creative commons
COMMONS DEED

저작자표시-비영리-변경금지 2.0 대한민국

이용자는 아래의 조건을 따르는 경우에 한하여 자유롭게

- 이 저작물을 복제, 배포, 전송, 전시, 공연 및 방송할 수 있습니다.

다음과 같은 조건을 따라야 합니다:

저작자표시. 귀하는 원저작자를 표시하여야 합니다.

비영리. 귀하는 이 저작물을 영리 목적으로 이용할 수 없습니다.

변경금지. 귀하는 이 저작물을 개작, 변형 또는 가공할 수 없습니다.

- 귀하는, 이 저작물의 재이용이나 배포의 경우, 이 저작물에 적용된 이용허락조건을 명확하게 나타내어야 합니다.
- 저작권자로부터 별도의 허가를 받으면 이러한 조건들은 적용되지 않습니다.

저작권법에 따른 이용자의 권리는 위의 내용에 의하여 영향을 받지 않습니다.

이것은 이용허락규약(Legal Code)을 이해하기 쉽게 요약한 것입니다.

Disclaimer

dCollection

Master's Thesis of Medicine

The clinical significance of [^{18}F]F-FAPI74 PET/CT in pancreatic ductal adenocarcinoma compared to [^{18}F]FDG PET/CT

췌장암에서 [^{18}F]FDG와 비교한 [^{18}F]F-FAPI74를 이용한 양전자방출단층촬영의 임상적 의의

August 2023

Graduate School of Medicine
Seoul National University
Surgery Major

Won-Gun Yun

The clinical significance of [^{18}F]F-FAPI74 PET/CT in pancreatic ductal adenocarcinoma compared to [^{18}F]FDG PET/CT

Jin-Young Jang

Submitting a master's thesis of
Medicine

April 2023

Graduate School of Medicine
Seoul National University
Surgery Major

Won-Gun Yun

Confirming the master's thesis written by
Won-Gun Yun

July 2023

Chair Gi Jeong Cheon (Seal)
Vice Chair JIN YOUNG JANG (Seal)
Examiner Wooil Kwon (Seal)

Abstract

Purpose: Considering how deadly pancreatic ductal adenocarcinoma (PDAC) is, correct staging is essential to developing effective treatment plans. Although positron emission tomography/computed tomography (PET/CT) with fluorine-18-fluorodeoxyglucose ([^{18}F]FDG) has been often employed as a pretreatment imaging technique in PDAC, its effectiveness in clinical staging is still unknown. Recent studies for advanced stage PDAC have used PET/CT to detect the expression of the fibroblast activation protein (FAP), which is more specific to PDAC than glucose metabolism. However, the effectiveness in early stage PDAC is unknown. Therefore, we aimed to evaluate the efficacy of [^{18}F]F-FAPI-74 PET/CT in clinical staging of early stage PDAC.

Methods: Twenty subjects with newly diagnosed PDAC were enrolled between 2021 and 2022 and had [^{18}F]FDG PET/CT and [^{18}F]F-FAPI-74 PET/CT examinations. 17 patients who underwent surgery with a curative goal had pathologic data available. The uptake of radiotracers and their diagnostic abilities were evaluated across imaging modalities.

Results: In assessing primary pancreatic lesions, [^{18}F]F-FAPI-74 PET/CT demonstrated a substantially higher maximum standardized uptake value (SUV) than [18F]FDG PET/CT (median [interquartile range]; 12.6 [10.7-13.7] vs. 6.3 [4.8-9.2]; $P < 0.001$). Contrarily, when comparing the evaluation of the background organ, [^{18}F]F-FAPI-74 PET/CT demonstrated a considerably lower mean SUV than [^{18}F]FDG PET/CT (0.8 [0.7-0.9] vs. 2.6 [2.3-2.7]) ($P < 0.001$). Additionally, [^{18}F]F-FAPI-74 PET/CT images

(50.0%) had a better sensitivity than [^{18}F]FDG PET/CT (0.0%) for detecting metastatic lymph nodes.

Conclusion: Compared to [^{18}F]FDG PET/CT, [^{18}F]F-FAPI-74 PET/CT is more effective at detecting primary pancreatic cancer and metastatic lymph nodes. Because of its better diagnostic value, [^{18}F]F-FAPI-74 PET/CT might be employed as a standard procedure for staging PDAC.

Keyword : pancreatic ductal adenocarcinoma, [^{18}F]F-FAPI-74 PET/CT , [^{18}F]FDG PET/CT, Diagnostic performance

Student Number : 2021-21786

Table of Contents

1. Introduction

One of the most fatal cancers, pancreatic ductal adenocarcinoma (PDAC), has a poor prognosis with a 5-year survival rate of only 10%.[1] For patients with PDAC, surgical resection still offers the best hope for long-term survival and cure; therefore, proper clinical staging is essential for a better prognosis.[2,3] However, it is challenging to identify the tumorous state from pancreatitis and determine the extent of the tumor because PDAC is commonly accompanied by inflammation and requires treatments such biliary drainage.[4,5]

The primary pretreatment imaging modality for PDAC according to National Comprehensive Cancer Network guidelines is contrast-enhanced computed tomography (CT) or magnetic resonance (MR), with limited recommendations for PET/CT for high-risk patients.[6] The use of [^{18}F]FDG PET/CT in PDAC is yet unknown, despite the fact that fluorine-18-fluorodeoxyglucose ([^{18}F]FDG) is currently the most often utilized radiotracer related oncologic malignancies for initial tumor staging and detection of recurrence. There is disagreement concerning the utility of [^{18}F]FDG PET/CT in evaluating metastatic lymph nodes, despite the fact that numerous studies have demonstrated its effectiveness in detecting extra-pancreatic metastasis.[7,8]

Fibroblast-activation protein inhibitor (FAPI), which may be taken up by a number of malignancies, including PDAC, has just been introduced as a promising tumor imaging agent.[9-13] PDAC frequently develops a dense, fibrotic stroma with an abundance of extracellular matrix as a result of the inflammation-induced desmoplastic response.[14] Cancer-associated

fibroblasts (CAF), which are linked to an immunosuppressive microenvironment and treatment resistance, are recognized to be the most major cellular component of the extracellular matrix.[15,16] The pan-marker of CAF is fibroblast-activation protein (FAP), and in PDAC, myofibroblast, which surrounds tumor cells, expresses FAP at high levels. In order to test the hypothesis that FAP expression would be more specific to tumorous circumstances than glucose metabolism, we compared the diagnostic utility and clinical relevance of [^{18}F]F-FAPI-74 and [^{18}F]FDG PET/CT.

