Tumor Characterization by [^{68}Ga]FAPI-46 PET/CT Can Improve Treatment Selection for Pancreatic Cancer Patients: An Interim Analysis of a Prospective Clinical Trial

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Correct and timely diagnosis of pancreatic cancer (PC) is essential for treatment selection but is still clinically challenging. Standard-of-care imaging methods can sometimes not differentiate malignancies from inflammatory lesions or detect malignant transformation in premalignant lesions. This interim analysis of a prospective clinical trial aimed to evaluate the diagnostic accuracy of [^{68}Ga]fibroblast activation protein inhibitor (FAPI)-46 PET/CT for PC and determine the sample size needed to demonstrate whether this imaging technique improves the characterization of equivocal lesions detected by standard-of-care imaging methods. **Methods:** [^{68}Ga]FAPI-46 PET/CT imaging was performed on 30 patients scheduled for surgical resection of suspected PC. Target lesions were delineated, SUV_{max} and SUV_{mean} were determined, and the results were compared with those of standard-of-care imaging. Receiver operating characteristics were calculated for the whole cohort and a subcohort of 11 patients with an equivocal clinical imaging work-up preoperatively. Postoperative histopathologic findings served as a reference standard, and the statistical power was determined. **Results:** Histopathologic examination revealed malignancy in 20 patients and benign lesions in 10 patients. Significantly elevated [^{68}Ga]FAPI-46 uptake was observed in malignant tumors compared with benign lesions ($P < 0.001$). Receiver-operating-characteristic analyses established optimal cutoffs for both SUVs for differentiation of malignant from nonmalignant pancreatic tumors. The optimal SUV_{max} cutoff was 10.2 and showed 95% sensitivity and 80% specificity for the whole cohort, as well as 100% diagnostic accuracy when considering the subcohort with equivocal imaging work-up only. For sufficient statistical power, 38 equivocal observations are needed. **Conclusion:** We conclude that [^{68}Ga]FAPI-46 PET/CT can accurately differentiate malignant from benign pancreatic lesions deemed equivocal by standard-of-care imaging. This trial will therefore continue to recruit a total of 120 patients to reach those 38 equivocal observations needed for sufficient statistical power. On the basis of our findings, we propose that [^{68}Ga]FAPI-46 PET/CT not only can be clinically applied as a complement but also could become a necessary tool when standard-of-care imaging is inconclusive.

Key Words: fibroblast activation protein; PET/CT; pancreatic cancer; ^{68}Ga-FAPI-46

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Pancreatic cancer (PC) is a leading cause of cancer-related deaths worldwide, with a 5-y relative survival rate of 11% for all stages combined (*1*). Among the reasons for this dismal outcome is the challenge of establishing a correct and timely diagnosis (*2*). Most patients are diagnosed in advanced stages of disease (*3*), and surgical resection combined with chemotherapy is the only potentially curative therapy.

Imaging plays an essential role in several aspects of PC management, including diagnosis and evaluation of resectability. Multiphase contrast-enhanced CT (CECT) is the current preferred standard-of-care imaging modality for diagnosis of PC and is recommended as the primary imaging modality by the guidelines of both the National Comprehensive Cancer Network and the European Society for Medical Oncology (*4,5*). The differential diagnosis of a pancreatic mass, however, does encompass a range of clinical entities, including benign lesions, such as mass-forming chronic, autoimmune, or paraduodenal pancreatitis (*6*), all of which may mimic PC on CECT, making correct characterization challenging (*7*). Additionally, small isoattenuating adenocarcinomas can be overlooked on CECT (*8*). Correct preoperative diagnosis is crucial, as misinterpretation may lead to a major pancreatic resection for benign disease, failure to operate on a potentially curable lesion, or even surgery in patients with disseminated disease, in whom systemic treatment would have been more appropriate. Previous studies show that inflammation accounts for 5%–10% of surgical resection for clinically suspected cancer (*9*).

