Non-invasive differentiation of pancreatic lesions: is analysis of FDG kinetics superior to semiquantitative uptake value analysis?

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Abstract. The diagnostic utility of fluorine-18 2-deoxy-D-glucose positron emission tomography (FDG PET) for the non-invasive differentiation of focal pancreatic lesions originating from cancer or chronic pancreatitis by combined visual image interpretation and semiquantitative uptake value analysis has been documented. However, in clinical routine some misdiagnosis is still observed. This is because there is potential overlap between the semiquantitative uptake values obtained for active inflammatory lesions and cancer. Therefore, this prospective study was undertaken to test the hypothesis that analysis of dynamic kinetics of focal pancreatic lesions based on FDG PET may more accurately determine the benign or malignant nature of such lesions. Thirty patients (56±17 years) were studied dynamically with FDG PET for a period of 60–90 min. Patients were assigned to one of four groups: control, acute pancreatitis, chronic pancreatitis or pancreatic cancer. Two observers, blinded to the clinical data, analysed the time-activity curves of FDG kinetics based on region of interest analysis. The diagnosis predicted by FDG PET was compared with the result of histological examination of the surgical specimen. Analysis of FDG kinetics revealed significant differences in the shape of the time-activity curve for controls, pancreatic cancer and inflammatory disease. Surprisingly, there was no significant difference in the time-activity curve shape for chronic pancreatitis and acute pancreatitis; this is, however, not a clinical issue. Furthermore, acquisition time (60 min vs 90 min) did not affect interpretation of the time-activity curve, so that scanning time may be regularly shortened to 60 min. Interobserver agreement was 1. Based on these findings, non-invasive differentiation between pancreatic cancer and chronic pancreatitis was correctly predicted in all cases, as confirmed by histology. In addition, the specificity was increased compared with that obtained from standardised uptake value analysis. Non-invasive differentiation between pancreatic cancer and chronic pancreatitis may best be achieved based on a dynamic FDG PET study including kinetic analysis. This approach yields results superior to those obtained from a semiquantitative analysis of pancreatic lesions.

Keywords: FDG – Positron emission tomography – Pancreas – Glucose metabolism – Kinetic analysis

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Introduction

Pancreatic cancer accounts for more than 24,000 estimated deaths per year in the United States [1]. This high mortality rate results from a poor outcome due mainly to the delay in diagnosis and staging because of the prolonged clinical non-appearance of symptoms. Furthermore, there is no adequate screening test for early diagnosis of pancreatic cancer. In addition, except for patients suffering from hereditary pancreatitis, no high-risk group has been identified [2]. Thus, the majority of patients present with metastatic and/or locally advanced disease. In that stage of disease, CA 19-9 is usually markedly elevated. However, such elevation can also be observed in diseases other than cancer of the pancreas [3].

While morphological imaging of the pancreas has made substantial progress [4], some problems remain unresolved. For example, the differentiation between chronic inflammation, either focal or diffuse, and cancer is uncertain. On the other hand, a negative fine-needle

biopsy result does not rule out cancer. Furthermore, a patient presenting with elevated CA 19-9 levels and yet normally depicted morphology of the pancreas on ultrasound and/or computed tomography may have a small cancer lesion which remains undetected until symptoms occur [5].

Since there is no non-invasive and highly sensitive test that can be employed for the early diagnosis of pancreatic cancer, attempts have been made to evaluate positron emission tomography (PET) using the fluorine-18 labelled glucose analogue 2-deoxy-D-glucose (FDG). The rationale for the use of FDG in tumour detection is that glycolysis is increased in tumour cells. This phenomenon was first noted by Warburg [6, 7]. At the molecular level, it is explained by an increased expression of the structural gene encoding the glucose transport protein, and elevated hexokinase activity [8, 9, 10]. Initial non-kinetic studies have shown that pancreatic cancer can be successfully imaged using FDG PET. Furthermore, semiquantitative uptake value (SUV) results have indicated that the method provides additional information for differentiation between chronic pancreatitis and pancreatic cancer [11, 12, 13, 14]. However, transfer of this approach to clinical routine has resulted in some misdiagnoses. A reason for this is presumably that there is potential overlap between SUVs obtained for reactivated chronic inflammatory lesions and those obtained in cases of highly differentiated cancer. Therefore, this study was undertaken to test the hypothesis that a simplified kinetic analysis of focal pancreatic lesions based on FDG PET may more accurately predict the benign or malignant nature of such lesions.

