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Early recurrence detected by ^{18}F-FDG PET/CT in patients with resected pancreatic ductal adenocarcinoma

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Abstract

^{18}F-fluoro-2-deoxy-D-glucose positron emission tomography integrated with computed tomography (^{18}F-FDG PET/CT) has been proved to be practical in detecting occult malignant lesions. However, the evidence of its utility in detecting early recurrence after resection of pancreatic ductal adenocarcinoma (PDAC) is lacking. Therefore, the primary aim of the present study is to evaluate the diagnostic value of ^{18}F-FDG PET/CT in the early postoperative period after radical resection of PDAC.

This retrospective study included 32 patients who had ^{18}F-FDG PET/CT scan within 6 months after radical resection of PDAC between January 2010 and December 2018.

In total, 10 positive PET results were found at surgical margins of remnant pancreas, 12 at locoregional lymph nodes, 5 at distant areas, with the corresponding mean maximum standard uptake value (SUV_{max}) of 5.8 ± 1.1, 5.9 ± 0.9, and 6.4 ± 0.7, respectively. The median follow-up time was 23.5 months (range: 8–75 months), and the median survival time was 39.5 months (95% confidence interval: 14.6–64.4 months) for the entire cohort. Patients with positive PET findings at either locoregional lymph nodes or distant areas obtained significantly poorer overall survival (OS) than those without increased FDG uptake at the corresponding areas ($P = .003$ and $P < .001$, respectively). Whereas comparisons of OS between patients with or without increased FDG uptake at the surgical margin of remnant pancreas presented no statistically difference ($P = .742$).

The early application of ^{18}F-FDG PET/CT after radical resection of PDAC could stratify the prognosis of patients well by detecting occult early recurrence at locoregional lymph nodes and distant areas efficiently.

Abbreviations: ^{18}F-FDG = ^{18}F-fluoro-2-deoxy-D-glucose, AJCC = American Joint Committee on Cancer, ISGPS = International Study Group of Pancreatic Surgery, MRI = magnetic resonance imaging, OS = overall survival, PDAC = pancreatic ductal adenocarcinoma, PET/CT = positron emission tomography integrated with computed tomography, POPF = postoperative pancreatic fistula, SD = standard deviation, SUV_{max} = maximum standard uptake value.

Keywords: early recurrence, overall survival, pancreatic ductal adenocarcinoma, positron emission tomography, postoperative

1. Introduction

Pancreatic ductal adenocarcinoma (PDAC) is one of the leading causes of tumor-related mortality, with a 5-year survival rate less than 10%.[1] Meanwhile, pancreas cancers are projected to surpass breast, prostate, and colorectal cancers to become the second cause of cancer-related death by 2030.[2] To date, radical surgical resection remains the only potential curative treatment option and one of the most significant prognostic factors for better survival.[3] However, more than 80% cases with radical surgical resection had different kinds of recurrence within 2 years postoperatively with a median recurrent time of 12.65 months.[4] Besides, recurrent PDAC is especially difficult to manage, as it is characterized by aggressive behavior and multiple recurrence patterns.[5–7] Nowadays, image modality remains the major choice to detect early recurrence of PDAC.

Traditional image modalities such as computed tomography (CT) and magnetic resonance imaging (MRI) have been used most frequently in the perioperative period of PDAC. Meanwhile, the validity of ^{18}F-fluoro-2-deoxy-D-glucose positron emission tomography (^{18}F-FDG PET) in multiple types of cancers has been accepted by oncologists in the past decade.[8–10] By combining both morphological and metabolic features, ^{18}F-FDG PET/CT represents a more sensitive modality to detect occult

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primary and metastatic pancreatic malignancies than traditional imaging modalities.[11,12] Besides, by directly assessing the degree of metabolic activity, it also represents a more functional measure in assessing treatment response.[13,14] Whereas, most studies focused on the recurrence of surgical resected PDAC still prefer traditional cross-sectional imaging modalities.[7,15] Instead of the primary choice, PET modalities were usually just performed to clarify ambiguous CT and MRI findings.