For detection of malignant transformation within pancreatic intraductal papillary mucinous neoplasia (IPMN), 3 current international guidelines recommend both CECT and MRI in the diagnostic work-up, with MRI being the preferred method (*10–12*). The accuracy of either method, or even both combined, for a specific diagnosis is, however, relatively low (61%) (*13*). Approximately 10% of all pancreatectomies performed in the United States are for IPMN (*14*). As a significant number of these operated IPMNs do not show invasive or high-grade histology, and since the morbidity

associated with resection is similar regardless of pathology, improved diagnostic accuracy is needed to aid in surgical selection. ^{68}Ga-labeled fibroblast activation protein inhibitor (FAPI), a new tracer for PET, targets fibroblast activation protein expressed on the surface of cancer-associated fibroblasts (*15,16*). As cancer-associated fibroblasts represent the most abundant cell type in the tumor stroma (*17*), application of FAPI-based tracers in PET imaging of various types of cancers with a high stromal content, including PC, has been proven successful (*18,19*). The purpose of this interim analysis, part of a prospective clinical trial, was to evaluate the diagnostic accuracy of [^{68}Ga]FAPI-46 PET/CT for PC and to determine the sample size needed to demonstrate the superiority of this imaging technique in characterizing equivocal lesions detected by standard-of-care imaging methods. We tested this hypothesis by performing [^{68}Ga]FAPI-46 PET/CT imaging on patients with suspected PC who were scheduled for surgery, comparing the results with those of standard-of-care imaging, using postoperative histopathology as a reference standard.

MATERIALS AND METHODS

Clinical Study Design and Patient Cohort

The presented study was part of an ongoing phase II exploratory trial approved by the Swedish Ethical Review Authority (diarienummer 2020-03400) and Medical Products Agency (EudraCT 2020-002568-30) and registered on ClinicalTrials.gov (NCT05172310). All patients provided written informed consent. As the origin of the cancer is sometimes difficult to determine before surgery (*20*), we enrolled subjects with suspected periampullary tumors other than PC as part of the consecutive patient group. These include duodenal and ampullary cancers as well as distal cholangiocarcinoma. Patients scheduled for surgical resection of the primary tumor were screened for eligibility during multidisciplinary conferences according to the inclusion and exclusion criteria listed in Supplemental Table 1 (supplemental materials are available at http://jnm.snmjournals.org). Subjects with nonmalignant tumors on postoperative histopathology served as a comparator group. [^{68}Ga]FAPI-46 PET/CT imaging was performed within 2 wk before surgery. The surgery was performed at Karolinska University Hospital, with an individual treatment strategy decided for every patient at multidisciplinary conferences according to clinical routine and the Swedish National Cancer Control Program. The diagnosis for the primary tumor and resected regional lymph nodes was confirmed after surgery as per the clinical routine. Operating surgeons did not know the [^{68}Ga]FAPI-46 PET/CT imaging results until after surgery, preventing any impact on choice of therapy. A CECT or MRI including MR cholangiopancreatography was performed on all patients as per the clinical routine and before inclusion in this study.

Radiopharmaceuticals and Image Acquisition

[^{68}Ga]FAPI-46 was radiosynthesized at the Karolinska Radiopharmacy facilities on an Eckert & Ziegler Modular-Lab PharmTracer synthesis module, using $^{68}GaCl_3$ eluate from a ^{68}Ge/^{68}Ga generator, as earlier described (*21*). FAPI-46 precursor was acquired from Sofie Biosciences. The amount of radioactivity injected depended on labeling yield and patient weight (4.0 MBq/kg if possible; minimum, 50 MBq; maximum, 370 MBq). Whole-body scanning was performed 1 h after injection, previously shown to be a suitable time point for tumor imaging with [^{68}Ga]FAPI-46 (*18,22–24*). A Biograph mCT PET/CT scanner (Siemens) and a Discovery MI scanner (GE Healthcare) were used.