2. Methods

Study Participants

The Institutional Review Board of Seoul National University Hospital granted approval for this single-center prospective study, which was carried out in compliance with the 1975 Helsinki Declaration and its updated versions (H-2101-064-1188). From October 2021 to September 2022, a total of 20 participants were sequentially sought for enrollment in this study. Age > 19, newly diagnosed PDAC by imaging or histologic evaluation, and signed informed permission in compliance with institutional and federal standards were the eligibility requirements. If a participant satisfied any of the following criteria, they were disqualified from the study: (1) pregnancy; (2) difficulty providing informed consent; (3) substantial comorbidities; (4) prior major abdominal surgery within four weeks of the trial; or (5) suspicion of distant metastases.

All participants were subjected to pancreatic CT, [^{18}F]FDG PET/CT, and blood tests including carbohydrate antigen 19-9 (CA 19-9, normal range [between 0 and 37 U/mL], non-secretors [2 U/mL on at least 3 examinations]) for initial evaluation, and [^{18}F]F-FAPI-74 PET/CT was performed for this study at the time of diagnosis in accordance with the institutional protocol.[17] Following the first PDAC evaluation, resectability, staging, and the participant's overall health were all carefully considered when determining the most effective treatment options. 20 people took part, 18 (90%) had surgery, and 2 (10%) had chemotherapy. One of the patients who underwent surgery underwent negative exploration due to the discovery of distant metastases at the colon mesentery. Therefore, only 17

patients who had curative-intent surgery were accessible for pathologic data from surgical specimens (Figure 1).

[^{18}F]FDG and [^{18}F]F-FAPI-74 PET/CT Protocol

Participants performed a fast of at least 8 hours before [^{18}F]FDG PET/CT imaging and had their blood sugar levels checked. When the blood glucose level was less than 200 mg/dL, participants received 5.18 MBq/kg of [^{18}F]FDG. A PET/CT scan was carried out 60 minutes after the [^{18}F]FDG injection following voiding. Participants received 185 MBq of [^{18}F]F-FAPI-74 for use in PET/CT imaging. 120 minutes following the radiotracer injection, a PET/CT scan was done.

Siemens Healthineers, Erlangen, Germany's Biograph TruePoint 40, Biograph mCT 40, and Biograph mCT 64 were the 3 specific PET/CT scanners we used. Without the use of contrast medium, a CT scan was done from the base of the skull to the proximal thigh. The scan's parameters were 120 kVp, 512 x 512 for the matrix and slice thickness (Truepoint 40) and 3 mm for mCT 40 and mCT 60, respectively. Following that, 7 to 9 bed positions were subjected to PET emission scans (2 minutes per bed for TruePoint; 1 minute per bed for mCT). The parameters for reconstructing attenuation-corrected PET images were as follows: TruePoint, 2 iterations, 21 subsets, 3-mm full-width half-maximum Gaussian filter, matrix 168 x 168; mCT, 2 iterations, 21 subsets, 5-mm full-width half-maximum Gaussian filter, matrix 200 x 200.

Image Interpretation

Software for image analysis (Syngo.via VB20, Siemens Healthineers) was used to examine PET/CT pictures. The photos were examined using both qualitative and semi-quantitative techniques. Total lesion activity (TLA; total lesion glycolysis; TLG; total lesion FAP expression; TLF) and maximum and mean standardized uptake values (SUV_{max}, SUV_{mean}) were measured as part of the semi-quantitative study. SUV threshold was used to measure volumetric characteristics at 40% of SUV_{max}. A 3 cm diameter sphere was used to create a volume of interest (VOI) in the right posterior portion of the liver to measure background activity. Positive findings were considered lymph nodes with higher activity than the area background in the qualitative analysis. The lymph node positive on the [^{18}F]FDG and [^{18}F]F-FAPI-74 PET/CT, respectively, were assessed by three nuclear medicine physicians (two senior resident physicians, HS and JG, and one experienced board-certified physician, HC), who then came to a consensus on the findings. Pathologic lymph nodes in pancreatic CT are lymph nodes greater than 10 mm.

Statistical Analysis

R software, version 4.2.2 (R Foundation for Statistical Computing), was used for all statistical analyses. Continuous variables are expressed as medians with interquartile ranges (IQR), and categorical variables are expressed as numbers with percentages. The Wilcoxon signed-rank test (skewed variables) was used to assess the SUV differences between [^{18}F]F-FAPI-74 and [^{18}F]FDG PET/CT. Comparing the predictive nodal status with postoperative histology in subjects who underwent curative-

intent surgery allowed researchers to determine the sensitivity, specificity, accuracy, positive predictive value, and negative predictive value of [^{18}F]F-FAPI-74 and [^{18}F]FDG PET/CT. The correlation between the CA 19-9 and TLA was discovered using Spearman correlation. All P-values were two-sided, and statistical significance was set at $P < 0.05$.

3. Results

Participant Characteristics

Table 1 provides a summary of the participants' initial characteristics. Age ranged from 66.0 to 77.3, with 69.0 being the median (IQR) age. There were 8 men (40.0%) and 12 women (60.0%). Four subjects (20.0%) did not secrete, and 13 (65.0%) exhibited elevated levels for CA 19-9. Lymph node metastasis was found in 10 of the participants who received curative-intent surgery (58.8%), and 14 (82.4%) of these cases were classified as reasonably early stage (I or II) cancers by the American Joint Committee on Cancer, 8^{th} edition.

Evaluation of Primary Pancreatic Lesions

With a 100% positive detection rate, [^{18}F]FDG and [^{18}F]F-FAPI-74 PET/CT assisted in the identification of all 20 primary pancreatic lesions. We further compared the SUV_{max} of primary pancreatic lesions and SUV_{mean} of background between [^{18}F]FDG and [^{18}F]F-FAPI-74 PET/CT images. The median [IQR] SUV_{max} for [^{18}F]F-FAPI-74 PET/CT in primary pancreatic lesions was higher than that for [^{18}F]FDG PET/CT (12.6 [10.7-13.7] vs. 6.3 [4.8-9.2], $P < 0.001$, Figure 2A). Additionally, [^{18}F]F-FAPI-74 PET/CT demonstrated lower median [IQR] SUV_{mean} than [^{18}F]FDG PET/CT in background organ as opposed to main pancreatic lesions (0.8 [0.7-0.9] vs. 2.6 [2.3-2.7], $P < 0.001$, Figure 2B).

Figure 3 shows the [^{18}F]FDG and [^{18}F]F-FAPI-74 PET/CT scans of a 72-year-old male. Compared to [^{18}F]FDG PET/CT, the main pancreatic lesions could be distinguished more clearly on [^{18}F]F-FAPI-74 PET/CT. Additionally,

[^{18}F]F-FAPI-74 PET/CT showed considerably reduced radiotracer uptake of adjacent organs than [^{18}F]FDG PET/CT, including the liver and colon. Although there was no difference in the incidence of primary pancreatic lesions detected with [^{18}F]FDG and [^{18}F]F-FAPI-74 PET/CT, a clear distinction in radiotracer uptake suggests that [^{18}F]F-FAPI-74 PET/CT may perform better for staging than [^{18}F]FDG PET/CT.

