CURRENT TREND

Role and limitations of $^{18}$F-FDG positron emission tomography (PET) in the management of patients with pancreatic lesions

Intérêt et limites de la tomographie par émission de positons au $^{18}$F-FDG couplée au scanner dans la prise en charge des patients atteints de tumeurs du pancréas

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Available online 4 August 2010

Summary

The $^{18}$-fluorine-$^{18}$-fluoro-2-deoxyglucose Positron Emission Tomography coupled with computed tomography is a non invasive exploration. Several studies have shown that PET-CT has superior efficacy over conventional imaging techniques in distinguishing a benign pancreatic tumor from a malignant one. It contributes to the diagnosis of cancer in patients with a doubtful mass, much more in case of chronic pancreatitis. PET-CT is also an important help for the diagnosis of cystic tumors of the pancreas; the results can affect the management strategy. It is interesting for the endocrine tumors, particularly since the emergence of new markers. The aim of this paper is to summarize the role and limitations of $^{18}$F-FDG PET-CT in the management of patients with pancreatic lesions (adenocarcinoma, cystic tumors, endocrine tumors, etc.) concerning the malignancy diagnosis, the detection of metastases, the monitoring after non surgical treatments and to evaluate interpretation difficulties, particularly in case of diabetes or chronic pancreatitis.

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Abbreviations

$^{18}$F-FDG PET fluorine-$^{18}$-fluoro-2-deoxyglucose positron emission tomography
PET positron emission tomography
CT computed tomography
CA 72-4 carbohydrate antigen 72-4
CEA carcinoembryonic antigen

18F-FDG PET is an imaging technique that detects tumor metabolism. Coupled with CT, the technique can provide complementar

Table 1 Comparative diagnostic performances with positron emission tomography (PET) and computed tomography (CT).

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>PET-CT (%)</th>
<th>CT (%)</th>
<th>P</th>
<th>PET alone (%)</th>
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<td>59</td>
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<td>Se 93</td>
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<td></td>
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<td>Sp 69</td>
<td>Sp 21</td>
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<tr>
<td>Casneuf et al. [12]</td>
<td>46</td>
<td>A 91.2</td>
<td>A 88.2</td>
<td></td>
<td>A 82.3</td>
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<tr>
<td>Saïf et al. [13]</td>
<td>12</td>
<td>A 94</td>
<td>A 75</td>
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<tr>
<td>Wakasabayashi et al. [14]</td>
<td>53</td>
<td>Se 92.5</td>
<td>Se 88.7</td>
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Se: sensitivity; Sp: specificity; A: diagnostic accuracy.

Introduction

18F-FDG PET is a scintigraphy technique based on the detection of hypermetabolic lesions, particularly neoplasms. Coupled with CT, the technique can provide complementar

Fundamental principles of positron emission tomography—computed tomography

18F-FDG PET is an imaging technique that detects tumor cells that exhibit an excess consumption of glucose. Uptake of the glucose derivative (deoxyglucose) radiolabelled with 18F, a positron emitter, indicates the hypermetabolism of neoplastic cells. Glycolysis in these cells is exaggerated due to their increased capacity for membrane transporta-

Pancreatic adenocarcinoma

Diagnosis of the primary tumor

In 2005, Heinrich et al. [11] showed that, in 59 patients presenting with 46 histologically proven cancers (43 adenocarcinomas), the sensitivity of PET–CT was the same as for CT (89% versus 93%, respectively; p = 0.69),
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but had superior specificity that did not reach significance for the diagnosis of cancer (69% versus 21%, respectively; P=0.07). In another series of 46 patients [12], PET–CT exhibited superior diagnostic accuracy over PET alone for pancreatic adenocarcinoma, but was equal to CT (91.2% for PET–CT, 88.2% for CT and 82.3% for PET alone). On the other hand, others have concluded that PET–CT is superior. For Saif et al. [13], PET–CT gave a better diagnostic yield than CT (94–75%), but this was a small series of only 12 patients. Wakasabayashi et al. [14] supported this finding, reporting on 53 patients with pancreatic cancer, including 30 who had histological proof (sensitivity of PET–CT and CT was 92.5 and 88.7%, respectively). However, the diagnostic performance of CT differs, depending on the technique employed (multiple-array scan, thin slices). The results of these studies are summarized in Table 1. In the light of these findings, it can be concluded that PET–CT is not indispensable for characterizing these tumors except where there remains some doubt over the diagnosis after conventional imaging.