Preceded by a low-dose non-CECT scan for attenuation correction, PET images were acquired from vertex to mid thigh (4 min/bed position). The obtained emission data were corrected for scatter, randoms, and decay and were reconstructed with an ordered-subset expectation maximization algorithm. The reconstruction parameters were carefully designed to ensure equivalent (within ±10% variation) SUV and contrast in a PET body phantom with spheres. Finally, diagnostic CECT was performed for anatomic correlation of PET findings and diagnostic-quality image fusion.

Image Analysis and Interpretation

[^{68}Ga]FAPI-46 PET/CT images were analyzed using Syngo.via (Siemens) individually by 2 readers, both board-certified radiologists, one of whom was a board-certified nuclear medicine specialist and the other a specialist in training. Both readers had access to patients' clinical imaging workup to facilitate localization of the target lesion. However, neither knew the histopathologic results. Differences in opinion were resolved by consensus, and previously described pitfalls in [^{68}Ga]FAPI PET/CT imaging were taken into consideration (*25*).

Lesions suspected of representing malignancy, with focal tracer uptake exceeding that of the surrounding background, were regarded as positive. SUV parameters were extracted from volumes of interest, defined using 40% threshold isocontouring. These were used for receiver-operating-characteristic (ROC) analyses. Positive [^{68}Ga]FAPI-46 PET/CT findings were defined as either an SUV_{max} or an SUV_{mean} at or above the respective optimal cutoff. Anatomic information from CT images was used to avoid inclusion of activity from adjacent nontumoral tissues and to exclude other potential causes of tracer uptake.

The clinical imaging work-up was interpreted by board-certified radiologists specialized in abdominal radiology and presented at multidisciplinary conferences as per the clinical routine. For this study, an additional reading was performed retrospectively by a board-certified radiologist who was specialized in abdominal radiology and did not know either the [^{68}Ga]FAPI-46 PET/CT or the histopathology results, and the results were classified as either positive, negative, or equivocal. To compare the performance of [^{68}Ga]FAPI-46 PET/CT with that of standard-of-care imaging in characterizing pancreatic tumors, SUV_{max} and SUV_{mean} were analyzed individually.

Statistical Analysis

For all statistical analyses, R software, version 4.2.1., was used, including the "pROC" and "cutpointr" packages for ROC analyses and cutoff determination for both PET parameters. Values below the cutoff were coded as [^{68}Ga]FAPI-46 PET–negative, whereas values equal to or above were coded as [^{68}Ga]FAPI-46 PET–positive. True-positive patients were defined as [^{68}Ga]FAPI-46 PET–positive with malignant histopathology; false-positive, as [^{68}Ga]FAPI-46 PET–positive with benign histopathology; false-negative, as [^{68}Ga]FAPI-46 PET–negative with malignant histopathology; and true negative, as [^{68}Ga]FAPI-46 PET–negative with benign histopathology. Accuracy, sensitivity, specificity, and positive and negative predictive values, including corresponding 95% CIs, were calculated using the "epiR" package. Power calculation was performed using the package "pwr," with CECT specificity set to 0.9 (*26*), the statistical significance level set to 0.05, and power set to 0.8. In all statistical tests, P values of less than 0.05 were considered statistically significant.

RESULTS

Patient Cohort and Imaging Acquisition

Thirty patients were recruited between September 2021 and May 2022 (17 men and 13 women; mean age, 66.9 ± 12.4 y; range, 27–85 y) with suspected pancreatic or periampullary cancer. All underwent [^{68}Ga]FAPI-46 PET/CT and subsequent surgery after a median of 5.5 d (interquartile range, 2.3–12.8 d). The mean injected activity was 272.5 ± 74.8 MBq, and the mean uptake time was 60.5 ± 2.5 min (range, 56–67 min). Six patients were reported