Diagnostic Performance of [^{18}F]FDG and [^{18}F]F-FAPI-74 PET/CT in Nodal Metastasis

10 of the 17 patients who received curative-intent surgery experienced lymph node metastases. In 5 (50.0%) of the 10 patients, [^{18}F]F-FAPI-74 PET/CT showed positive lymph nodes, but only in 0 (0.0%) and 3 (30.0%) of the participants for [^{18}F]FDG PET/CT and pancreatic CT, respectively (Table 2). The specificity was 100.0% (0/7) in [^{18}F]FDG and [^{18}F]F-FAPI-74 PET/CT, and 85.7% (6/7) in pancreatic CT. In addition, when compared to [^{18}F]FDG PET/CT or pancreatic CT, [^{18}F]F-FAPI-74 PET/CT had the highest accuracy, positive predictive value, and negative predictive values in detecting metastatic lymph nodes.

Figure 4 shows pancreatic CT, [^{18}F]FDG, and [^{18}F]F-FAPI-74 PET/CT images of a 66-year-old lady with newly discovered pancreatic head carcinoma showing lymph node at station number 17. On preoperative pancreatic CT, a 10.2 mm sized lymph node #17 was identified as a pathologic lymph node, and radiotracer uptake was also detected with [^{18}F]F-FAPI-74 PET/CT, unlike [^{18}F]FDG PET/CT. During surgery, lymph node #17 was in fact dissected, and the final pathology report confirmed

the presence of metastasis in lymph node.

Correlation between CA 19-9 and parameters of [^{18}F]FDG and [^{18}F]F-FAPI-74 PET/CT

The correlation between CA 19-9, a representative tumor marker in PDAC, and TLA of primary pancreatic lesions, a representative indicator of tumor burden, was examined in order to assess the clinical relevance of PET/CT data (Figure 5). The correlation between CA 19-9 and TLA was not seen in either [^{18}F]FDG or [^{18}F]F-FAPI-74 PET/CT images of 20 patients, including four CA 19-9 non-secretors (Figure 5A, 5B). The correlation coefficient (R^2) between CA 19-9 and TLA increased in both [^{18}F]FDG (0.01 → 0.26 and [^{18}F]F-FAPI-74 [0.05 → 0.57] PET/CT images, especially in [^{18}F]F-FAPI-74 PET/CT as compared with [^{18}F]FDG PET/CT (Figure 5C, 5D), when four CA 19-9 non-secretors were excluded from the analysis.

4. Discussion

Although accurate clinical staging is crucial for managing PDAC, high-risk patients are only seldom advised to undergo FDG PET/CT as a supplement to pancreatic CT.[6] FAPI, an imaging agent for the visualization of the tumor stroma, represents a promising alternative to FDG.[9] This study showed that PDAC is a highly FAPI-avid tumor, and [^{18}F]F-FAPI-74 PET/CT showed some superiorities to [^{18}F]FDG PET/CT in the detection of primary pancreatic cancer and metastatic lymph nodes. In addition, we discovered that [^{18}F]F-FAPI-74 PET/CT offered additional characteristics that were clinically applicable than [^{18}F]FDG PET/CT. As a result, PET/CT imaging with [^{18}F]F-FAPI-74 is helpful for the clinical management of PDAC patients and may lead to novel applications in staging.

Optimizing the scope of surgical resection is a crucial problem because it is still the only treatment for PDAC that has the potential to be curative. The extent of a pancreatectomy may be easily estimated, however the extent of a lymph node dissection has occasionally generated controversy. Pathologic examination should be carried out when pathologic lymph nodes around the superior mesenteric artery, celiac axis, and aorta are suspected in the preoperative assessment, despite some randomized controlled trials reporting that extended lymph node dissection does not improve oncologic outcomes compared with standard lymph node dissection when performing pancreaticoduodenectomy.[18-22] However, neither FDG PET/CT nor pancreatic CT performed well at detecting metastatic lymph nodes, despite the fact that adding FDG PET/CT to pancreatic CT can increase the sensitivity of detecting metastatic lesions.[8] This study demonstrated that

[^{18}F]F-FAPI-74 PET/CT was more effective at detecting metastatic lymph nodes than [^{18}F]FDG PET/CT or pancreatic CT. Figure 6 shows the pancreatic CT, [^{18}F]FDG, and [^{18}F]F-FAPI-74 PET/CT scans of a 72-year-old patient with newly discovered pancreatic head cancer. Preoperative pancreatic CT revealed a 7.3 mm-sized lymph node at station 14 close to the superior mesenteric artery (Figure 6A). Although this lymph node did not exhibit radiotracer uptake in [^{18}F]FDG PET/CT pictures (Figure 6B), [^{18}F]F-FAPI-74 PET/CT images (Figure 6C) clearly demonstrated radiotracer uptake. Since the lymph node #14 was not included in the pancreaticoduodenectomy's conventional lymph node dissection, it was visible on a pancreatic CT taken three months after surgery (Figure 6D). However, local recurrence around superior mesenteric artery eventually occurred at 10 months after surgery following adjuvant chemotherapy as the size progressively grew and metabolic activity was observed (Figure 6E, 6F). Additionally, Zhang et al (2022) also reported that Gallium-68 [^{68}Ga]Ga-DOTA-FAPI-04 PET/MR might better than [^{18}F]FDG PET/CT in the detection of suspicious lymph node metastasis in PDAC.[23] However, it was a comparison between PET/MR and PET/CT, and many of the participants (63.3%, 19/30) were in the advanced stage (stage III or IV). Our study has strengths in that it is a comparison between PET/CT and the majority of the participants were operable.

Over the past few decades, a lot of research has been done on both the diagnostic effectiveness and clinical significance of [^{18}F]FDG PET/CT. SUV_{max}, MTV, and TLG on preoperative [^{18}F]FDG PET/CT demonstrated good performance on survival prediction in surgically treated PDAC,

according to Moon et al. (2022) and Lee at al. (2014).[24,25] According to Lee et al. (2021), decreased radiotracer uptake of [^{18}F]FDG PET/CT following neoadjuvant chemotherapy was associated with better survival results.[26] In this study, by comparing the tumor-to-background ratio in [^{18}F]F-FAPI-74 and [^{18}F]FDG PET/CT, we discovered that FAP expression is more PDAC-specific than glucose metabolism. According to Kawase et al. (2015), immunohistochemical results showing moderate to strong stromal FAP staining intensity were indicative of a poor prognosis.[27] CAFs are the primary site of FAP expression, and it is known that these cells secrete CXCL12 to create an immunosuppressive environment.[15] These findings open up the possibility of employing FAP expression as a prognostic indicator as well as a predictor of the efficacy of immunotherapy or chemotherapy. Although CA 19-9 is currently the most prevalent tumor marker in PDAC, there are still a small percentage of patients (5–10%) that lack the Lewis antigen and have sparse CA 19-9 secretion. Parameters provided by [^{18}F]F-FAPI-74 PET/CT can be PDAC-specific markers that can replace CA 19-9, especially in CA 19-9 non-secretors. This possibility needs to be verified through a large-scale prospective study in the future.

