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Comparative Analysis of Lesion Detection and Uptake Characteristics of ^{68}Ga-FAPI PET/CT versus ^{18}F-FDG PET/CT in Gastric Cancer: A Preliminary Translational Study

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Abstract

Purpose

This study aimed to compare lesion detection and uptake characteristics of ^{68}Ga-FAPI PET/CT and ^{18}F-FDG PET/CT in patients undergoing imaging for gastric cancer (GC) staging.

Methods

A total of 24 patients with histopathologically confirmed GC were retrospectively evaluated. All patients underwent ^{18}F-FDG PET/CT followed by ^{68}Ga-FAPI PET/CT within a short interval as part of their clinical staging workup. Lesion detection rates and semi-quantitative parameters, including SUVmax and tumor-to-background ratio (TBR), were compared between the two modalities.

Results

^{68}Ga-FAPI PET/CT demonstrated significantly higher SUVmax values than ^{18}F-FDG PET/CT across primary tumors and metastatic lesions ($p < 0.05$). TBRs were also markedly higher for FAPI due to lower physiological background activity. In lesion-based analysis, ^{68}Ga-FAPI PET/CT identified a higher number of nodal and distant metastases compared to ^{18}F-FDG PET/CT; however, these differences did not reach statistical significance ($p = 0.25$). Notably, discordant findings were observed in a subset of patients, in which lesions—particularly peritoneal metastases—were detected by FAPI but not by FDG. ROC analysis demonstrated higher AUC values for FAPI (0.87) compared to FDG (0.79), suggesting improved discriminative performance.

Conclusion

^{68}Ga-FAPI PET/CT provides higher tracer uptake and improved TBR compared to ^{18}F-FDG PET/CT in GC. Although lesion detection rates were numerically higher with FAPI, statistical significance was not reached in this cohort. These findings suggest a potential complementary role of FAPI PET/CT, particularly in detecting peritoneal disease and in cases with low FDG avidity. Larger prospective studies are warranted to clarify its clinical impact.

Introduction

Gastric cancer (GC) remains one of the leading causes of cancer-related morbidity and mortality worldwide, ranking fifth in incidence and fourth in cancer-related deaths globally [1]. Accurate staging at diagnosis is critical for determining appropriate therapeutic strategies and predicting prognosis. In this

context, imaging modalities play a central role in the assessment of primary tumors, regional lymph node involvement, and distant metastases.

Fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography (¹⁸F-FDG PET/CT) has been widely utilized in oncologic imaging and is included in the clinical staging of various malignancies, including GC. However, ¹⁸F-FDG PET/CT has well-known limitations in GC, particularly in detecting diffuse-type and mucinous histological subtypes, which often demonstrate low or absent FDG uptake [2, 3].

Recent advances in molecular imaging have introduced novel radiotracers that may overcome some of these limitations. One such promising agent is ⁶⁸Ga-labeled fibroblast activation protein inhibitor (⁶⁸Ga-FAPI), which targets cancer-associated fibroblasts (CAFs) in the tumor stroma—a feature abundant in desmoplastic tumors such as GC [4]. Early clinical studies have demonstrated that ⁶⁸Ga-FAPI PET/CT may provide superior lesion contrast, higher tumor uptake, and improved detection rates compared to ¹⁸F-FDG PET/CT, particularly in tumors with low FDG avidity [5, 6].

In this study, we aimed to compare lesion detection and uptake characteristics of ^{18}F-FDG PET/CT and ^{68}Ga-FAPI PET/CT in patients with gastric cancer undergoing imaging for clinical staging. Given the known limitations of FDG in certain histological subtypes, we further explored whether FAPI PET/CT may provide additional diagnostic information, particularly in cases with low FDG avidity.

Materials and Methods

This retrospective study included patients with histopathologically confirmed gastric cancer who underwent both ^{18}F-FDG PET/CT and ^{68}Ga-FAPI PET/CT as part of their clinical staging workup. All imaging studies were originally performed for staging purposes, and retrospective analysis was conducted focusing on lesion detection and semi-quantitative imaging parameters.