TABLE 1
Patient Demographics and Clinical Characteristics

Patient no.	Sex	Age (y)	Clinical imaging work-up	Clinical work-up findings	[^{68}Ga]FAPI-46 PET/CT findings	SUV_{max}	SUV_{mean}	Histologic diagnosis
1	M	62	CECT	Positive	Positive	18.4	10.9	Cholangiocarcinoma
2	F	69	CECT	Positive	Positive	15.1	9.9	PC
3	F	85	CECT	Positive	Positive	23.9	14.4	PC
4	F	74	CECT + MRI	Positive	Positive	19.0	10.7	PC
5	M	60	CECT	Equivocal	Negative	7.1	4.0	Distal choledocholithiasis
6	F	72	CECT	Positive	Positive	24.9	15.0	PC
7	F	80	CECT	Positive	Positive	18.5	11.1	Ampullary carcinoma
8	M	66	CECT	Positive	Positive	22.0	12.4	PC
9	M	64	CECT + MRI	Positive	Positive	15.0	8.4	PC
10	F	49	MRI	Positive	Positive	18.5	11.4	PC
11	M	75	CECT	Positive	Positive	10.5	6.2	Autoimmune pancreatitis
12	F	27	CECT	Equivocal	Negative	1.0	0.7	Duodenal adenoma
13	F	80	CECT + MRI	Positive	Positive	17.4	10.9	PC
14	M	83	CECT	Equivocal	Positive	15.4	8.5	Ampullary carcinoma
15	M	63	CECT + MRI	Negative	Positive	15.4	8.2	Chronic pancreatitis
16	F	58	CECT	Positive	Positive	16.6	9.8	PC
17	M	73	CECT	Equivocal	Negative	2.2	1.3	IPMN
18	M	53	CECT	Positive	Positive	10.4	6.0	Cholangiocarcinoma
19	M	78	CECT	Equivocal	Positive	10.2	5.9	Duodenal carcinoma
20	M	57	CECT + MRI	Equivocal	Negative	3.7	2.2	PanIN
21	M	73	CECT + MRI	Positive	Positive	12.1	7.3	PC
22	F	69	MRI	Equivocal	Negative	2.2	1.5	IPMN
23	M	74	CECT	Positive	Positive	18.8	11.5	PC
24	M	65	CECT	Positive	Positive	15.6	9.0	PC
25	M	69	CECT + MRI	Equivocal	Negative	1.1	0.5	PanIN
26	F	59	CECT + MRI	Equivocal	Positive	11.4	7.9	Ampullary carcinoma
27	F	47	MRI	Equivocal	Negative	1.4	1.0	IPMN
28	M	66	CECT + MRI	Equivocal	Negative	5.3	2.9	IPMN
29	F	79	CECT	Positive	Positive	9.9	6.3	PC
30	M	78	CECT	Positive	Positive	22.5	13.6	PC

PanIN = pancreatic intraepithelial neoplasia.

as unresectable because of macroscopic peritoneal carcinomatosis ($n = 3$), extensive venous involvement ($n = 1$), excessive inflammation and fibrosis ($n = 1$), or significant celiac trunk stenosis ($n = 1$). The diagnosis in these patients was confirmed either by perioperative cryosection in the case of peritoneal carcinomatosis or by perioperative core-needle biopsy or endoscopic ultrasound-guided fine-needle biopsy in the remaining cases deemed irresectable.

Histopathologic analysis revealed carcinoma in 20 patients and benign lesions in 10 patients. The demographics and clinical characteristics of the participants are presented in Table 1.

TABLE 2
SUV_{max} and SUV_{mean} in Pancreatic Lesions with Malignant Vs. Benign Histopathology

	Malignant		Benign		
Parameter	Mean ± SD	Range	Mean ± SD	Range	*P*
SUV_{max}	17.0 ± 5.0	9.9–24.9	5.0 ± 5.0	1.0–15.4	<0.001
SUV_{mean}	10.0 ± 2.7	5.9–15.0	2.8 ± 2.6	0.5–8.2	<0.001