Several studies have validated the utility of preoperative PET modalities in predicting outcome and recurrence for PDAC.[16–21] To the best of our knowledge, however, none of these studies focused on the postoperative PET findings in the early phase after pancreatectomy. Therefore, the primary aim of the present study was to evaluate the diagnostic value, especially the utility in detecting early recurrence, of ^{18}F-FDG PET/CT in the early postoperative period after radical resection of PDAC.

2. Methods

2.1. Study population

The Institutional Research Ethics Committee of our institution approved this retrospective study. Patients who had both radical resection for primary resectable PDAC and ^{18}F-FDG PET/CT scan within 6 months postoperatively between 2010 and 2018 were included from the institutional database. Exclusion criteria were distant metastases at the time of resection, extended lymph node dissection during operation, grossly positive resection margin, and 60-day postoperative mortality. Patients with incomplete follow-up information were also excluded. The primary outcomes of interest were positive FDG PET results, and overall survival (OS).

2.2. ^{18}F-FDG PET/CT

The patients had been administered with ^{18}F-FDG (5 MBq/kg body weight) and imaged for 2.5 minutes per bed after approximately 1-hour ^{18}F-FDG injection on a Gemini 16 PET/CT scanner (Philips Healthcare, Eindhoven, the Netherlands) to identify potential recurrence. ^{18}F-FDG PET/CT images and data of the surgical resection site of remnant pancreas, locoregional lymph nodes, and any distant metastases were reviewed and collected. Areas with a maximum standard uptake value (SUV_{max}) of 3 or higher were considered with positive PET results.

2.3. Clinical data and follow-up

The clinical data of perioperative demographics, clinicopathologic, complications, and treatment variables were extracted from the retrospective database of PDAC of our center. Patients with elevated amylase content of the drain fluid 3 times greater than the upper normal serum value from the postoperative day 3 were considered with biochemical leak or postoperative pancreatic fistula (POPF).[22] Recurrence was mainly detected by imaging modalities and serum tumor markers, which was further confirmed by biopsy whenever possible. Telephone calls, office visits, and outpatient clinic appointments were conducted for follow-up of the included patients in July and August 2019 for all patients, providing a potential follow-up time in months. OS was defined as the number of months from the date of resection to the time of mortality or last contact. Cases with mortality classified as not being associated with PDAC were excluded in follow-up.

2.4. Statistical analyses

Continuous data are expressed as mean ± standard deviation (SD). Categorical data are presented as numbers and their frequencies as proportions (%), which were compared by Pearson χ^2 tests wherever possible. Kaplan–Meier curves were plotted and log-rank tests were performed to analyze and compare OS. $P < .05$ was considered to indicate a statistically significant difference. All the statistical analyses were performed by IBM SPSS 21.0 statistical software (IBM, Corp., Armonk, NY).

3. Results

3.1. Patient demographics

Between January 2010 and December 2018, 38 patients had ^{18}F-FDG PET/CT scans within 6 months after radical resection for PDAC in our center. Three patients were lost during follow-up, 2 patients were excluded for grossly positive resection margin (R2), and 1 patient was excluded for postoperative mortality with 60 days. As a result, 32 patients were included for further analysis. There were 21 males and 11 females in this cohort, with a mean age of 55.6 ± 10.4 years. All the included patients had been diagnosed with PDAC by operation and pathology, with 19 tumors in the head of pancreas and 13 in the body and tail of pancreas. According to the 8th edition of the American Joint Committee on Cancer (AJCC) Staging System, at the time of diagnosis, more than half of these patients were classified as stage II (n = 18, 56.3%), with no presence of stage IV disease preoperatively. The basic characteristics of the entire study population are summarized in Table 1.

Table 1

Basic characteristics of the included patients.