Materials and methods

Patients. Between September 1996 and August 1999, 30 non-diabetic patients (25 presenting with a pancreatic mass, 5 controls; 10 women, 20 men; age 56±17 years) referred for clinically indicated PET imaging were entered in this prospective study, which was approved by the Institutional Review Board. All patients gave their written informed consent. Patients were assigned by the referring clinician to the control group (CON, *n*=5), the acute pancreatitis group (AP, *n*=3), the chronic pancreatitis group (CP, *n*=11) or the pancreatic cancer group (PC, *n*=11). Patient data are listed in Table 1. All patients underwent a fasting period of 12 h. Serum glucose (normal ≤6.1 mmol/l) was measured prior to FDG injection. The two PET observers were blinded to the clinical information. None of the controls had prior pancreatic disease as assessed by the patient's history, blood cell count, amylase, lipase, γ-glutamyltransferase and alkaline phosphatase.

Radiopharmaceutical. Patients were injected with 370 MBq FDG over 30 s into a peripheral vein while acquisition of the serial transaxial tomographic images was started. The tracer was synthesised and produced as previously reported [15].

PET imaging. After obtaining a 30-min blank scan and a 20-min transmission image for photon attenuation correction, FDG images were acquired on a Siemens/CTI ECAT Exact 921/31 tomograph. The device records 31 image planes simultaneously. The axial field of view is 10.8 cm. Ultrasound guidance was used for correct position of the pancreas in the tomographic field of view. All subjects were imaged in the supine position.

For acquisition, a 90-min and a 60-min protocol were used, the latter in order to answer the question of whether shortening of acquisition time may also permit non-invasive differentiation between pancreatic cancer and chronic pancreatitis. The protocol included twelve 10-s, four 30-s, sixteen 60-s, five 300-s, three 600-s (for 90 min imaging only) and one 900-s frame. Cross-sectional images for all studies were reconstructed employing a Hann filter with a cut-off of 0.4 of the Nyquist frequency, yielding an in-plane spatial resolution at the centre of the plane of about 8 mm full-width at half-maximum. In addition, images were reconstructed iteratively based on maximum likelihood (ML) reconstruction for emission tomography and expectation maximisation (EM) reconstruction algorithms for emission and transmission tomography [16, 17]. Furthermore, accelerated image reconstruction using ordered subsets (OS) of projection data was used [18]. In brief, 12 subsets and six iterations were used for the OSEM reconstruction.

Data analysis. PET images were analysed by visual interpretation and SUV analysis [19]. Furthermore, a kinetic analysis was performed. The latter was based on irregular regions of interest (ROIs) which were drawn over the normal pancreas or pancreatic lesions on the last acquired image corresponding to time 45–60 min or 75–90 min post injection. To avoid operator dependence, appropriate placement of each ROI was assured by a consensus of the two blinded PET investigators. These ROIs were then copied to the dynamic image set to generate pancreatic tissue time-activity curves (average counts/pixel per second). For standardisation, the curves were normalised for blood pool and the curve peak was set to 1. By dividing the tissue time-activity curve by the blood pool time-activity curve, decay was dropped out.