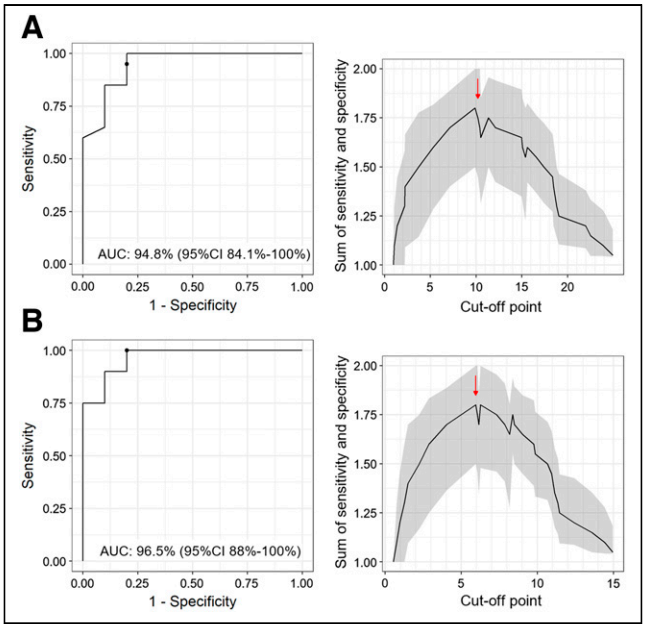

FIGURE 1. ROC curves depicting sensitivity and specificity of SUV_{max} (A) and SUV_{mean} (B) for diagnosis of PC. Graphs to right show optimum for different potential cutoffs; arrow indicates optimal cutoff for each parameter. AUC = area under curve.

Patient Safety

All subjects were monitored during examination, with blood pressure, heart rate, and body temperature registered before [^{68}Ga]FAPI-46 injection and after examination (~1.5-h interval). No related pharmacologic or physiologic effects were recorded, and none of the participants reported any new symptoms.

Image Interpretation and Diagnostic Performance

Visual assessment showed high tracer activity in primary tumors and low background tracer activity, especially in the brain, but also in the uninvolved parts of the pancreatic parenchyma and in the liver, heart, and gastrointestinal tract, yielding a purposive image contrast. All 20 malignant lesions showed intense [^{68}Ga]FAPI-46 uptake (Table 2). At the same time, 2 of the benign lesions also showed tracer uptake above the cutoffs (Supplemental Fig. 1). ROC analyses rendered optimal cutoffs of 10.2 for SUV_{max} and 5.9 for SUV_{mean} as presented in Figure 1. Table 3 provides the diagnostic performance data with corresponding 95% CIs for both parameters, regarding differentiation of malignancies from benign lesions, in the whole cohort and in the subcohort with equivocal clinical imaging work-up.

Comparison with Standard-of-Care Imaging

All patients classified as equivocal on standard-of-care imaging ($n = 11$) were correctly classified as either positive or negative for PC by [^{68}Ga]FAPI-46 PET/CT, for both SUV_{max} and SUV_{mean} ($P < 0.001$) (Table 1; Fig. 2).

Power Analysis

At trial initiation, power analysis was not possible because of a lack of published data. An interim analysis was therefore included in this study to serve as a basis for calculating the sample size needed to detect a significant difference in specificity between CECT and [^{68}Ga]FAPI-46 PET/CT. On the basis of a recently reported CECT specificity of 90% (*26*) and that of [^{68}Ga]FAPI-46 PET/CT for the whole cohort (80%), 195 observations are needed. When considering the equivocal cohort only, with [^{68}Ga]FAPI-46 PET/CT specificity of 100%, 38 observations are needed.

DISCUSSION

The differential diagnosis of pancreatic masses remains a challenge for diagnostic imaging despite modern cross-sectional techniques with CECT and MRI. To improve the diagnostic yield, we applied a new tracer with high affinity for epithelial cancers, FAPI. In this interim analysis, we evaluated the accuracy of [^{68}Ga]FAPI-46 PET/CT for the diagnosis of pancreatic tumors and determined the sample size needed for sufficient power. We observed a significantly higher [^{68}Ga]FAPI-46 uptake in malignant tumors than in benign lesions (Table 2), demonstrating high accuracy for diagnosis of PC, for both SUV_{max} and SUV_{mean} (Table 3). In patients with equivocal standard-of-care imaging results, sample size calculations show that 38 observations are needed for sufficient statistical power. This trial will therefore continue to recruit a total of 120 patients to reach 38 equivocal observations by standard-of-care imaging.