There is currently no widely accepted protocol for FAPI PET/CT. As a result, different medical facilities have different radioactive isotopes and different turnaround times for imaging after radiotracer injection. Other investigations frequently employ ^{68}Ga-labeled FAPI molecules; this study, however, employed an ^{18}F-labeled radiotracer. Comparing ^{18}F-labeled compounds to ^{68}Ga-labeled compounds, which have a shorter half-life of 68 minutes and require a generator, the former have the benefit of being

commercially available supplements. Due to the 110-minute half-life of ^{18}F-labeled substances, it is possible to gather delayed PET/CT scans and offers more clinical alternatives.[28] Although the previous analysis only included 120-minute [^{18}F]F-FAPI-74 PET/CT pictures, we also acquired 60-minute images. Although the 120-minute images were superior, the 60-minute [^{18}F]F-FAPI-74 PET/CT images also shown higher diagnostic performance than [^{18}F]FDG PET/CT. Pang et al (2021) also stated that the delayed FAPI PET/CT images were more suited for differentiating between inflammatory and tumorous situations.[29] However, we discovered that [^{18}F]F-FAPI-74 PET/CT at 60 and 120 minutes demonstrated physiologic or benign radiotracer accumulation in the biliary tract. 19 (95.0%) of the 20 patients displayed radiotracer accumulation in the biliary tract. In reading [^{18}F]F-FAPI-74 PET/CT images for biliary tract cancer, it can be a mistake. Therefore, more study is required to design an imaging procedure and choose the best radiotracer for the type of carcinoma.

Our study had a few limitations. First, the sample size of our study was somewhat small (n = 20), and more research is needed to corroborate these results. Second, despite the fact that CA 19-9 and TLF of [^{18}F]F-FAPI-74 PET/CT showed a strong connection, limited follow-up made it unable to evaluate TLF's predictive ability. Therefore, future research should be based on a sizable sample size with a protracted follow-up time.

In conclusion, our findings demonstrated that for individuals with PDAC, [^{18}F]F-FAPI-74 PET/CT was more effective than [^{18}F]FDG PET/CT at detecting the main tumor and metastatic lymph nodes. Furthermore, there was a strong correlation between TLF from [^{18}F]F-FAPI-74 PET/CT and CA

19-9. These results imply that [^{18}F]F-FAPI-74 PET/CT may provide a clinical staging option to [^{18}F]FDG PET/CT in PDAC.

5. References

1. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2022. *CA Cancer J Clin*. Jan 2022;72(1):7-33. doi:10.3322/caac.21708

2. Kang MJ, Yun EH, Jung KW, Park SJ. Incidence, mortality and survival of gallbladder, extrahepatic bile duct, and pancreatic cancer using Korea central cancer registry database: 1999-2019. *Ann Hepatobiliary Pancreat Surg*. Aug 31 2022;26(3):220-228. doi:10.14701/ahbps.22-041

3. Park W, Chawla A, O'Reilly EM. Pancreatic Cancer: A Review. *JAMA*. Sep 7 2021;326(9):851-862. doi:10.1001/jama.2021.13027

4. Wolske KM, Ponnatapura J, Kolokythas O, Burke LMB, Tappouni R, Lalwani N. Chronic Pancreatitis or Pancreatic Tumor? A Problem-solving Approach. *Radiographics*. Nov-Dec 2019;39(7):1965-1982. doi:10.1148/rg.2019190011

5. Schima W, Bohm G, Rosch CS, Klaus A, Fugger R, Kopf H. Mass-forming pancreatitis versus pancreatic ductal adenocarcinoma: CT and MR imaging for differentiation. *Cancer Imaging*. Jul 23 2020;20(1):52. doi:10.1186/s40644-020-00324-z

6. Tempero MA, Malafa MP, Al-Hawary M, et al. Pancreatic Adenocarcinoma, Version 2.2021, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw*. Apr 1 2021;19(4):439-457. doi:10.6004/jnccn.2021.0017

7. Farma JM, Santillan AA, Melis M, et al. PET/CT fusion scan enhances CT staging in patients with pancreatic neoplasms. *Ann Surg Oncol*. Sep 2008;15(9):2465-71. doi:10.1245/s10434-008-9992-0

8. Wang Z, Chen JQ, Liu JL, Qin XG, Huang Y. FDG-PET in diagnosis,

staging and prognosis of pancreatic carcinoma: a meta-analysis. *World J Gastroenterol*. Aug 7 2013;19(29):4808-17. doi:10.3748/wjg.v19.i29.4808

9. Loktev A, Lindner T, Mier W, et al. A Tumor-Imaging Method Targeting Cancer-Associated Fibroblasts. *J Nucl Med*. Sep 2018;59(9):1423-1429. doi:10.2967/jnumed.118.210435

10. 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*. Mar 2019;60(3):386-392. doi:10.2967/jnumed.118.215913

11. Kratochwil C, Flechsig P, Lindner T, et al. (68)Ga-FAPI PET/CT: Tracer Uptake in 28 Different Kinds of Cancer. *J Nucl Med*. Jun 2019;60(6):801-805. doi:10.2967/jnumed.119.227967

12. Lang M, Spektor AM, Hielscher T, et al. Static and Dynamic (68)Ga-FAPI PET/CT for the Detection of Malignant Transformation of Intraductal Papillary Mucinous Neoplasia of the Pancreas. *J Nucl Med*. Feb 2023;64(2):244-251. doi:10.2967/jnumed.122.264361

13. Ding J, Qiu J, Hao Z, et al. Prognostic value of preoperative [(68)Ga]Ga-FAPI-04 PET/CT in patients with resectable pancreatic ductal adenocarcinoma in correlation with immunohistological characteristics. *Eur J Nucl Med Mol Imaging*. Jan 25 2023;doi:10.1007/s00259-022-06100-4

14. Pandol S, Edderkaoui M, Gukovsky I, Lugea A, Gukovskaya A. Desmoplasia of pancreatic ductal adenocarcinoma. *Clin Gastroenterol Hepatol*. Nov 2009;7(11 Suppl):S44-7. doi:10.1016/j.cgh.2009.07.039

15. Liu T, Han C, Wang S, et al. Cancer-associated fibroblasts: an emerging target of anti-cancer immunotherapy. *J Hematol Oncol*. Aug 28

2019;12(1):86. doi:10.1186/s13045-019-0770-1

16. Zhang T, Ren Y, Yang P, Wang J, Zhou H. Cancer-associated fibroblasts in pancreatic ductal adenocarcinoma. *Cell Death Dis*. Oct 25 2022;13(10):897. doi:10.1038/s41419-022-05351-1