Evaluation of locoregional vascular and nodal extension

The search for locoregional extension is essential for determining tumor resectability. In a 2006 meta-analysis by Bipat et al. [15], the sensitivity and specificity of spiral CT observed in the 68 reports analyzed was 81 and 82%, respectively, for identifying locoregional nodal and vascular extension. Yet, according to Wakasabayashi et al. [14], the sensitivity of CT and PET–CT in the assessment of vascular extension was 100 and 22.2%, respectively, whereas, for locoregional nodal invasion, it was 78.6 and 54.1%, respectively. Thus, CT is better than PET–CT, and remains the gold standard in the search for locoregional vascular and nodal extension.

Detection of distant metastases

One of the primary uses for whole-body exploration is to detect secondary localizations of malignant tumors, particularly colorectal tumors. For potentially resectable pancreatic adenocarcinoma, PET–CT can enable identification of other synchronous pancreatic tumors, PET–CT can enable identification of particularly colorectal tumors. For potentially resectable tumors may also be detected, thereby affecting the therapy. Involving large cohorts have confirmed these data (PET–CT: sensitivity, 70–80%; specificity, 90–95%).

In the detection of peritoneal metastases, PET–CT sensitivity was lower than for liver metastases but in other cancers at 25 to 43%, depending on the series [14,18], while CT also exhibited low sensitivity (57%) [14]. Lesions missed measured less than 1 cm, so there is a size threshold below which an invasive technique is needed for detection.

This suggests that PET–CT may be contributory to the search for adenocarcinoma extension, as the results can affect the management strategy in 16% of patients due to the discovery of occult metastases [11]. Nevertheless, according to the thesaurus of the French National Society of Digestive Cancer [19], PET–CT protocols still need to be validated, as the sensitivity remains insufficient for small metastases and peritoneal carcinomatosis.

Prognostic value of positron emission tomography—computed tomography

SUV, used for semiquantitative analyses of PET–CT results, can be calculated for a defined zone of the pancreatic parenchyma. However, the measure is limited in its reproducibility and is highly variable from one study to another. PET–CT images can also be interpreted visually by comparing the zone of uptake under study (tumor) with adjacent organs used as the reference.

SUVmax is an arbitrarily set threshold beyond which tracer uptake is considered pathological. In the above-mentioned studies, SUVmax was set within a range from 2.5 to 12. In 2003, Sperti et al. [2] evaluated 60 patients who had undergone PET–CT as part of their preoperative work-up for pancreatic cancer. Their median SUV was 4.0. Two groups were determined: those with an SUV greater than 4.0 and those with a SUV less or equal to 4.0. The two groups were comparable for age, gender, degree of diabetes, tumor stage, CA 19-9 level, histological grade and type of treatment. On multivariate analyses, tumor stage and SUV were found to be independent factors predictive of survival. At 1 year, none of the patients with a SUV greater than 4.0 had survived, whereas 75% of those with a SUV less or equal to 4.0 were still alive.

Another study [20] set the cutoff point at 3.0 (median SUV) and found an important difference in survival duration between the two groups (14 versus 5 months). The authors concluded that SUV was not an independent prognostic factor for survival except in patients with nonresectable tumors [21]. This suggests that the SUV may be a survival factor that is not directly correlated with tumor stage, yet expressing the metabolic activity of tumors and possibly their aggressiveness.