CECT has a reported sensitivity of 89%–91% and a specificity of 85%–90% for the diagnosis of PC in recent metaanalyses (*26,27*). Our data indicate that [^{68}Ga]FAPI-46 PET/CT has at least an equally high diagnostic accuracy as CECT for the diagnosis of primary PC, within a 95% CI. In fact, in all 11 cases in which the clinical imaging workup findings were equivocal, [^{68}Ga]FAPI-46 PET/CT correctly differentiated malignant from benign lesions, yielding a diagnostic accuracy of 100%. SUV_{mean} had a slightly larger area under the ROC curve than SUV_{max} (96.5% vs. 94.8%),

TABLE 3
Diagnostic Performance of SUV_{max} with Cutoff of 10.2 and SUV_{mean} with Cutoff of 5.9 in Diagnosis of PC

	Whole cohort ($n = 30$)		Subcohort with equivocal clinical imaging ($n = 11$)	
Parameter	SUV_{max}	SUV_{mean}	SUV_{max}	SUV_{mean}
Sensitivity	95 (75–100)	100 (83–100)	100 (29–100)	100 (29–100)
Specificity	80 (44–97)	80 (44–97)	100 (63–100)	100 (63–100)
Positive predictive value	90 (70–99)	91 (71–99)	100 (29–100)	100 (29–100)
Negative predictive value	89 (52–100)	100 (63–100)	100 (63–100)	100 (63–100)
Overall accuracy	90 (73–98)	93 (78–99)	100 (72–100)	100 (72–100)

Data are percentages, with 95% CIs in parentheses.

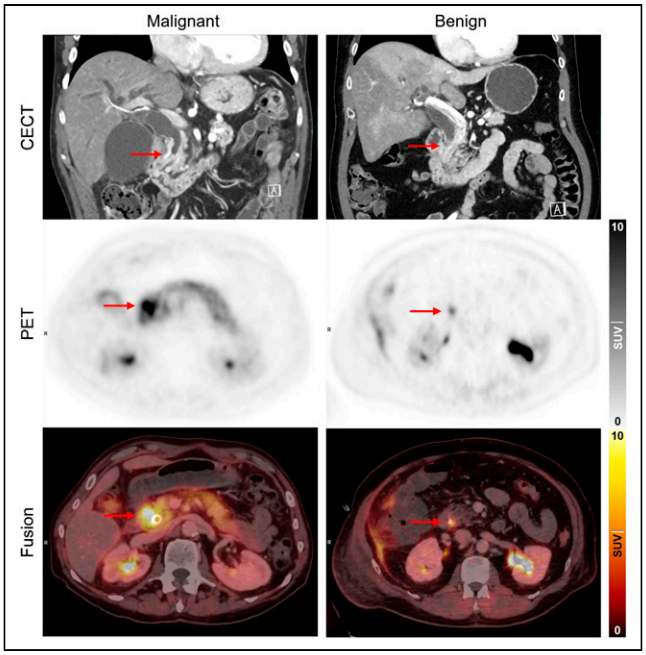

FIGURE 2. CECT, axial PET, and fused images of malignant (left) and benign (right) periampullary lesion obstructing bile duct (arrow).

suggesting that the parameter might be somewhat more accurate (Fig. 1). However, both parameters are convincing because of their high diagnostic accuracy, and as more data are collected, new ROC analyses will be performed. In the subanalysis of patients with an equivocal imaging work-up, both parameters showed 100% accuracy. To our knowledge, we are the first to report such high accuracy for the method in the diagnosis of PC, and on the basis of these results, we expect [^{68}Ga]FAPI-46 PET/CT imaging to have a significant impact on the diagnostic work-up of PC patients. The wide span of the 95% CI for [^{68}Ga]FAPI-46 PET/CT is probably due to the relatively few cases in our study and should narrow as more subjects are included.