A total of 24 patients with pathologically verified GC (16 males, 8 females; mean age, 62.2 years; age range, 21–79 years) were evaluated. All patients initially underwent ^{18}F-FDG PET/CT for staging purposes, followed—after an interval of three days—by ^{68}Ga-FAPI PET/CT. Informed consent was obtained from every participant prior to both imaging. Two experienced nuclear medicine physicians reviewed the examinations independently, and inter-modality comparisons were performed to assess diagnostic accuracy.

Patient Preparation and Imaging

Prior to ^{18}F-FDG PET/CT, patients fasted for a minimum of six hours and discontinued intravenous glucose intake. Capillary blood glucose levels were required to be ≤150 mg/dL. Intravenous tracer administration consisted of 3.5–5.5 MBq/kg for ^{18}F-FDG and 2 MBq/kg for ^{68}Ga-FAPI-04.

All imaging was carried out on a Discovery IQ PET/CT system (GE Healthcare, Milwaukee, WI, USA) equipped with five detector rings and a 20-cm axial field of view. Whole-body acquisitions were obtained one hour post-injection, extending from the cranial vertex to the mid-thigh.

CT scans were performed at 120 kV and 80 mAs per slice, with a 700-mm field of view, 64 × 0.625 mm collimation, and reconstructed to a 3.3-mm slice thickness. PET data were acquired in 3D mode under identical positioning, with an acquisition time of 2.5 minutes per bed position, and reconstructed using dedicated software.

Image Evaluation and Statistical Methods

All PET/CT datasets were interpreted in axial, coronal, and sagittal orientations. Semi-quantitative measurements were performed using AW VolumeShare software (GE Healthcare), with tracer uptake expressed as maximum standardized uptake value (SUVmax). Volumes of interests (VOIs) were manually delineated in three orthogonal planes for both primary tumors and metastatic lesions.

Statistical analyses were carried out using SPSS software (version 27, IBM Corp., Armonk, NY, USA). Continuous variables were reported as mean, median, minimum, and maximum, while categorical variables were expressed as counts and percentages. The Wilcoxon signed-rank test was used to compare paired non-parametric SUVmax values between FDG and FAPI PET/CT scans. Spearman's rank correlation coefficient (ρ) was used to evaluate the strength and direction of associations between SUVmax values and clinical parameters such as age, primary tumor localization, and lymph node involvement. A p-value of < 0.05 was considered statistically significant.

Results

A total of 24 patients with histopathologically confirmed GC were included in the study. The mean age was 62.2 ± 11.9 years (range 21–79), and the majority were male (66.7%). Regarding histopathological subtypes, adenocarcinoma was the most common (54.2%), followed by signet-ring cell adenocarcinoma (29.2%), mucinous adenocarcinoma (12.5%), and poorly differentiated adenocarcinoma (4.1%). Tumors were most frequently located in the antrum (50%), with lower frequencies in the corpus (25.0%), cardia (8.3%), pylorus (8.3%), and corpus–antrum region (8.3%). The median tumor size was 5.0 cm (range 3–10 cm) (Table 1).

Table 1. Patient Demographic and Clinical Characteristics.

Variable	Value, Mean±SD (Range) or n (%)
Age, years	62.2 ± 11.9 (21–79)
Gender, Male/Female	16 (66.7%) / 8 (33.3%)
Histopathology	
Adenocarcinoma	13 (54.2%)
Signet-ring cell adenocarcinoma	7 (29.2%)
Mucinous adenocarcinoma	3 (12.5%)
Poorly differentiated adenocarcinoma	1 (4.1%)
Tumor location	
Antrum	12 (50%)
Corpus	6 (25.0%)
Cardia	2 (8.3%)
Pylorus	2 (8.3%)
Corpus–Antrum	2 (8.3%)
Tumor size (cm)	5.0 (3–10)