Table 1. Patient data

Category	CON	AP	CP	PC
Pancreatic mass size (cm)	n.d.	7.3±1.1	3.3±0.75	3.2±1.85
α-Amylase (N ≤120 U/l)	40.5±20.3	50.9±66.5	117±103	80.4±46.6
Lipase (N ≤190 U/l)	85.2±16.3	147±127.3	157.5±207.7	65.2±57.8
C-reactive protein (N <5 mg/l)	1.2±0.4	19.1±5.2	4.1±2.0	7.1±8.9
Leucocytes (N 3,800–10,500/µl)	5,400±1,200	13,100±2,400	9,100±3,200	9,400±3,400
Ca 19-9 (N ≤37 U/ml)	9±11	n.d.	79.8±115.5	262±374

N, Normal; n.d., not done

Diagnostic criteria applied for kinetic analysis. All time-activity curves were subdivided into three theoretical phases according to the time-dependent biological phenomena of FDG delivery into pancreatic tissue. Phase I is characterised by FDG influx based on regional perfusion, capillary extraction and diffusion via third space to the cell membrane including initial glucose carrier transport (rapidly increasing slope to curve peak for all conditions). After the peak, the FDG concentration decreases via venous drainage (phase II, rapid decrease in CON and AP, but moderate and limited decrease in CP and PC). In the final phase, FDG is transported continuously into the cells via glucose transporter 1 and phosphorylation, and consequently there is a continuous increase in the intracellular concentration of FDG-6-phosphate, which, in the case of cancer, will result in a glycolysis plateau curve (phase III, continuously rising slope for PC in contrast to continuously decreasing slope for the other conditions). The rationale for applying these time-activity curve characteristics is supported by results of a Northern blot analysis which showed intense Glut-1 expression in PC patients but not in patients with mass-forming pancreatitis [20].

Histological confirmation. Diagnosis of CP, AP and PC was histologically proven following laparotomy by a specialised pathologist. Because fine-needle biopsy of the pancreas in subjects without signs and symptoms of a disease of the pancreas was found to be unjustified, the sum of normal laboratory test results and imaging results served as the criterion for the definition of normal.

Statistical analysis. Results are expressed as mean values ± standard deviation (SD). The paired *t* test was used for the comparison of SUVs derived from individual patient images reconstructed based upon filtered back-projection and iterative reconstruction. A *P* value of less than 0.05 was considered significant. Interobserver agreement was calculated with the use of the kappa statistic [21], along with 95% confidence intervals, for the non-invasive differentiation between a potentially malignant and a benign lesion of the pancreas. The kappa statistic is a measure of agreement of two observers with respect to a categorical variable. A kappa of 1 represents perfect agreement, while a kappa of 0 indicates just chance agreement.

Results

Phase characterisation of the time-activity curves

The hypothesised phase characterisation of the time-activity curve shape was in fact observed for the various conditions (Fig. 1).

Normal pancreas

All controls were correctly identified by the two observers based on visual interpretation, SUV analysis (1.9±0.4) and kinetic analysis.