Tumor monitoring after treatment: role of positron emission tomography—computed tomography

The contribution of PET after neoadjuvant treatment for esophageal cancer has been investigated, although the response to neoadjuvant chemotherapy is difficult to assess because of the tissue remodeling induced by such treatments. It has been reported that patients considered to have a complete response on the basis of conventional imaging have, in fact, residual lesions in 30 to 50% of cases when the esophagus is systematically resected [22]. One study
focused on the usefulness of PET in this context. SUV was measured before and after neoadjuvant chemotheraphy, and was shown to decline significantly more in responders than in nonresponders (72% versus 42%, respectively) [23]. On the other hand, sensitivity was too low (63%) to serve as the basis of a surgical decision after neoadjuvant treatment solely with this exploratory technique [24]. Also, for pancreatic adenocarcinoma, response to radiochemotherapy is difficult to assess with CT because of remodeling. However, when PET was assessed in this context, there was a correlation between the variations observed in the SUV before and after radiochemotherapy and tumor necrosis. Rose et al. [25] observed four cases of decreased PET–CT uptake among nine patients given radiochemotherapy who had no signs of tumor regression on CT, thus allowing subsequent surgical resection. In another study [16], PET–CT visualized signs of tumor regression on CT, thus allowing subsequent carcinoid and six controls. Histology was available for all patients with chronic pancreatitis, three with acute pancreatitis, 27 with adenocarcinoma and six controls. Histology was available for all patients except the controls. A cutoff point was determined for each condition. For the cancers, the SUV was greater than 4.0, whereas it was 3.0 to 4.0 for chronic pancreatitis and less than 3.0 for the controls. Using these cutoffs, the sensitivity and specificity of PET–CT for the diagnosis of adenocarcinoma were 96 and 100%, respectively, and for chronic pancreatitis, 10 and 97%, respectively.

For Friess et al. [6] and Zimny et al. [31], chronic pancreatitis did not appear to be a major source of false-positive PET–CT findings. The SUV was less than for carcinoma (3.09 versus 0.87). However, in the event of complications (such as bleeding pseudocyst or nasobiliary drainage), focal uptakes can hinder interpretation [6].

Van Kouwen et al. [5] compared the PET–CT results in three groups of patients: chronic pancreatitis alone (n = 77); adenocarcinoma with chronic pancreatitis (n = 6); and adenocarcinoma without associated chronic pancreatitis (n = 26). They found that 83% of the patients in the second group and 92% in the third group exhibited pathological uptakes versus only 13% in the first group (chronic pancreatitis alone). This suggests that PET–CT can contribute to the diagnosis of adenocarcinoma in chronic pancreatitis, as the SUV can disclose different degrees of tracer uptake.

Autoimmune pancreatitis

As autoimmune pancreatitis can also simulate cancer, particularly localized forms, the diagnosis requires a combination of clinical, biological (elevated serum IgG4) and imaging evaluations. Also, should any diagnostic doubt persist, Lévy et al. [32] suggest that a corticosteroid therapeutic test over at least 4 weeks would be less deleterious than surgical resection or chemotherapy erroneously delivered to a patient with autoimmune pancreatitis. Indeed, strong, sometimes diffuse, uptakes can be observed on the PET–CT scans of patients with autoimmune pancreatitis, leading to potential confusion with cancer. The 18F-FDG uptake pattern is, however, somewhat different in cancer compared with autoimmune pancreatitis. In cancer, there is a heterogeneous pattern of uptake appearing as nodular and unique foci whereas, in autoimmune pancreatitis, the pattern is more homogeneous, with multifocal longitudinal uptakes (Fig. 1) [33].

PET–CT can also be used to localize extrapancreatic involvement and to assess objective responses to corticosteroids (a supplementary argument for ruling out cancer). Nakajo et al. [34] observed a decreased SUV or total absence of uptake on PET–CT after corticosteroid treatment in six patients.

Cystic tumors (mucinous and serous cystadenoma, cystadenocarcinoma, IPMNP)

For apparently benign cystic tumors suggestive of mucinous cystadenoma or IPMNP, it is important to identify imaging features that argue either for or against surgery—in particular, cyst size or ductal dilatation, or the presence of peritumoral anomalies or a mass. Sperti et al. have published several studies of the role of PET–CT in these indications. In 2001 [35], their series included 56 patients with cystic lesions of the pancreas, including 17 malignant lesions (eight
PET and pancreatic tumors

Figure 1 Images showing: (A, B) pancreatic cancer, with nodular and unique heterogeneous uptakes; and (C, D) autoimmune pancreatitis, with longitudinal and multiple homogeneous uptakes.