Analysis of SUVmax values demonstrated that FAPI uptake was significantly higher than FDG uptake across primary tumors and metastatic sites. For primary gastric tumors, mean FAPI SUVmax was 14.49 ± 4.14 compared to FDG SUVmax of 6.18 ± 6.24 ($p = 0.006$). In histological subgroups, FAPI uptake remained consistently higher, with significant differences in adenocarcinoma (14.01 ± 4.77 vs. 7.38 ± 7.73; $p < 0.05$) and signet-ring cell carcinoma (16.33 ± 2.23 vs. 4.97 ± 2.57; $p < 0.01$). It was also higher in mucinous adenocarcinoma (20.6 ± 6.8 vs. 3.25 ± 1.77; $p < 0.01$); however, it was not statistically significant due to the low number of patients. In terms of background uptake, hepatic SUVmean was markedly lower for FAPI (0.5 ± 0.2) compared to FDG (2.0 ± 0.7; $p < 0.001$), indicating superior tumor-to-liver contrast. For nodal metastases, FAPI showed significantly higher uptake (9.6 ± 3.8 vs. 5.2 ± 2.1; $p = 0.040$), with consistent findings in both N1 and N2 subgroups. Similarly, distant metastases demonstrated greater FAPI activity (13.5 ± 4.2 vs. 7.4 ± 2.8; $p = 0.030$), with significant differences across liver ($p = 0.040$), bone ($p = 0.030$), and peritoneal ($p = 0.020$) lesions (Table 2., Figure 1.).

Table 2. Comparison of FDG and FAPI SUVmax values for primary tumors.

Parameter	FDG SUVmax	FAPI SUVmax	p-value
	(Mean ± SD, Range) or n (%)		
Primary tumor (cm)	6.18 ± 6.24 (2.0–26.4)	14.49 ± 4.14 (6.6–19.0)	0.006
Adenocarcinoma (AdenoCA)	7.38 ± 7.73	14.01 ± 4.77	< 0.05
Signet-ring cell AdenoCA	4.97 ± 2.57	16.33 ± 2.23	< 0.01
Mucinous adenocarcinoma	3.25 ± 1.77	20.6 ± 6.8	0.06
Poorly differentiated a AdenoCA	4.3	19.2	–
Liver SUVmean	2.0 ± 0.7	0.5 ± 0.0	< 0.001
Lymph node (any)	5.2 ± 2.1	9.6 ± 3.8	0.040
– N1	4.8 ± 1.7	8.9 ± 3.5	0.050
– N2	6.1 ± 2.2	10.3 ± 4.1	0.040
Distant metastases (any)	7.4 ± 2.8	13.5 ± 4.2	0.030
– Liver	6.9 ± 2.6	12.8 ± 4.1	0.040
– Bone	7.2 ± 3.1	14.2 ± 3.8	0.030
– Peritoneum	6.5 ± 2.9	13.0 ± 4.4	0.020

When evaluating metastatic involvement, FAPI PET/CT identified a higher number of positive cases compared to FDG PET/CT. For lymph nodes, FAPI detected 11/24 patients (45.8%), whereas FDG detected 8/24 (33.3%). Similarly, for distant metastases, FAPI was positive in 11/24 (45.8%), while FDG was positive in 8/24 (33.3%). Of these three patients with positive FAPI and negative FDG, two had peritoneal metastasis and one had bone metastasis.

In both sites (lymph nodes and distant metastases), there were three additional patients who were positive only on FAPI, and importantly, there were no cases positive on FDG but negative on FAPI. The majority of patients were concordant (n = 8) across both tracers. However, despite the higher detection rate of FAPI, the differences did not reach statistical significance (p = 0.25 for both lymph nodes and distant metastases) (Table 3.).

Table 3. Comparison of metastasis detection rates between FDG and FAPI PET/CT.

Site	FDG positive n (%)	FAPI positive n (%)	Concordant (+/+)	Discordant (FDG+/FAPI–)	Discordant (FDG–/FAPI+)	p-value
Lymph nodes	8 (33.3%)	11 (45.8%)	8	0	3	0.25
Distant metastasis	8 (33.3%)	11 (45.8%)	8	0	3	0.25

In the assessment of metastatic detection, FAPI PET/CT demonstrated numerically higher detection rates; however, these differences did not reach statistical significance. ROC curve analysis demonstrated higher AUC values for FAPI PET/CT (0.87) compared to FDG PET/CT (0.79), suggesting improved discriminative performance. However, this finding should be interpreted with caution given the limited sample size and lack of statistical comparison between AUC values (Figure 2).