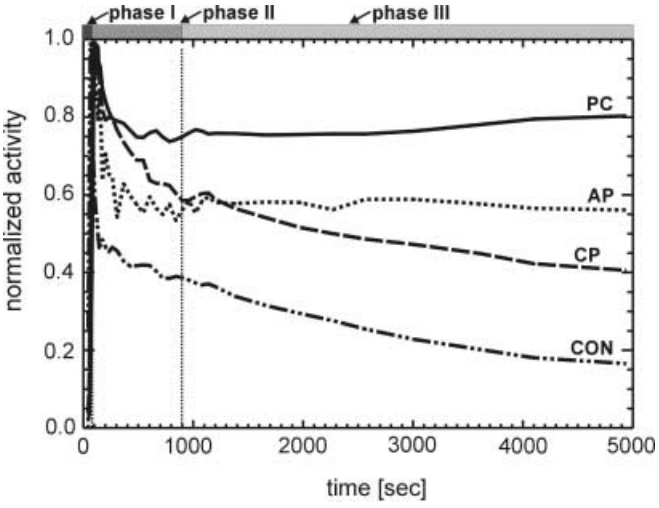

Fig. 1. Phase characterisation of the time-activity curve shape for different pancreatic diseases and controls. Each time-activity curve represents the mean of all patients studied for the respective category. There is a continuously rising slope for pancreatic cancer (PC) in phase III of the time-activity curve. In contrast, the non-malignant conditions (CON, CP, AP) present a continuously decreasing slope in phase III. While there is potential overlap in the shape of the time-activity curve for the considered conditions in phases I and II, phase III shows a characteristic curve pattern (continuously rising slope) in cases of cancer. Therefore, differentiation based on dynamic FDG PET imaging may greatly assist in the differential diagnosis between cancer and inflammation of the pancreas. The slopes for phase III are –0.25±0.01 per hour for CON, –0.355±0.004 per hour for CP, –0.09±0.01 per hour for AP and 0.01±0.04 per hour for PC

Acute pancreatitis

The three patients were misdiagnosed by both observers based on visual inspection (showing focally increased FDG uptake, Fig. 2) and SUV analysis (5.2±2.1), but were correctly classified for non-malignant disease by kinetic analysis.

Chronic pancreatitis

Both observers correctly identified all 11 patients by kinetic analysis. However, visual inspection (showing focally increased FDG uptake, which occurs in cancer, too) and SUV analysis (3.5±0.4) were not conclusive for either observer in two patients (SUV 4.0 and 3.9) because the semiquantitative criterion for CP is an SUV between 3.0 and 3.9 at 90 min post injection, as previously established [22].

Pancreatic cancer

Kinetic analysis enabled correct identification in all 11 patients by both observers. Furthermore, combined