17. Parra-Robert M, Santos VM, Canis SM, Pla XF, Fradera JMA, Porto RM. Relationship Between CA 19.9 and the Lewis Phenotype: Options to Improve Diagnostic Efficiency. *Anticancer Res*. Oct 2018;38(10):5883-5888. doi:10.21873/anticanres.12931

18. Farnell MB, Pearson RK, Sarr MG, et al. A prospective randomized trial comparing standard pancreatoduodenectomy with pancreatoduodenectomy with extended lymphadenectomy in resectable pancreatic head adenocarcinoma. *Surgery*. Oct 2005;138(4):618-28; discussion 628-30. doi:10.1016/j.surg.2005.06.044

19. Nimura Y, Nagino M, Takao S, et al. Standard versus extended lymphadenectomy in radical pancreatoduodenectomy for ductal adenocarcinoma of the head of the pancreas: long-term results of a Japanese multicenter randomized controlled trial. *J Hepatobiliary Pancreat Sci*. May 2012;19(3):230-41. doi:10.1007/s00534-011-0466-6

20. Jang JY, Kang MJ, Heo JS, et al. A prospective randomized controlled study comparing outcomes of standard resection and extended resection, including dissection of the nerve plexus and various lymph nodes, in patients with pancreatic head cancer. *Ann Surg*. Apr 2014;259(4):656-64. doi:10.1097/SLA.0000000000000384

21. Jang JY, Kang JS, Han Y, et al. Long-term outcomes and recurrence patterns of standard versus extended pancreatectomy for

pancreatic head cancer: a multicenter prospective randomized controlled study. *J Hepatobiliary Pancreat Sci*. Jul 2017;24(7):426-433. doi:10.1002/jhbp.465

22. Ignjatovic I, Knezevic S, Knezevic D, et al. Standard versus extended lymphadenectomy in radical surgical treatment for pancreatic head carcinoma. *J BUON*. Jan-Feb 2017;22(1):232-238.

23. 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*. Jul 2022;49(8):2877-2888. doi:10.1007/s00259-022-05729-5

24. Moon D, Kim H, Han Y, et al. Preoperative carbohydrate antigen 19-9 and standard uptake value of positron emission tomography-computed tomography as prognostic markers in patients with pancreatic ductal adenocarcinoma. *J Hepatobiliary Pancreat Sci*. Oct 2022;29(10):1133-1141. doi:10.1002/jhbp.845

25. Lee JW, Kang CM, Choi HJ, et al. Prognostic Value of Metabolic Tumor Volume and Total Lesion Glycolysis on Preoperative (1)(8)F-FDG PET/CT in Patients with Pancreatic Cancer. *J Nucl Med*. Jun 2014;55(6):898-904. doi:10.2967/jnumed.113.131847

26. Lee W, Oh M, Kim JS, et al. Metabolic activity by FDG-PET/CT after neoadjuvant chemotherapy in borderline resectable and locally advanced pancreatic cancer and association with survival. *Br J Surg*. Dec 17 2021;109(1):61-70. doi:10.1093/bjs/znab229

27. Kawase T, Yasui Y, Nishina S, et al. Fibroblast activation protein-alpha-expressing fibroblasts promote the progression of pancreatic ductal

adenocarcinoma. *BMC Gastroenterol*. Sep 2 2015;15:109. doi:10.1186/s12876-015-0340-0

28. Giesel FL, Adeberg S, Syed M, et al. FAPI-74 PET/CT Using Either (18)F-AlF or Cold-Kit (68)Ga Labeling: Biodistribution, Radiation Dosimetry, and Tumor Delineation in Lung Cancer Patients. *J Nucl Med*. Feb 2021;62(2):201-207. doi:10.2967/jnumed.120.245084

29. Pang Y, Zhao L, Shang Q, et al. Positron emission tomography and computed tomography with [(68)Ga]Ga-fibroblast activation protein inhibitors improves tumor detection and staging in patients with pancreatic cancer. *Eur J Nucl Med Mol Imaging*. Mar 2022;49(4):1322-1337. doi:10.1007/s00259-021-05576-w

Table 1. Baseline Characteristics of Study Participants

Variables	Value
Number of participants	20
Age, median, interquartile range, y (N = 20)	69.0 (66.0 – 77.3)
Sex (N = 20)	
Male	8 (40.0%)
Female	12 (60.0%)
ASA classification (N = 20)	
I / II	19 (95.0%)
III / IV	1 (5.0%)
Location (N = 20)	
Head	6 (30.0%)
Body/Tail	14 (70.0%)
CA 19-9, U/mL (N = 20)	
Normal	3 (15.0%)
Elevated	13 (65.0%)
Non-secretors	4 (20.0%)
Treatment strategy (N = 20)	
Chemotherapy	2 (10.0%)
Surgery	18 (90.0%)
Surgery (N = 18)[a]	
PD/PPPD	5 (27.8%)
DP	12 (66.7%)
Negative exploration	1 (5.5%)
Pathological T stage (N = 17)[b]	
T1	3 (17.6%)
T2	12 (70.6%)
T3	2 (11.8%)
T4	0 (0.0%)
Pathological N stage (N = 17)[b]	
N0	7 (41.2%)
N+	10 (58.8%)

Pathological AJCC stage (N = 17)[b]	
I	5 (29.4%)
II	9 (53.0%)
III	3 (17.6%)

[a]Participants who underwent surgery
[b]Participants who underwent curative-intent surgery
Abbreviations: ASA, american society of anesthesiologists; CA 19-9, carbohydrate antigen 19-9; PD, pancreaticoduodenectomy; PPPD, pylorus-preserving pancreaticoduodenectomy; DP, distal pancreatectomy.

Table 2. Comparison of performance in predicting nodal status among imaging modalities

	Pancreatic CT		**[^{18}F]FDG PET/CT**		**[^{18}F]F-FAPI-74 PET/CT**	
	cN+	**cN0**	**cN+**	**cN0**	**cN+**	**cN0**
pN+	3	7	0	10	5	5
pN0	1	6	0	7	0	7
Sensitivity	30.0%		0.0%		50.0%	
Specificity	85.7%		100.0%		100.0%	
Accuracy	52.9%		41.2%		70.6%	
PPV	75.0%		Not applicable		100.0%	
NPV	46.2%		41.2%		58.3%	

Note. Unless otherwise specified, data are numbers of patients.
Abbreviations: CT, computed tomography; PPV, positive predictive value; NPV, negative predictive value.