Correlation analysis revealed no significant association between tumor size and SUVmax values. For tumor size, the correlation with FDG SUVmax was weak (r = 0.04, p = 0.897), and similarly, with FAPI SUVmax was low (r = 0.27, p = 0.402), indicating no meaningful relationship. In addition, the direct comparison between FDG and FAPI SUVmax values also demonstrated a negligible correlation (r = 0.07, p = 0.829) (Table 4.).

Table 4. Correlation between SUVmax values (FDG vs FAPI) and tumor size.

Parameter	FDG SUVmax r (p)	FAPI SUVmax r (p)
Tumor size (cm)	0.04 (p = 0.897)	0.27 (p = 0.402)
FAPI SUVmax	r = 0.07 (p = 0.829)	-

Discussion

GC remains one of the most common malignancies worldwide, particularly in East Asia, Eastern Europe, and parts of South America. Adenocarcinoma accounts for more than 95% of cases, and synchronous peritoneal metastases are observed in approximately 15–30% of patients at diagnosis [7]. Other frequent metastatic sites include the liver and lungs [8]. These metastatic patterns, particularly peritoneal dissemination, have a substantial impact on staging accuracy and therapeutic decision-making.

Accurate staging of GC is critical for determining prognosis and guiding treatment strategies. Conventional imaging modalities such as contrast-enhanced computed tomography (CT), magnetic resonance imaging (MRI), and endoscopic ultrasound (EUS) are widely used. However, CT has limited sensitivity in detecting peritoneal metastases and small nodal disease [9]. MRI has shown promise in evaluating peritoneal and hepatic lesions [10], while EUS is effective for local staging but operator-dependent [11]. Laparoscopic staging remains the gold standard for peritoneal dissemination but is

invasive and not routinely performed. In this context, molecular imaging techniques have emerged as valuable complementary tools.

^{18}F-FDG PET/CT provides functional imaging based on glucose metabolism and plays a role in GC staging. However, its diagnostic performance is influenced by tumor biology, including histological subtype, tumor size, and physiological gastric uptake [12–14]. In particular, diffuse-type and mucinous tumors often demonstrate low FDG avidity. Moreover, ^{18}F-FDG PET/CT has limited sensitivity for peritoneal metastases, which represents a major limitation in surgical planning [15]. Therefore, ^{18}FDG PET/CT cannot be considered a stand-alone modality for staging GC.

The introduction of ^{68}Ga-FAPI PET/CT represents a novel stromal-targeted imaging approach. By binding to fibroblast activation protein expressed in cancer-associated fibroblasts (CAFs), which may constitute a substantial portion of tumor mass in GC [16–18], FAPI imaging provides high TBR. Previous studies have demonstrated increased uptake and improved lesion conspicuity with FAPI, particularly in FDG-negative tumors [19, 20].

In the present study, ^{68}Ga-FAPI PET/CT demonstrated significantly higher tracer uptake and TBR compared to ^{18}F-FDG PET/CT across primary tumors and metastatic lesions. These findings are consistent with prior reports by Chen et al. [21] and Kuten et al. [22], who also observed higher SUVmax values and improved detection, particularly in peritoneal disease.

In lesion-based analysis, ^{68}Ga-FAPI PET/CT identified a higher number of nodal and distant metastatic lesions compared to ^{18}F-FDG PET/CT. However, these differences did not reach statistical significance ($p = 0.25$), likely due to the limited sample size. Therefore, our findings should be interpreted as hypothesis-generating rather than definitive evidence of superiority.

Importantly, discordant findings were observed in a subset of patients, in which metastatic lesions—particularly peritoneal and bone involvement—were detected by FAPI but not by FDG. Notably, no FDG-positive/FAPI-negative cases were observed. These discordant cases may be clinically relevant, as peritoneal metastases represent a key determinant in treatment planning, and even small differences in detection may significantly influence therapeutic decisions.