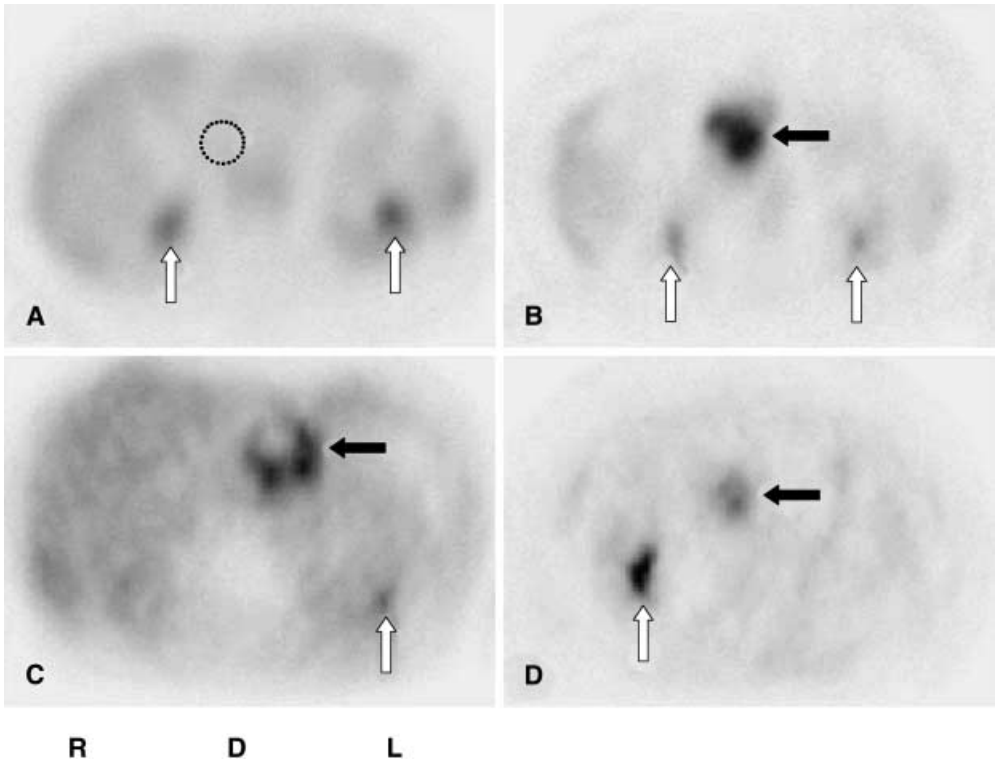

Fig. 2A–D. Representative transaxial iterative images at the level of the head of the pancreas for the four conditions studied. Despite the renal elimination of FDG with its inherent illustration of the renal pelvis and collecting system (*white arrows*), there is unremarkable FDG uptake in the region (*dotted circle*) of the pancreas for CON (**A**). In contrast, PC (**B**), AP (**C**) and CP (**D**) all present with moderate to intense focal increase in FDG uptake (*black arrows*). Therefore, it is not possible to reliably separate these conditions by visual interpretation in a clinical setting

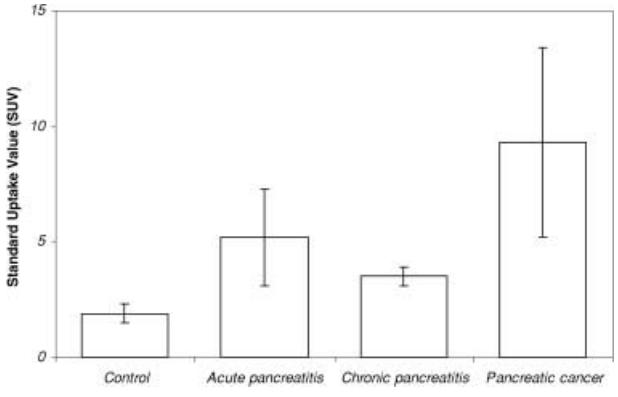

Fig. 3. Results of the SUV (mean±1SD) analysis. SUVs are corrected for body weight, since the accuracy of SUV analysis was not improved by correction for blood glucose or tumour size or by normalisation for body surface area or lean body weight [23]. There is potential overlap of SUVs between acute pancreatitis, chronic pancreatitis and pancreatic cancer. In a clinical setting, this means that an acute inflammatory episode in a case of chronic pancreatitis can be misdiagnosed as pancreatic cancer based on visual interpretation and SUV analysis

visual interpretation and SUV analysis (9.3±4.1) by both observers also rendered a correct diagnosis of cancer.

Interobserver agreement

The overall interobserver agreement for the kinetic analysis was 1 (perfect agreement).

Table 2. Comparison of SUV results obtained with iterative (it) reconstruction and filtered back-projection (fbp)

Category	No.	SUV (it)	SUV (fbp)	*P*
CON	5	1.90±0.4	1.85±0.35	0.3
AP	3	5.20±2.1	5.24±2.18	0.7
CP	11	3.50±0.4	3.55±0.52	1.0
PC	11	9.30±4.1	9.42±5.05	0.1

SUV analysis

The results of the SUV analysis are presented in Fig. 3. Comparison of the SUV results obtained from images reconstructed iteratively and by filtered back-projection is shown in Table 2. No significant differences were observed (*P*=NS).

Imaging time

In terms of differential diagnostic poerformance, no differences were observed between kinetic analysis for 60 min acquisition time and that for 90 min acquisition time

Histological analysis

Histological examination revealed acute pancreatitis in three of three patients, chronic pancreatitis in 11 of 11 patients and pancreatic cancer in 11 of 11 patients.

Discussion

The results of this study indicate that a simplified kinetic analysis of focal lesions of the pancreas based on FDG PET may predict the benign or malignant nature of such lesions more accurately than does an SUV analysis. Furthermore, there is potential overlap in SUVs between acute pancreatitis, chronic pancreatitis and pancreatic cancer, which is an important finding in the light of recent studies [11, 12, 13, 14]. In a clinical setting, this means that, based on visual interpretation and SUV analysis of FDG PET, an acute inflammatory episode in the case of chronic pancreatitis may be misdiagnosed as pancreatic cancer or highly differentiated pancreatic cancer may be misinterpreted as chronic pancreatitis.