Figure 1. Flow diagram of participants enrolled

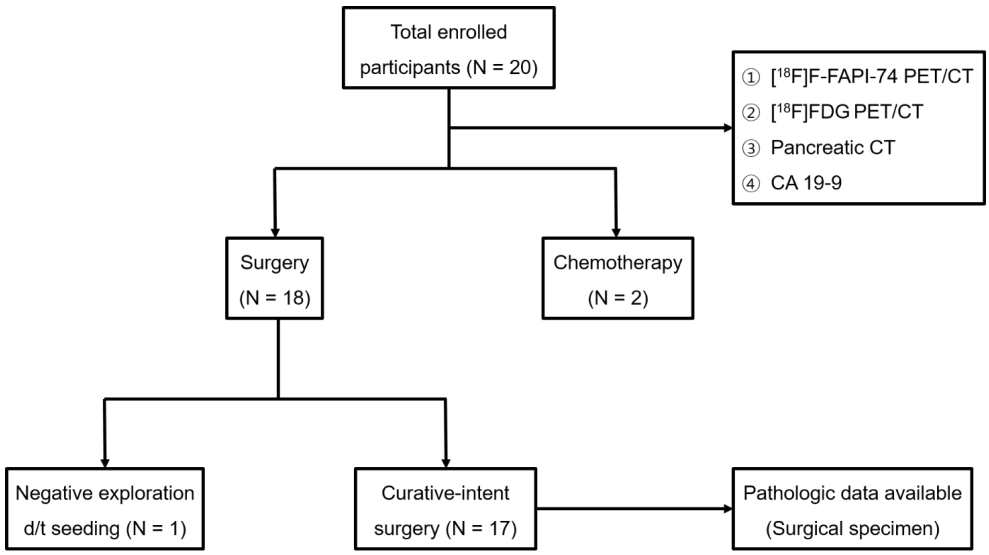


Figure 2. Differences of radiotracer uptake between [^{18}F]FDG and [^{18}F]F-FAPI-74 PET/CT.

(a) [^{18}F]F-FAPI-74 PET/CT shows significantly higher radiotracer uptake of primary pancreatic lesions than [^{18}F]FDG PET/CT. (b) [^{18}F]F-FAPI-74 PET/CT shows significantly lower radiotracer uptake of background organs than [^{18}F]FDG PET/CT.

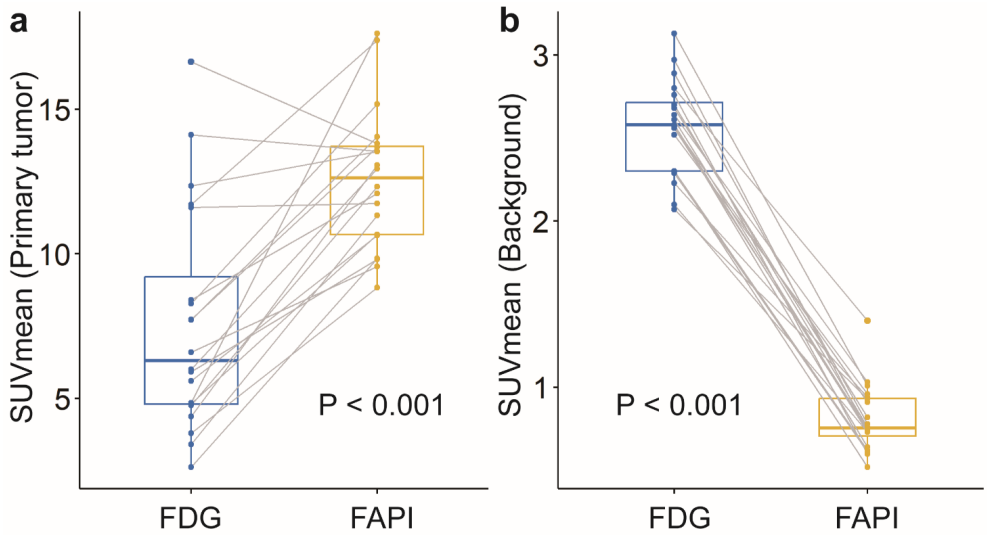


Figure 3. Images of a 72-year-old man with newly diagnosed pancreatic tail cancer for tumor staging.

(a) [^{18}F]FDG PET/CT, (b) [^{18}F]F-FAPI-74 PET/CT.

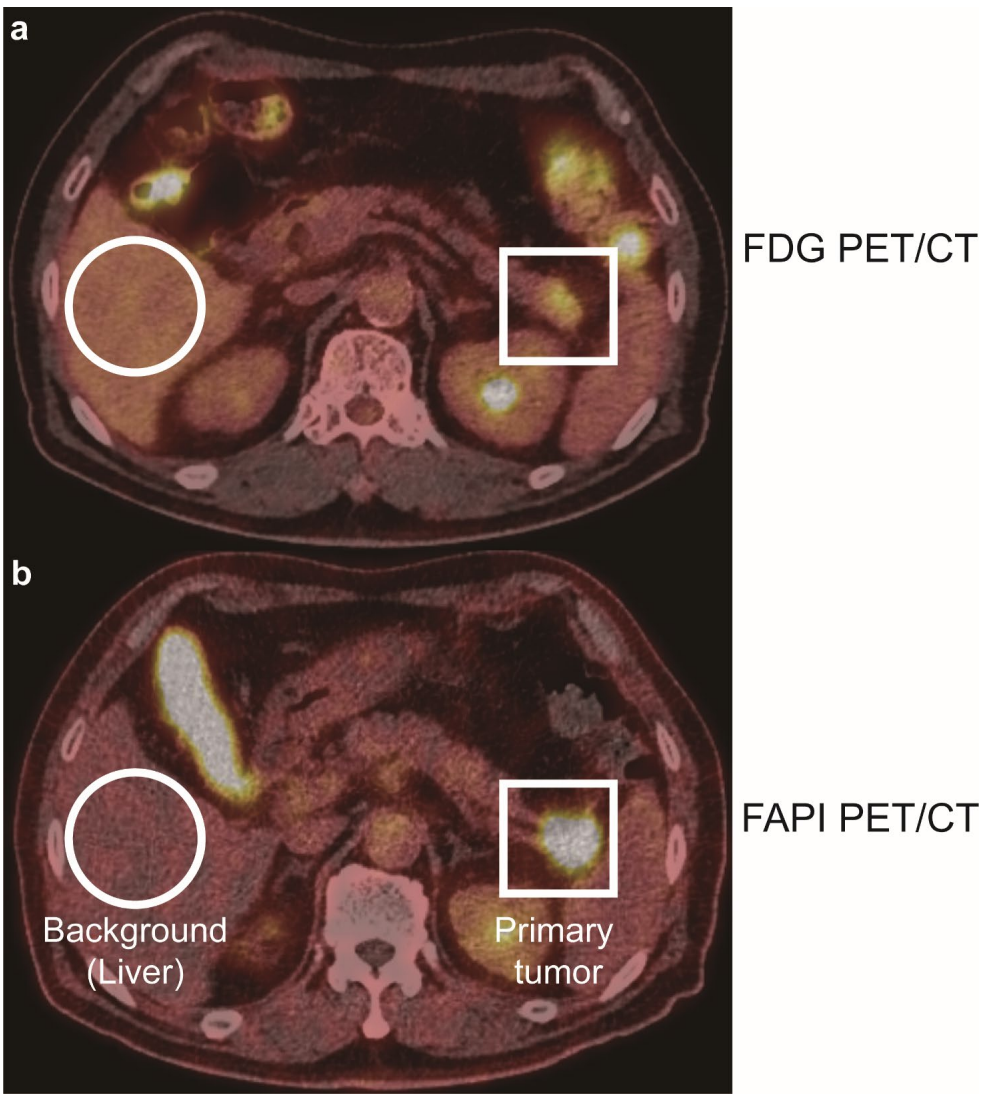


Figure 4. Preoperative images of a 66-year-old woman with newly diagnosed pancreatic head cancer for tumor staging.