ROC analysis demonstrated higher AUC values for FAPI PET/CT compared to FDG PET/CT, suggesting improved discriminative performance. However, this finding should be interpreted cautiously given the limited cohort size and absence of statistical comparison between AUC values. Rather than replacing FDG PET/CT, our findings suggest that FAPI imaging may provide complementary diagnostic information, particularly in biologically heterogeneous tumors and in cases with low FDG avidity. Several meta-analyses have reported higher sensitivity of FAPI PET/CT compared to FDG in gastric cancer [23-27]. However, our study contributes to the literature by providing real-world data and highlighting clinically relevant discordant cases, particularly in peritoneal metastases. This may be particularly

relevant in clinical scenarios where treatment decisions rely heavily on accurate detection of peritoneal disease.

Gao et al. [23] pooled 141 patients and demonstrated significantly higher sensitivity for FAPI compared to FDG (0.95 vs. 0.84). 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. Ruan et al. [24] confirmed FAPI's superiority across T, N, and M staging, while Pang et al. [25] and Lin et al. [26] both showed enhanced detection of primary and metastatic disease. Watabe et al. [27] demonstrated FAPI's markedly higher sensitivity for peritoneal metastases compared to FDG. ^{68}Ga-FAPI PET/CT shows higher accumulation in primary sites and metastatic lesions compared with ^{18}F-FDG PET/CT, especially for the detection of peritoneal carcinomatosis. In our cohort, FAPI showed significantly higher tracer uptake in both primary tumors and metastases (Figure 3).

Selçuk et al. [28] demonstrated that FAPI PET/CT led to stage modification in a significant proportion of FDG-negative or equivocal cases. Although a formal staging change analysis was beyond the scope of our study, the detection of additional lesions by FAPI in our cohort suggests a potential impact on clinical decision-making.

Translational Perspective

Beyond diagnostic performance, our findings suggest a potential translational impact of ^{68}Ga-FAPI PET/CT in gastric cancer. Improved detection of peritoneal metastases may contribute to more accurate preoperative staging, potentially preventing unnecessary surgical interventions. In this context, FAPI PET/CT may enhance patient selection and support individualized treatment strategies.

Clinical Implications and Future Directions

The clinical implications of these findings are noteworthy. Incorporating FAPI PET/CT into the diagnostic workflow may improve detection of otherwise occult disease. In addition, its high TBR may facilitate radiotherapy planning and opens the door for theranostic applications using FAP-targeted radioligands. However, larger prospective studies are required to validate these findings.

Study Limitations

Despite these promising findings, our study has several limitations. It is a retrospective, single-center study with a relatively small sample size, which may limit the generalizability of the results. Histopathological confirmation of all metastatic lesions was not feasible, introducing a potential risk of verification bias. In addition, although FAPI uptake is strongly tumor-associated, it is not entirely specific, as inflammatory and fibrotic processes may also demonstrate tracer uptake [31]. Furthermore, this study focused primarily on diagnostic performance and did not evaluate the relationship between imaging

findings and treatment response or survival outcomes. Finally, the absence of long-term follow-up data precludes assessment of prognostic implications.

Conclusion

^{68}Ga-FAPI PET/CT demonstrates higher tracer uptake and improved TBR contrast compared to ^{18}F-FDG PET/CT in GC. Although lesion detection rates were numerically higher with FAPI, statistical significance was not reached in this cohort. These findings support a potential complementary role of FAPI PET/CT, particularly in detecting peritoneal disease and in cases with low FDG avidity. Further large-scale prospective studies are needed to define its clinical utility.

Declarations

Ethics Approval and Consent to Participate

This study did not receive any specific funding from public, commercial, or not-for-profit organizations. The present retrospective study was conducted with the approval of the Clinical Research Ethics Committee of Gaziantep University (Approval No: 2025/171) and adhered to the ethical standards set forth in the Declaration of Helsinki.

Author Contribution

E.K. and E.E.Y. contributed to study conception and design. E.K., E.Y., and B.E.S. were involved in data collection and image analysis. E.K. performed the statistical analysis and drafted the manuscript. U.E. and E.Ş. supervised the study and contributed to critical revision of the manuscript. V.M.Ç. contributed to data interpretation and manuscript editing. All authors reviewed and approved the final version of the manuscript.

Data Availability

Data Availability StatementThe data that support the findings of this study are available from the corresponding author upon reasonable request. The data are not publicly available due to privacy and ethical restrictions.