Characteristic	No.	%
Age (mean ± SD)	55.6	±10.4
Gender		
Male	21	65.6
Female	11	34.4
Tumor marker (mean ± SD)		
CA 19-9	413.9	±72.4
CEA	4.2	±0.9
Tumor location		
Head	19	59.4
Body/Tail	13	40.6
Tumor differentiation		
Well-moderate	13	40.6
Poor	19	59.4
AJCC stage*		
I	12	37.5
II	18	56.3
III	2	6.2
IV	0	0
Positive follow-up PET findings		
Surgical margin	10	31.3
Locoregional lymph node	12	37.5
Distant areas	5	15.6

AJCC = American Joint Committee on Cancer, PET = positron emission tomography, SD = standard deviation.
* Staging at the time of diagnosis.

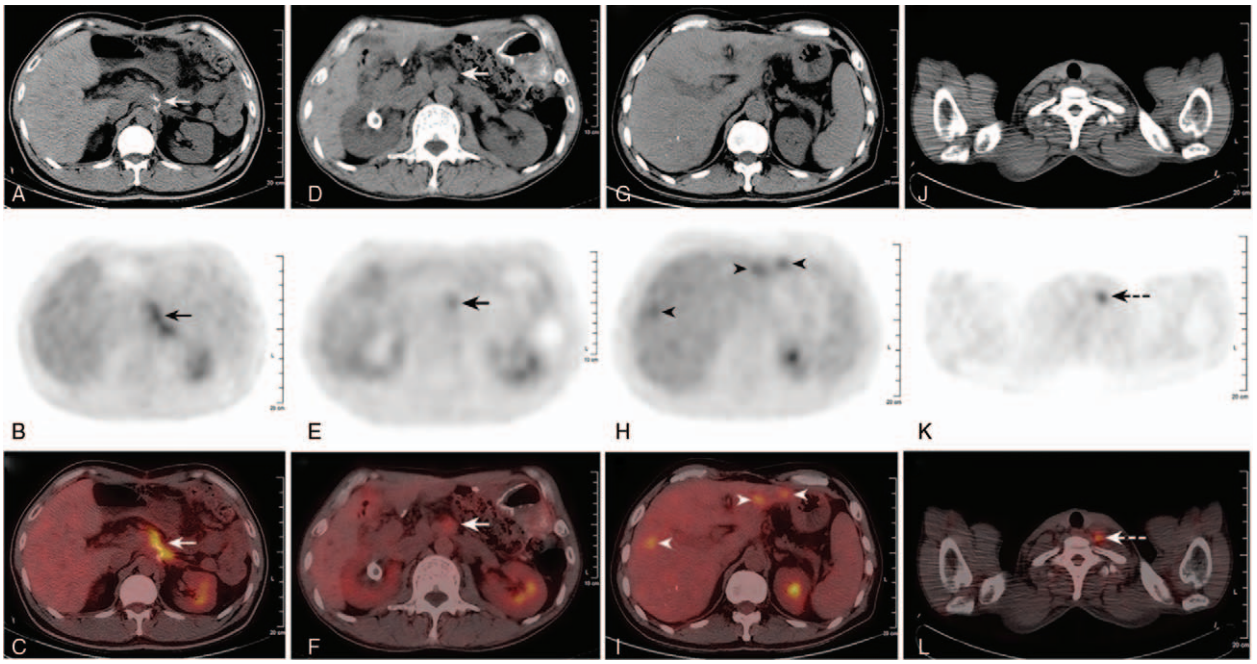

Figure 1. Postoperative FDG PET/CT findings at surgical margin of remnant pancreas (A–C), locoregional lymph node (D–F), and distant sites (G–L). (A) CT image showed the resection margin of remnant pancreas after distal pancreatectomy (thin arrow). (B and C) FDG PET/CT revealed increased FDG uptake at the same site (thin arrows). (D) CT image showed an enlarged para-aortic lymph node with the diameter of 15 mm (thick arrow), (E and F) FDG PET/CT revealed increased FDG uptake at this lymph node (SUV_{max} of 3.2, thick arrows). (G) CT image showed ambiguous low density of liver. (H and I) FDG PET/CT revealed obvious increased FDG uptake of lesions within liver (SUV_{max} of 5.9, arrow heads). (K and L) obvious increased uptake of FDG at left supraclavicular lymph node (SUV_{max} of 4.4, dashed arrows).