(a) Pathologic 10.2mm-sized lymph node #17 on pancreatic CT, (b) No distinguishable radiotracer uptake of lymph node #17 on [^{18}F]FDG PET/CT, and (c) Distinguishable radiotracer uptake of lymph node #17 on [^{18}F]F-FAPI-74 PET/CT.

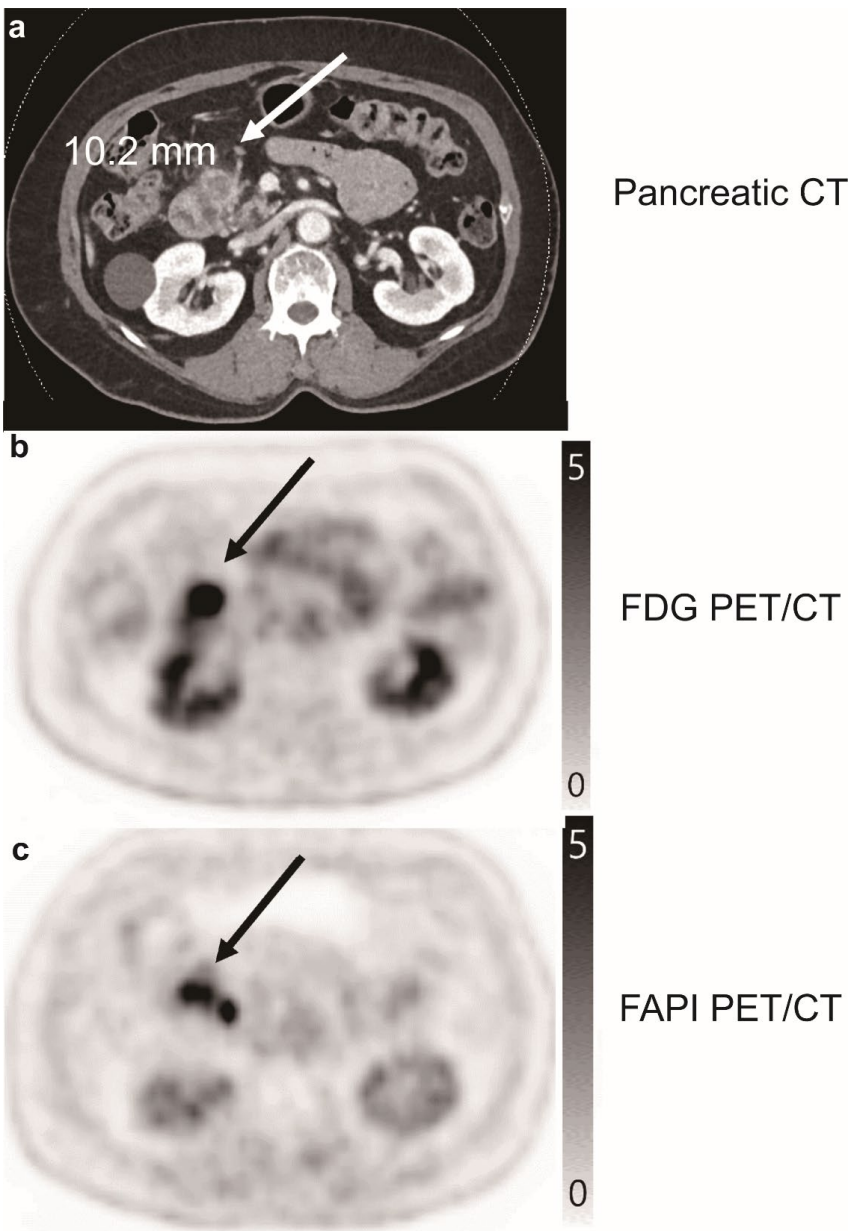


Figure 5. Correlation between CA 19-9 and total lesion activity of PET/CT

Total lesion activity of (a) [^{18}F]FDG, and (b) [^{18}F]F-FAPI-74 PET/CT in total 20 participants. Total lesion activity of (c) [^{18}F]FDG, and (d) [^{18}F]F-FAPI-74 PET/CT in 16 participants after excluding CA 19-9 non-secretors.