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Figures

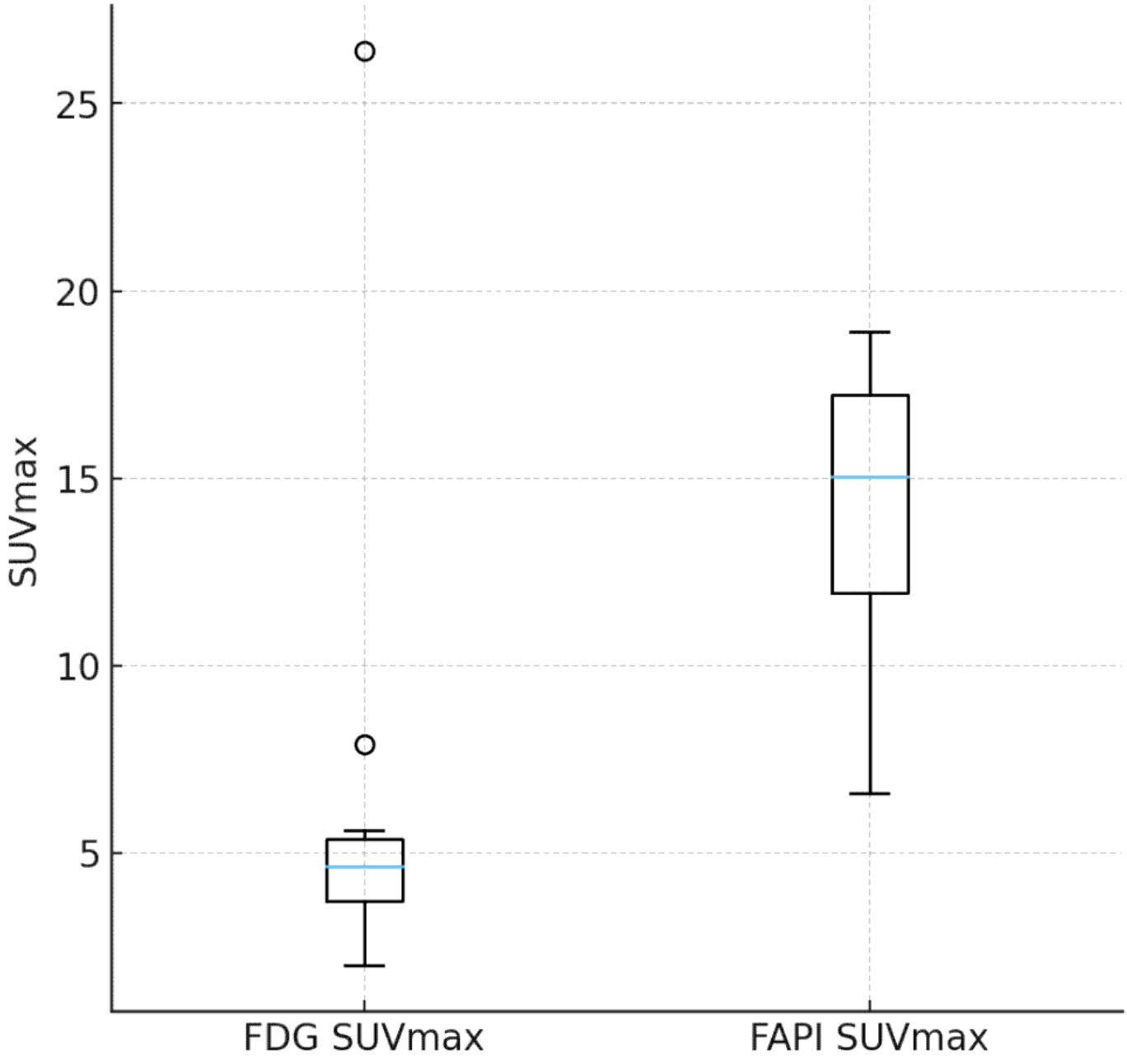


Figure 1

SUVmax distribution of lesions for FDG and FAPI.

