaging* 2022; 49(8): 2877-88.
33. Calais J, Mona CE. Will FAPI PET/CT Replace ^{18}F-FDG PET/CT in the Next Decade? Point-An Important Diagnostic, Phenotypic, and Biomarker Role. *Am J Roentgenol* 2021; 216(2): 305-6.

34. Liu X, Jiang T, Gao C et al. Detection rate of fluorine-18 prostate-specific membrane antigen-1007 PET/CT for prostate cancer in primary staging and biochemical recurrence with different serum PSA levels: A systematic review and meta-analysis. *Front Oncol* 2022; 12: 911146.

35. Mlinarić A, Horvat M, Šupak Smolčić V. Dealing with the positive publication bias: Why you should really publish your negative results. *Biochem Med (Zagreb)* 2017; 27(3): 030201.