18F-fluorodeoxyglucose positron emission tomography for characterization and initial staging of pancreatic tumors

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RÉSUMÉ
Objectifs — Étudier l’intérêt diagnostique et décisionnel de la tomodensitométrie par émission de positon (TEP) au (18F)fluorodeoxyglucose (FDG) dans l’évaluation initiale des tumeurs du pancréas.

Malades et méthodes — Les 24 malades atteints d’une tumeur pancréatique et qui ont eu une TEP avant tout traitement ont été inclus. Vingt-deux malades avaient une tumeur maligne et 2 une tumeur bénigne. Les TEP ont été réalisées après injection de FDG avec une gamma caméra conventionnelle double-tête. La référence était l’examen anatomopathologique biopsie ou exérèse de la tumeur (n = 24), des métastases hépatiques (n = 5), péritonéales (n = 5) ou ganglionnaires (n = 5). L’absence de métastases ou d’adénopathies malignes était jugée sur l’exploration chirurgicale ou estimée sur le résultat normal des autres examens morphologiques et sur l’évolution dans les deux mois.

Résultats — La sensibilité de la TEP pour le diagnostic de tumeur primitive pancréatique était de 64 % (intervalle de confiance à 95 % : 44 %-84 %). Pour les métastases ganglionnaires juxta-tumorales, la TEP n’était pas interprétable. Elle a reconnu des métastases hépatiques dans 3 cas sur 5 et des métastases péritonéales dans 4 cas sur 5, dont une fois de façon douteuse, mais il y avait deux faux positifs. Sur 4 tumeurs kystiques, les 2 tumeurs malignes fixaient le FDG et les 2 tumeurs bénignes ne le fixaient pas. La TEP a eu un intérêt décisionnel pour un seul des 24 malades.

Conclusions — La sensibilité de la TEP pour le diagnostic de tumeur pancréatique maligne est faible. L’intérêt décisionnel de la TEP au FDG paraît être surtout le dépistage de métastases ou d’adénopathies à distance de la tumeur, qui contre-indiquent une intervention. Néanmoins, la sensibilité de la TEP n’atteint pas celle de la laparoscopie pour les métastases péritonéales. La TEP au FDG doit donc être intégrée dans une réflexion critique concernant ses indications et une perspective décisionnelle.

SUMMARY
Aim — To evaluate positron emission tomography (PET) with 18F-fluorodeoxyglucose (FDG) for characterizing and initial staging of pancreatic tumors and to determine its impact on therapeutic strategy.

Patients and methods — This study included 24 patients with pancreatic tumor who underwent PET before treatment. Twenty-two patients had a malignant tumor and two had a benign tumor. The PET scan was performed after intravenous injection of FDG with a gamma camera. PET findings were compared with histology of the pancreatic tumor (n = 24), liver metastases (n = 5), peritoneal metastases (n = 5), and lymph node metastases (n = 5). Absence of metastasis or lymph node involvement was determined by surgery or by CT scan, ultrasonography, magnetic resonance imaging and at least two months follow-up.

Results — The sensitivity of the PET scans to identify pancreatic carcinoma was 64% (95% confidence interval 44-84%). PET scans could not be interpreted for lymph node involvement adjacent to the tumor. For liver metastases, the PET scan was positive in 3 out of 5 patients. For peritoneal metastases, the PET scan was positive in 4 out of 5 patients but was doubtful in one. There were two false positives. Among the 4 cystic tumors, the PET scan was positive for 2 malignant tumors and negative for 2 benign tumors. Surgical strategy was modified in only one of the 24 patients on the basis of PET findings.

Conclusion — The sensitivity of PET for the diagnosis of primary malignant pancreatic tumor was found to be low. The contribution of FDG-PET to the surgical decision appears to be limited to the detection of metastases or lymph node involvement distant from the tumor, contraindicating surgery. Nevertheless, the sensitivity of FDG-PET is lower than that of laparoscopy for peritoneal metastases. Indications for PET should be included in an evaluation of therapeutic decision making and cost analysis.