3.2. Positive ^{18}F-FDG PET findings

Within 6 months postoperatively, positive PET results had been found in 10 patients at surgical sites of remnant pancreas, 12 at locoregional lymph nodes, and 5 at the sites of potential distant metastases, with the corresponding mean SUV_{max} of 5.8 ± 1.1, 5.9 ± 0.9, and 6.4 ± 0.7, respectively. ^{18}F-FDG PET/CT revealed the increased FDG uptake of occult lesions mentioned above in a morphologic way, which might not be discovered by traditional cross-sectional images (Fig. 1). Besides, ^{18}F-FDG PET/CT scans were usually performed in a whole-body way, which had the priority to detect occult distant metastases (e.g., Fig. 1J–L). Interestingly, despite the absence of statistical significance, patients with positive PET findings at the sites of surgical margin of remnant pancreas within half a year postoperatively had both higher incidence of biochemical leakage and POPF (30.0% vs 9% and 20.0% vs 4.5%, respectively) (Table 2). It is plausible that because of the relatively small cohort, the statistical power was insufficient to reflect the utility of ^{18}F-FDG PET/CT in detecting POPF.

Table 2

Difference between PET-positive and negative results.

	^{18}F-FDG PET		
	+	−	*P*
Resection margin			
SUV_{max}	5.8 ± 1.1	NA	NA
Biochemical leakage rate (%)	30.0%	9.0%	.131
POPF rate (%)	20.0%	4.5%	.164
CA19-9, U/mL	529.6 ± 137.4	361.5 ± 84.5	.289
Median survival time, mo	25 (95% CI: 20.2–29.8)	39.5 (95% CI: 29.9–49.0)	.742
Locoregional lymph node			
SUV_{max}	5.9 ± 0.9	NA	NA
CA19-9, U/mL	584.2 ± 105.9	311.9 ± 91.2	.068
Median survival time, mo	25 (95% CI: 19.9–30.1)	50 (95% CI: 43.1–56.9)	.003
Distant areas			
SUV_{max}	6.4 ± 0.7	NA	NA
CA19-9, U/mL	439.1 ± 84.3	278.2 ± 71.6	.428
Median survival time, mo	16 (95% CI: 9.4–22.6)	45.6 (95% CI: 32.6–58.6)	<.001

^{18}F-FDG PET = ^{18}F-fluoro-2-deoxy-D-glucose positron emission tomography, NA = not applicable, POPF = postoperative pancreatic fistula, SUV_{max} = maximum standard uptake value.