Images kindly provided by Dr Y. Ozaki, Department of Medicine, Gastroenterology, Shinshu University School of Medicine, Matsumoto, Japan.

cystadenocarcinoma, five adenocarcinoma, two endocrine carcinoma, one pseudopapillary and solid tumor, and one degenerated IPMNP) and 39 benign lesions (11 serous cystadenoma, eight pseudocysts, six mucinous cystadenoma, two cysts, eight IPMNP and four ‘others’). The authors noted pathological tracer uptakes on the PET–CT of 16/17 patients with degenerated benign cysts, although malignancy was suspected in only 12 on the basis of CT and elevated serum CA 19-9. Also, there was one false positive—pathological uptake in a patient with benign mucinous cystadenoma. In all, the sensitivity and specificity of PET–CT in the diagnosis of malignancy were 94 and 97%, respectively, while the rates of conventional imaging were 65 and 87%, respectively.

In 2005, the same authors published a series of 50 patients with benign lesions of the pancreas [1]. There were two false positives with PET–CT and four with CT. In 2007, they published a series of 64 patients [36] with IPMNP, all of whom had undergone CT, cholangiopancreatic MRI and PET–CT, all of whom had histological proof. Of the 26 patients with malignant IPMNP, 24 exhibited pathological uptakes, including 21 with infiltrating carcinoma and four with carcinoma in situ, while signs of malignancy were found on either the CT or MRI studies of only 15 of these patients. Uptake was observed in none of the PET–CT explorations in patients with benign tumor, nor in seven of the eight patients with borderline tumors. In contrast, conventional imaging misclassified four of 30 benign tumors and three of eight borderline tumors as malignant. In this series, the sensitivity, specificity, positive predictive value and negative predictive value of PET–CT in the diagnosis of malignancy were 92, 95, 96 and 91%, respectively, compared with 58, 81, 79 and 61%, respectively, for conventional imaging (CT and/or MRI). Fig. 2 shows the pathological uptake on PET–CT in a patient with malignant IPMNP.

In addition, PET–CT correctly identified all benign and malignant tumors (no false positives, no false negatives) in a different series of 28 patients with IPMNP [37].

The problem with cystic tumors is to identify malignancy preoperatively, thus allowing surgery before symptom onset in patients who have none of the classical criteria for resection (IPMNP of the secondary ducts, small-size cystic lesions) and whose conventional imaging findings are not particularly suggestive of malignancy. In addition, the decision of what type of resection is appropriate for IPMNP would theoretically depend on the detection of noncontiguous uptake foci on PET–CT. Thus, PET–CT appears to be a high-performance tool for the diagnosis of malignant cystic tumors of the pancreas.

However, in 2006, Mansour et al. [4] published different conclusions. Their series included 68 patients with cystic lesions of the pancreas, including seven malignant tumors (five cystadenoma, two degenerated IPMNP). The authors found that, in the diagnosis of malignancy, the sensitivity and specificity of PET–CT were 57 and 85%, respectively,
Figure 2  Example of a pathological positron emission tomography–computed tomography showing intraductal papillary mucinous neoplasm of the pancreas (IPMN) in the head and tail.
leading to their conclusion that this exploration is not indispensable in the preoperative work-up of cystic tumors of the pancreas, despite the small number of malignant tumors in this series (n = 7 versus 26 in the study by Sperti et al. [36]). The results of all these studies are summarized in Table 2.

Nevertheless, PET–CT can be more sensitive and more specific than conventional imaging, and can potentially contribute to therapeutic decision-making where there is doubt concerning the appropriate treatment or in cases of highly suspected malignancy. At present, however, the use of PET–CT cannot be recommended systematically, but still has to be discussed on a case-by-case basis while awaiting the publication of prospective multicenter data. For this reason, a study within the framework of the Club français du pancréas (French Pancreas Club) has been initiated with the objective of evaluating the usefulness of PET–CT in the preoperative evaluation of IPMNP degeneration.