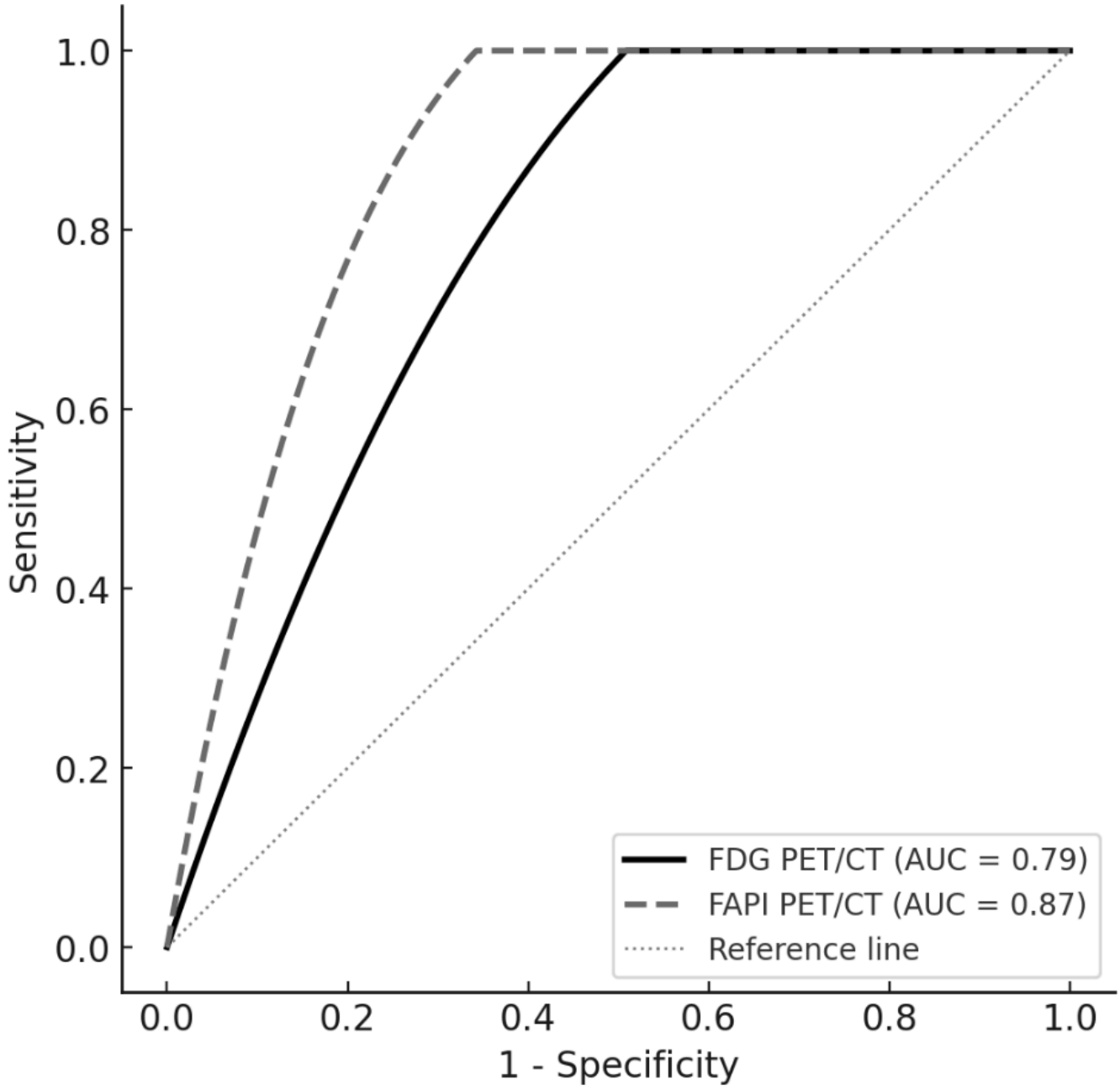


Figure 2

ROC Curves Comparing FDG and FAPI PET/CT for Metastasis Detection

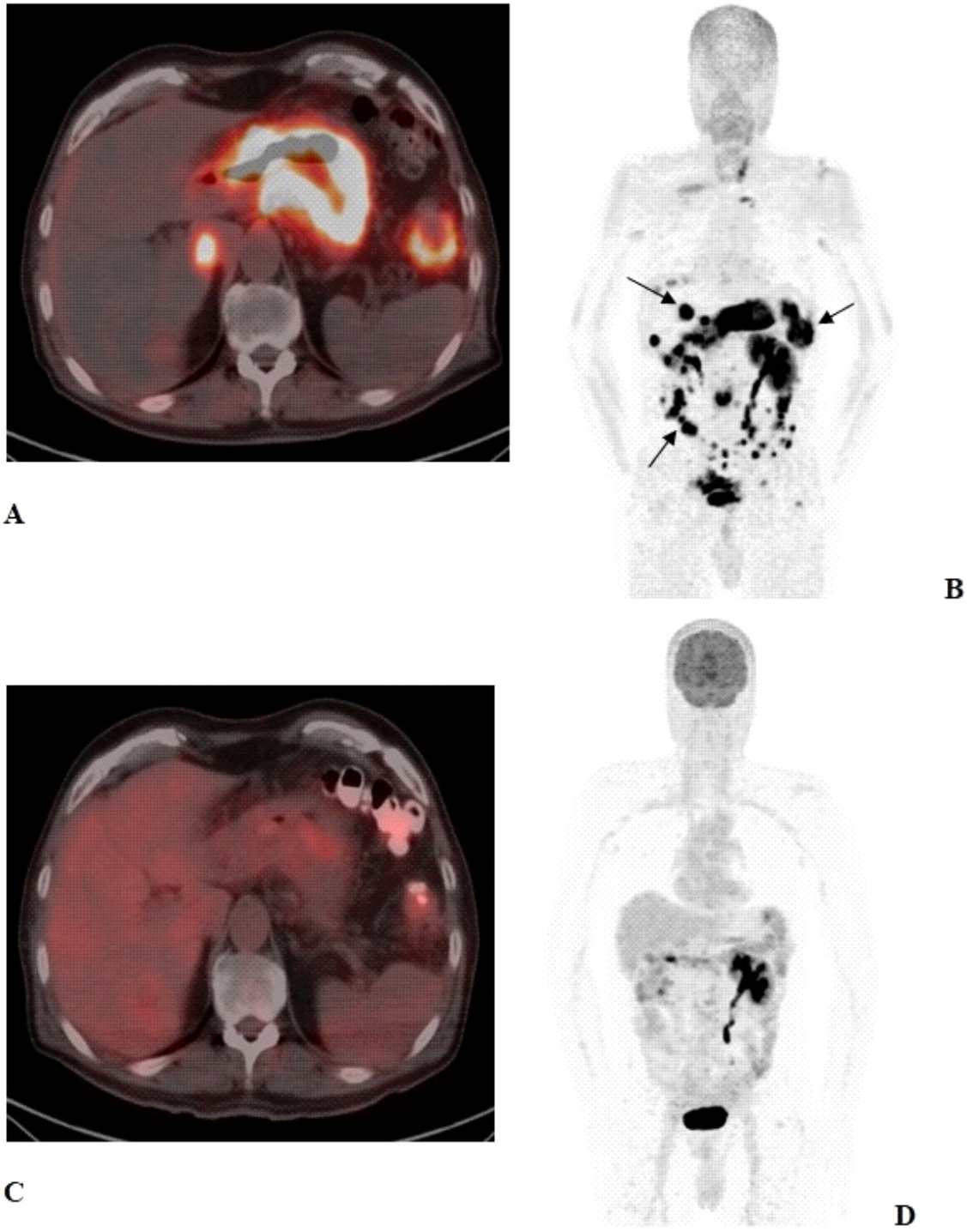


Figure 3

A 56-year-old male patient with gastric adenocarcinoma. ^{68}Ga-FAPI-04 PET/CT images (A, axial; B, maximum intensity projection) demonstrate markedly increased radiotracer uptake in the primary gastric tumor as well as in hepatic and peritoneal metastases (arrows). In comparison, ^{18}F-FDG PET/CT images (C, axial; D, maximum intensity projection) show considerably lower tracer accumulation in the same sites.