Study limitations

One limitation of this study is that only 30 patients were included; therefore, the statistical relevance of the results reported is limited. Another shortcoming is that diabetic patients were not included. Whether kinetic FDG PET imaging of the pancreas for non-invasive differentiation between benign and malignant lesions of the pancreas is useful in diabetic patients remains undetermined. A major contributor to data heterogeneity is the operator dependence of the ROI analysis. For this reason, the regions were drawn by consensus of the two observers prior to further analysis.

Combined visual image interpretation and SUV analysis versus kinetic analysis of FDG PET

In a blinded scenario, the observers misdiagnosed acute pancreatitis as pancreatic cancer in all cases. While the diagnosis of acute pancreatitis does not depend clinically on FDG PET, this phenomenon nevertheless requires attention in a clinical setting, because an acute episode of chronic pancreatitis may mimic cancer. There is evidence from the results derived from this study that application of dynamic PET imaging, including a kinetic analysis, may help to overcome the commonly observed problem in static imaging – cancer or inflammation?

A potential disadvantage of dynamic PET imaging is that it is time-consuming compared with static PET imaging. However, the results of this study imply that dynamic imaging may be shortened at least to 1 h. Looking at patient throughput, there is evidence from our laboratory that about 60 of 1,100 patients who present for FDG PET imaging each year do so for non-invasive differentiation of a pancreatic mass. Since a negative fine-needle biopsy result does not rule out cancer, PET may yield important additional information. If cancer is ruled out, unnecessary surgery may be prevented. On the other hand, the clinical presentation of pancreatic cancer sometimes resembles chronic pancreatitis; if a cancer diagnosis is then established by PET, the indication for surgery is supported. A somewhat simpler but also time-consuming approach using delayed imaging after 1, 2 and 3 h, SUV analysis and calculation of a retention index (RI) was recently reported by Nakamoto et al. [13]. They observed a higher RI for PC than for CP. However, they described both positive RIs (i.e. a positive slope) and negative RIs (i.e. a negative slope) for PC and CP. In contrast, our results indicate a negative slope for CP but a positive slope for PC. There are several possible reasons for such contradictory findings, including calculation of slope versus RI, the respective time periods considered, use of framing rate versus three static images for calculation, and normalisation to blood pool, performed in this study. Finally, the report by Nakamoto et al. does not contain a reference to the use of an image re-alignment method to overcome the problem of malposition between transmission images and serial delayed static emission images. Image misalignment may have introduced substantial bias in their data, and thereby also contributed to the observation of positive and negative RIs in both CP and PC.

Iterative versus filtered back-projection image reconstruction

At present, iterative image reconstruction is considered to be the standard reconstruction method for oncological PET studies. However, results obtained from kinetic studies in the past have relied on reconstructed images using filtered back-projection. The results of this study indicate that there was no significant difference between iterative and filtered back-projection image reconstruction, at least concerning the SUVs. Whether iteratively reconstructed images may be used to calculate rate constants of biological phenomena based on kinetic modelling remains unanswered by this study.

Alternative radiopharmaceuticals

Results from a recent experimental study indicate that 5-[^{18}F]fluoro-2′-deoxyuridine may offer some potential for assessment of proliferation in vivo in pancreatic cancer [24]. However, both the agent and results from its clinical use are unavailable.

Study implications

The results of this study provide evidence that diagnosis of pancreatic cancer using the proposed dynamic FDG PET approach will in all probability represent a true-positive finding, permitting more aggressive planning of surgery or multimodal therapy.

Conclusion

It is concluded that a kinetic analysis of focal pancreatic lesions based on FDG PET may more accurately predict the benign or malignant nature of such lesions.

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