### Pseudopapillary and solid tumors

For these rare tumors, the published data have come from a limited number of cases, thereby allowing no definitive conclusions to be drawn. Sato et al. [38] described two patients with pseudopapillary and solid tumors whose PET–CT visualized strong 18F-FDG uptakes. However, surgical resection performed in both patients and histopathology examination were unable to identify any evidence of malignancy.


However, these tumors are sometimes difficult to recognize when they are atypical. Although PET–CT can reveal pathological tracer uptake, it is not discriminating enough to make an accurate diagnosis of the type of pancreatic tumor preoperatively. Nevertheless, pathological uptake constitutes a supplementary argument in favor of surgery.

### Endocrine tumors

Endoscopic ultrasound remains the gold standard for endocrine tumors (75 to 100% sensitivity, 100% specificity) together with OctreoScan™ imaging, which can demonstrate the presence of 90% of pancreatic endocrine tumors measuring more than 2 cm [38]. The sensitivity of OctreoScan™ increases with histological differentiation and tumor size, but also depends on tumor type and localization. Sensitivity is 90% for pancreatic gastrinoma, but only 30% for insulinoma, and varies from 73 to 100% for all functional or nonfunctional endocrine tumors, yet is low for undifferentiated tumors [40,41]. The usefulness of PET differs in all of these situations.

### Poorly differentiated tumors

In 1998, Adams et al. [42] studied the performance of 18F-FDG PET–CT versus OctreoScan™ DTPA-octreotide scintigraphy in 15 patients with endocrine tumors, including seven tumors involving the gut and pancreas. They demonstrated that aggressive, poorly differentiated, tumors (high proliferation index) exhibit pathological uptakes on PET–CT while OctreoScan™ remains negative. The inverse was noted for well-differentiated tumors (low proliferation index). Thus, the performance of 18F-FDG PET–CT was inadequate for well-differentiated tumors because of the very slow tumor growth. It is, however, indicated for poorly differentiated tumors, where its use can replace OctreoScan™ [43].

PET–CT can also provide prognostic information, as suggested by Pasquali et al. [44], as uptake foci correspond to tumors exhibiting strong proliferative activity. There is, however, a detection limit set at 8 mm by Nakamoto et al. [45].

### Insulinoma

Evidence for the use of 18F-FDG PET–CT to detect insulinoma is insufficient at present, although the diagnostic performance so far appears to be low. Noninvasive explorations (ultrasound, CT, MRI) are contributory only for tumors measuring more than 15 mm. Endoscopic ultrasound is the gold standard, detecting tumors measuring less than 5 mm with good reliability [46].

Another technique, however, appears to have the potential to detect and localize insulinoma: 18F-DOPA PET (18F-fluorodihydroxyphenylalanine). This technique is based on the properties of endocrine tumors: ρ-DOPA uptake and decarboxylation. When the technique was assessed and

<table>
<thead>
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<th>Table 2</th>
<th>Diagnostic yields with positron emission tomography (PET), computed tomography (CT) and magnetic resonance imaging (MRI).</th>
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<tr>
<td></td>
<td>PET–CT</td>
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<tr>
<td></td>
<td>Sensitivity (%) Specitivity (%)</td>
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<tr>
<td>Sperti et al. [35]</td>
<td>56 cystic lesions 94 97</td>
</tr>
<tr>
<td>Sperti et al. [1]</td>
<td>50 cystic lesions 94.4 94.7</td>
</tr>
<tr>
<td>Sperti et al. [37]</td>
<td>64 TIPMP 92 95</td>
</tr>
<tr>
<td>Mansour et al. [4]</td>
<td>68 cystic lesions 57 85</td>
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</table>

In these studies, histology (the gold standard) was carried out on surgical, percutaneous needle biopsy or endoscopic cytology specimens, which was available for 55 patients in the first study, 35 patients in the second, 47 patients in the third and 47 patients in the fourth. The other patients presented with no signs of malignancy on conventional imaging and were followed-up with other imaging explorations.
compared with CT and MRI in 10 patients with organic hyperinsulinism [47], the sensitivity of 18F-DOPA PET was 90% for tumor localization versus 30% for CT and 40% for MRI.