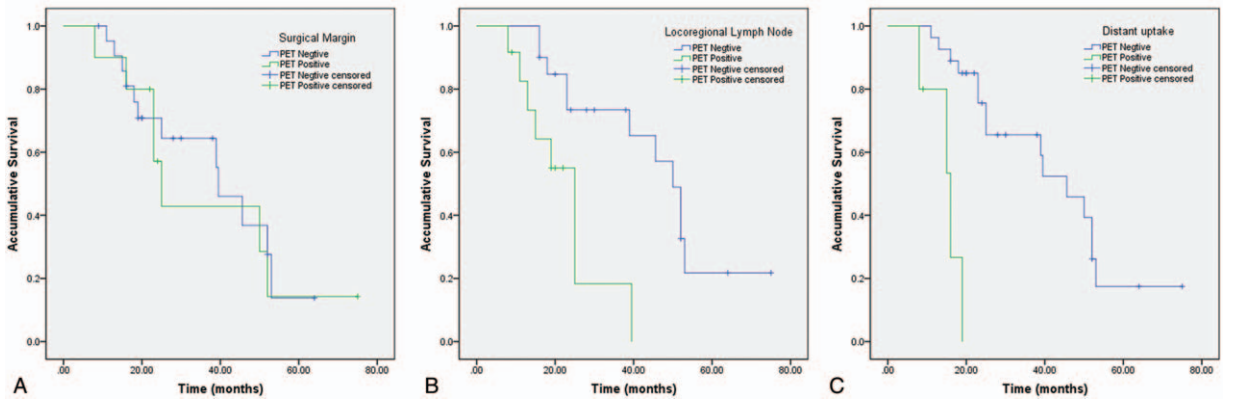

Figure 2. Kaplan–Meier curves showing survivals by different FDG-avid areas. (A) Difference between the survivals of patients with or without increased FDG uptake at the surgical margin of remnant pancreas was not statistically significant ($P = .742$). (B) Patients with increased FDG uptake at locoregional lymph obtained significantly poorer survival than those without ($P = .003$). (C) Patients with increased distant FDG uptake obtained significantly poorer survival than those without ($P < .001$).

3.3. Overall survival

Follow-up was conducted in July and August 2019, eventually developing a median follow-up time of 23.5 months (range: 8–75 months), with 19 patients (59.4%) followed to death. The median survival time was 39.5 months [95% confidence interval (95% CI): 14.6–64.4] for the entire cohort, 53.0 months (95% CI: 31.8–74.2) for patients in stage I, and 25.0 months (95% CI: 19.4–30.6) for patients in stage II and III. Compared with stage II and III, patients in stage I obtained significantly better survival ($P = .027$).

As to the main concern of this study, the corresponding median survival time for different FDG-avid areas is presented in Table 2. Meanwhile, OS between patients with positive and negative PET findings is compared in Fig. 2 by different FDG-avid areas respectively. As a result, patients with positive PET findings at either locoregional lymph nodes or distant areas had significantly poorer OS than patients without increased FDG uptake at the corresponding areas ($P = .003$ and $P < .001$, respectively). Whereas, different PET results of the surgical margin of remnant pancreas did not stratified the OS of the present cohort ($P = .742$).

4. Discussion

A clear definition of early recurrence after radical resection of PDAC is currently lacking. The cut-off values between early and late varies throughout the published studies, for instance 6 months,[23] 8 months,[24] and 12 months.[25] Considering the poor median survival time of patients with PDAC, we speculated that 12 months might not be "early" enough to address this issue properly. For instance, in the study conducted by Groot et al,[26] more than 40% of the total patients (n = 957) recurred within 12 months, and 80% of them already had distant metastases. Therefore, in the present study, we reviewed the ^{18}F-FDG PET/CT images within 6 months postoperatively of patients with radical resection of PDAC to identify the utility of ^{18}F-FDG PET/CT in detecting early recurrence. As a result, increased FDG uptake were found in 10 (31.3%) cases at the surgical margin of remnant pancreas, 12 (37.5%) at locoregional lymph nodes, and 5 (15.6%) at distant sites.

The patterns of recurrence after radical resection of PDAC varied a lot among studies. For instance, the liver recurrence rates varied between 6.7% and 60.9% from 59 studies in a meta-analysis.[7] The relatively smaller proportion of positive PET results at distant areas in the present study might be caused by the following two reasons: First, the ^{18}F-FDG PET/CT modality had been conducted for the present cohort within half a year postoperatively, which might present some false-positive findings due to inflammation of the surgical region, and consequently decreased the proportion of positive distant results. Second, most patients of the present study had ^{18}F-FDG PET/CT scans preoperatively, which lower the probability of occult distant metastases before resection. Just as reported previously, there was a great possibility that the majority of patients had already developed occult distant metastases before the radical resections for PDAC.[4,27,28]