The high [^{68}Ga]FAPI-46 uptake in malignant lesions and the significantly lower uptake in benign lesions, together with negligible background activity, gave satisfactory image contrast and is consistent with the results of previous [^{68}Ga]Ga-FAPI PET/CT studies on pancreatic and other cancers (*28,29*). Röhrich et al. evaluated the clinical impact of PET/CT using [^{68}Ga]FAPI-4 and [^{68}Ga]FAPI-46 in the staging of primary and recurrent pancreatic ductal adenocarcinoma, reporting clinically meaningful changes in the staging of both groups (*30*). Similarly, Pang et al. observed that [^{68}Ga]FAPI-4 PET/CT improves tumor detection and staging in PC (*31*). Lang et al. also concluded that [^{68}Ga]FAPI-74 PET/CT could predict malignant transformation within IPMN with high accuracy (*32*). Our study sets itself apart from these studies because our findings were histologically validated and inclusion of nonmalignant conditions allowed the accuracy of [^{68}Ga]FAPI-46 PET/CT for the diagnosis of PC to be determined, an essential step for application to clinical practice. The high sensitivity suggests that no malignancy would be missed and that the specificity we assessed is acceptable and comparable to that of the current best standard. The 2 false-positive cases represented inflammation (Supplemental Fig. 1). However, this issue has been addressed in previous publications, showing that the addition of multiple-time-point and dynamic imaging techniques facilitates differentiation of malignancy from pancreatitis (*30,31,33*).

A major limitation of this study is the small sample size, especially with regard to patients with equivocal results on standard-of-care imaging, and conclusions from these data should therefore be drawn with caution. Larger exploratory studies are needed as our power calculations suggest. Furthermore, even though small (±10%), the variations in image quality and SUV measurements resulting from the use of different cameras could have affected the results, especially in patients with an SUV in the vicinity of the cutoffs.

CONCLUSION

Characterization of pancreatic mass lesions remains clinically challenging because various inflammatory tumors may mimic PC on imaging, leading to major pancreatic surgery for benign disease in a substantial number of patients (*6–9,34*). Such surgery is associated with high costs, high morbidity rates, and a significant decline in quality of life (*35–39*) and should therefore be avoided if possible. Our results show that [^{68}Ga]FAPI-46 PET/CT can accurately differentiate malignant from benign pancreatic lesions deemed equivocal by standard-of-care imaging. For this differentiation, we propose semiquantitative cutoffs for both SUV_{max} and SUV_{mean}. In this trial, we will therefore continue to recruit a total of 120 patients to reach those 38 equivocal observations needed for sufficient statistical power. On the basis of our findings, we conclude that [^{68}Ga]FAPI-46 PET/CT not only might represent a new complementary imaging technique in primary diagnosis of PC but also could become a necessary tool when standard-of-care imaging results are inconclusive. A prospective clinical trial is currently ongoing in our department, but even larger, multicenter trials will be needed for clinical translation of [^{68}Ga]FAPI-46 PET/CT in PC.

DISCLOSURE

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KEY POINTS

QUESTION: Can [^{68}Ga]FAPI-46 PET/CT improve characterization of equivocal pancreatic lesions detected by standard-of-care imaging, and how many observations are needed for sufficient statistical power?

PERTINENT FINDINGS: In this interim analysis of a prospective clinical trial, analysis of 30 surgical patients showed that [^{68}Ga]FAPI-46 PET/CT can accurately differentiate malignant from benign pancreatic lesions deemed equivocal by standard-of-care imaging. For sufficient statistical power, this trial will continue to recruit a total of 120 patients to reach 38 equivocal observations by standard-of-care imaging.

IMPLICATIONS FOR PATIENT CARE: Our findings suggest that [^{68}Ga]FAPI-46 PET/CT not only can be clinically applied as a complement but also could become a necessary tool when standard-of-care imaging on PC is inconclusive.

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