However, PET—CT cannot be recommended for the assessment of all endocrine tumors of the pancreas. For undifferentiated tumors, it can contribute to the initial work-up and perhaps in monitoring the response to treatment. Nevertheless, PET—CT and 18F-DOPA PET appear to have potential for the work-up of insulinomas with high proliferation indices. According to Montravers et al. [48], PET—CT and 18F-DOPA PET can be expected to become first-line scintigraphic explorations for carcinoid tumors, with OctreoScan remaining the gold standard for noncarcinoid tumors.

**Positron emission tomography—computed tomography and diabetes**

As this technique is based on the metabolism of glucose, results may be erroneous in diabetics because endogenous glucose is in competition with the radioactive glucose analog, leading to potentially false-negative results. Also, it is necessary to measure blood glucose and correct it with insulin, if necessary, just before the exploration.

In 1998, Diederichs et al. [49] emphasized the importance of correct glucose control for interpreting preoperative PET—CT. In a study of 171 patients (100 cancer, 46 chronic pancreatitis and 25 benign pancreatic lesions), they examined the performance of PET—CT for characterizing lesions before surgery. Its sensitivity for detecting a malignant component was 83% in nondiabetics versus 69% in diabetics, and 86% in patients with blood glucose less or equal to 7.2 mmol/L versus 42% in those with blood glucose greater than 7.2 mmol/L.

**Cost of positron emission tomography—computed tomography**

Cost has to be taken into consideration because PET—CT has a reputation for being an expensive exploration. Heinrich et al. [11] investigated the issue in 2005 in a series of 59 patients. The cost per patient included: the initial tumor work-up; PET—CT; costs related to biopsies of secondary localizations detected with PET—CT; and costs related to surgery. Their analyses did not include the cost of palliative treatment for patients whose proposed surgery was ruled out after PET—CT; however, postsurgical patients sometimes receive adjuvant chemotherapy, which would have tended to balance out these two patient groups. Thus, extra costs were related to PET—CT and any related biopsies, whereas cost-savings were related to the surgical resections not performed after detection of metastases. The savings per patient was US$1066 if PET—CT was performed in all patients with a pancreatic tumor, and US$2844 if it was used only in patients with a tumor that was considered resectable at the initial work-up.

**Conclusion**

PET—CT is a noninvasive exploration that appears to be preoperatively relevant for patients with pancreatic tumors. It contributes to the diagnosis of cancer in patients with a doubtful tumor, and can help to detect tumor foci within pancreatic tissue remodeled by chronic pancreatitis. It is, on the other hand, of little use in the assessment of locoregional vascular and nodal extensions, for which CT remains the gold standard.

For cystic tumors, PET—CT can modify the management of one out of five patients, particularly those with precancerous lesions (IPMNP, mucinous cystadenoma). For this reason, a prospective multicenter study is being initiated by the French Pancreas Club with the objective of evaluating, in a large cohort, the contribution of preoperative PET—CT for patients with IPMNP.

PET—CT is a useful exploration for endocrine tumors with a high proliferation index (poorly differentiated or undifferentiated tumors), while 18F-DOPA PET performed better than OctreoScanTM in the detection of insulinoma. New tracers may further boost the performance of these types of exploration.

Although the cost of PET—CT is not negligible, the technique can still lead to savings by allowing modification of therapeutic strategies.

Finally, according to the 2006 recommendations for good clinical practices in France, PET—CT is ‘‘the gold standard for the preoperative assessment of pancreatic cancers’’ (level of proof B) and ‘‘pathological uptake of FDG is an indication for wide resection and the absence of uptake is in favor of a benign tumor which could be treated by limited resection or simple surveillance’’ [50]. Thus, PET—CT can be used within the framework of good medical practices in well-defined situations.

**Conflicts of interest statement**

Nicolas Regenet: study protocol, as main investigator, multicenter prospective study under the auspices of the Club français du pancréas; Claire Pery: same study protocol, principal author.

**References**