With a relative shorter interval as 6 months postoperatively to distinguish early and late recurrence, there were still some proportion of patients with potential recurrence on ^{18}F-FDG PET/CT images in this cohort, and up to 37.5% of these patients had increased FDG uptake at locoregional lymph nodes. Lymphadenectomy is quite critical in the radical resection procedure of PDAC for better prognosis. Previous prospective studies suggested that extended lymph node dissection in patients underwent resection of PDAC was not justified.[29,30] However, these retained lymph nodes, such as periaortic, celiac, and superior mesenteric artery nodes, have been proved to be associated with malignant issues in several recent studies.[31,32] Also, in the present study, more than one-third of patients had positive PET findings at the region of locoregional lymph nodes with 6 months postoperatively. Besides, patients with suspicious locoregional lymph nodes recurrence reflected by ^{18}F-FDG PET/CT had significantly poorer OS than patients with normal uptake of FDG (Fig. 2B). Therefore, we speculated that the extent of standard and extended lymph node dissection of radical resection for PDAC might require renegotiation. Meanwhile, as expected, patients with positive PET findings at the sites of suspicious distant metastases also presented significantly poorer survival than those without abnormal uptake of FDG (Fig. 2C), which further validate the diagnostic value of ^{18}F-FDG PET/CT in detecting occult early recurrence of surgically resected PDAC.

Of particular importance, we found higher rates of both postoperative biochemical leakage and POPF in patients with increased FDG uptake at the surgical margin of remnant pancreas, while the OS, which was mostly affected by malignant

issues, of them was comparable. Indeed, limitations of PET, such as glucose intolerance of PDAC; overlap in FDG uptake between malignant and inflammatory issues of pancreas; lack of intravenous contrast, have weakened the ability of PET modalities in assessing tumor (T) staging of PDAC.[21,33] Considering the results of the present study, ^{18}F-FDG PET/CT might not be practical enough to detect early recurrence at the surgical site of remnant pancreas in the early period postoperatively. As one of the main disadvantages of PET, false-positive findings due to inflammation in patients with malignant tumors were usually considered as a nuisance to oncologists who had to realize that FDG is not a cancer specific tracer.[34,35] Whereas, increasing number of new applications of FDG for assessing diseases beyond cancer have been accepted by clinicians in the past decade.[15] According to the definition by the International Study Group of Pancreatic Surgery (ISGPS), POPF is diagnosed by the measure of amylase content of the drain fluid.[22] Indeed, the leakage of pancreatic juice and subsequent POPF after partial pancreatectomy are consequences of the impaired sealing of pancreatic parenchyma.[36,37] Therefore, an imaging modality, such as ^{18}F-FDG PET/CT, which could detect the metabolic feature of the surgical site of remnant pancreas might assist the early detection of POPF before the drainage of pancreatic juice. However, this needs to be confirmed by further studies with larger sample size.

As noted above, the main limitation of this study is the relatively small sample size. As the charge of ^{18}F-FDG-PET/CT was expensive, only a small proportion of patients with radical resection of PDAC had ^{18}F-FDG PET/CT scans in the first 6 months postoperatively. Also, limited by the sample size, we could not perform further multivariate analyses for factors may affect the survival of these patients. Meanwhile, the retrospective nature of our study might bring some potential error and variation when collecting information, such as the details of operation and adjuvant therapy. However, even though the number of patients was limited, the number of positive PET findings was sufficient to show statistically significant and clinically relevant differences.

The present study demonstrated the early postoperative findings of ^{18}F-FDG PET/CT after radical resection of PDAC, and conclude that the application of ^{18}F-FDG PET/CT may assist the early detection of occult recurrence, especially for locoregional lymph nodes and distant metastases, and further stratify the prognosis of these patients. Whereas, the ^{18}F-FDG PET/CT results may be affected by both malignant and inflammatory issues at the sites of surgical margin of remnant pancreas in the early phase postoperatively. Further larger studies are in need to validate our findings and explore the applicability of PET modalities in assessing the inflammation of remnant pancreas and relative complications, such as POPF, after pancreatectomy.

Author contributions

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Software: Ping Dong, Weiguo Wang.
Supervision: Weiming Hu, Xubao Liu, Bole Tian.
Writing – original draft: Li Wang, Bole Tian.
Writing – review & editing: Xubao Liu.

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