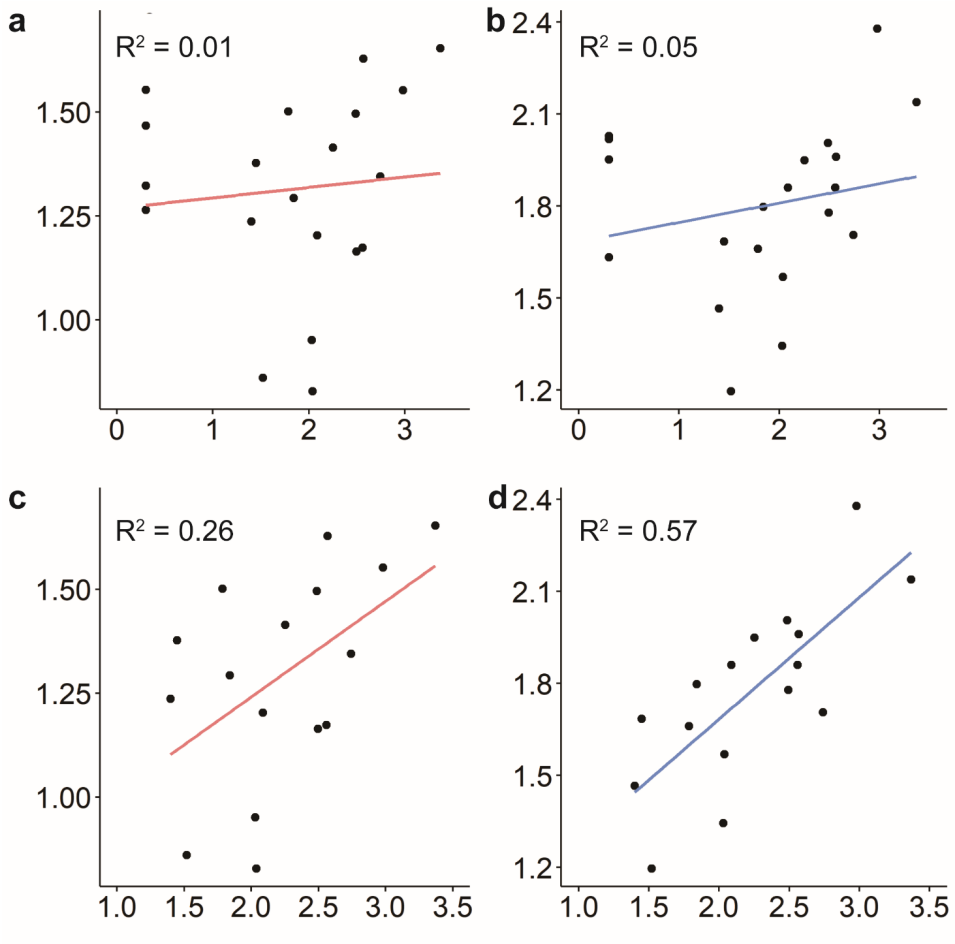
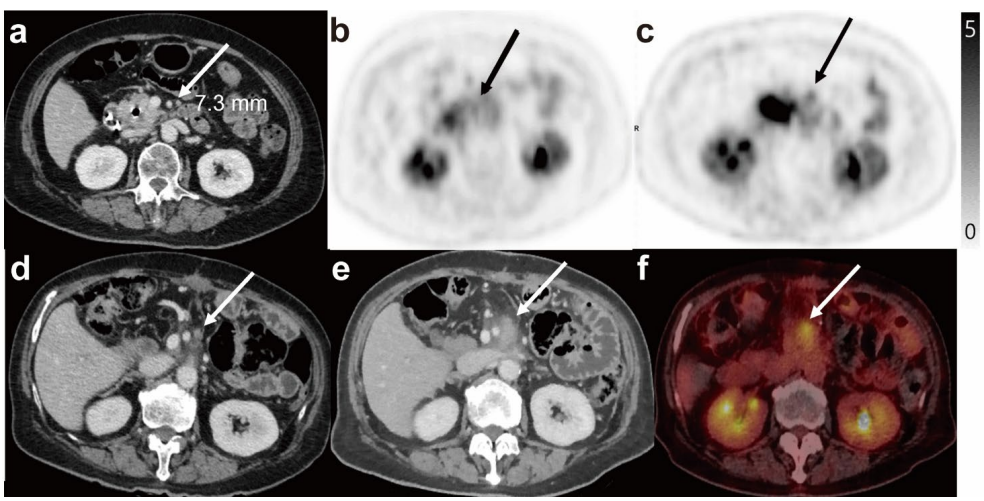


Figure 6. Preoperative and follow-up images of a 72-year-old woman with newly diagnosed pancreatic head cancer

(a) Non-pathologic 7.3mm-sized lymph node #14 on preoperative pancreatic CT, (b) No distinguishable radiotracer uptake of lymph node #14 on preoperative [^{18}F]FDG PET/CT, (c) Distinguishable radiotracer uptake of lymph node #17 on preoperative [^{18}F]F-FAPI-74 PET/CT, (d) Remaining lymph node #14 on postoperative 3 months pancreatic CT, (e) Local recurrence around superior mesenteric artery on postoperative 10 months pancreatic CT, and (f) high metabolic activity of locally recurred lesions in [^{18}F]FDG PET/CT



Abstract (Kor.)

목적: 췌장암은 매우 치명적인 암이며, 정확한 병기 설정이 최적의 치료 전략을 수립하기 위해 중요합니다. 췌장암의 임상적 병기 설정에 있어 F-18 fluorodeoxyglucose ([^{18}F]FDG) 양전자 방출 단층 촬영/컴퓨터 단층 촬영이 자주 사용되고 있지만 아직까지도 임상 병기 결정에 효과는 불분명합니다. 최근, 비교적 진행성 췌장암을 대상으로 포도당 대사보다 췌장암에 더 특이적인 섬유아세포 활성화 단백질 발현을 감지하는 양전자 방출 단층 촬영/컴퓨터 단층 촬영이 일부 연구에서 수행되었습니다. 그러나, 여전히 비교적 조기 췌장암에서의 효과는 알려져 있지 않으며, 본 연구에서는 조기 췌장암의 임상적 병기 설정에서 F-18 fibroblast activation protein inhibitor ([^{18}F]F-FAPI-74) 양전자 방출 단층 촬영/컴퓨터 단층 촬영의 효과를 평가하는 것을 목표로 했습니다.

방법: 2021년과 2022년 사이에 새로 진단된 췌장암 참가자 20명을 등록하고 [^{18}F]FDG 및 [^{18}F]F-FAPI-74 양전자 방출 단층 촬영/컴퓨터 단층 촬영을 검사하였습니다. 수술 검체를 바탕으로 한 병리학적 정보는 근치적 목적의 수술을 받은 17명의 참가자들에서 사용이 가능하였습니다. 이를 바탕으로 양전자 방출 단층 촬영/컴퓨터 단층 촬영들 간의 방사성 표지자의 흡수 및 진단 성능을 비교하였습니다.

결과: [^{18}F]F-FAPI-74 양전자 방출 단층 촬영/컴퓨터 단층 촬영 (중위수 [사분위간 범위]; 12.6 [10.7–13.7])은 [^{18}F]FDG 양전자 방출 단층

촬영/컴퓨터 단층 촬영 (6.3 [4.8–9.2])에 비해 췌장암 병변에 대해 훨씬 높은 최대 표준화섭취를 보였습니다 (P <0.001). 반면, [^{18}F]F-FAPI-74 양전자 방출 단층 촬영/컴퓨터 단층 촬영 (중위수 [사분위간 범위]; 0.8 [0.7–0.9])는 [^{18}F]FDG 양전자 방출 단층 촬영/컴퓨터 단층 촬영 (2.6 [2.3–2.7])에 비해 주변부 장기에 대해 훨씬 낮은 평균 표준화섭취를 보였습니다 (P <0.001). 또한 전이 림프절 검출 시 [^{18}F]F-FAPI-74 양전자 방출 단층 촬영/컴퓨터 단층 촬영 영상은 [^{18}F]FDG 양전자 방출 단층 촬영/컴퓨터 단층 촬영에 비해 훨씬 높은 민감도를 보였습니다 (50.0% vs. 0.0%).

결론: [^{18}F]F-FAPI-74 양전자 방출 단층 촬영/컴퓨터 단층 촬영 영상은 췌장암 병변 및 전이성 림프절의 검출에서 [^{18}F]FDG 양전자 방출 단층 촬영/컴퓨터 단층 촬영에 비해 우수합니다. 따라서 [^{18}F]F-FAPI-74 양전자 방출 단층 촬영/컴퓨터 단층 촬영 영상은 향상된 진단 능력을 바탕으로 췌장암 병기 설정을 위한 표준적인 영상 방법으로 사용될 수 있습니다.