Positron emission tomography (PET) with 18F-fluorodeoxyglucose (FDG) is a functional exploration based on increased capacity for transmembrane glucose transportation, particularly Glut-1, and increased activity of glycolysis enzymes in tumor cells [1-3]. After entering the cell, FDG is metabolized by hexokinase into FDG-6-phosphate which cannot cross the cell membrane [4]. Positrons emitted by 18-fluorine labeled FDG trapped inside the more active tumor cells can then be visualized by tomography [5]. The first application in oncology was reported in 1987 for astrocytomas [6].

The few reports on PET-FDG in pancreas tumors have been reported by teams in Japan [7-10], Germany [11-15] and North America [16, 17]. Results have been somewhat discordant. In addition, few studies have attempted to assess the impact of results on decision making.

The purpose of the present work was to ascertain the diagnostic contribution of PET-FDG for pretherapeutic decision making in patients with pancreatic tumors.
Patients and methods

Patients

Between March 1998 and August 2001, we performed 33 PET-FDG explorations in patients with pancreatic tumors. We retained for analysis here the 24 patients who underwent PET scan prior to surgery (the 9 other explorations were performed for monitoring purposes after surgery). The preoperative diagnosis of pancreatic tumor was established on the basis of morphological evidence (ultrasound in 20 patients, and/or computed tomography (CT) in 15 patients, and/or endosonography (17 patients) and/or magnetic resonance imaging in 3 patients). During the study period, a PET was not performed for 19 patients with pancreatic tumors due to lack of availability (18FDG or camera). The study cohort included 15 men and 9 women, mean age 62 years (range, 20 – 78). Four patients had well-controlled type 2 diabetes, 8 had excessive alcohol intake, and 4 had chronic pancreatitis. The tumor was located in the cephalic area in 15 patients and in the body or tail in 9.

PET-FDG

PET-FDG was performed during the week preceding scheduled surgery. Patients were in a fasting state for at least six hours before the scan. 18FDG (2 to 3 MBq/kg) was injected intravenously via an antebra
chal venous line (saline solution) 45 to 60 before the PET scan. The patient rested in a reclining position until the exploration was completed and urinated after de-perfusion. A conventional double-head gamma camera equipped with an electronic detector of coincident photons with 19-mm detector crystals (Picke
r) was used. A whole body scan was acquired followed by one or more tomographic acquisitions centered on the upper half of the abdomen and suspected areas as needed. An iterative algorithm was used to reconstruct the images that were read by a nuclear medicine specialist experienced with the technique who was aware of the patient’s history and the results of other morphological explorations. Zones were considered pathological when exhibiting zones of excessive FDG uptake. The histology of the tumors and the therapeutic interventions are detailed in table I. Fourteen patients underwent subse
quent surgery. Surgery was not performed in 10 patients who had distant metastasis (liver, n = 5; peritoneum, n = 5; both, n = 1) or non-Hodgkin lymphoma (n = 1).

Reference diagnosis

A surgical or biopsy specimen was obtained in all cases to establish the pathological diagnosis. There were 22 malignant tumors and 2 benign tumors (table I). Liver (n = 5), peritoneal (n = 5), and lymph node (n = 5) metastases were confirmed at pathology. Thirteen patients were considered to be free of metastasis on the basis of the surgical exploration. A metastasis in the vicinity of the tumor because it was impossible to distinguish tumor uptake from satellite node uptake. One patient exhibited two uptake foci (figure 1) interpreted as a primary tumor and an metastasis (figure 2).

Table I. – Diagnosis and treatment in the 24 studied patients

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exocrine adenocarcinoma</td>
<td>17 (11)</td>
</tr>
<tr>
<td>Cystadenocarcinome</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Mucinous cystadenoma</td>
<td>2 (0)</td>
</tr>
<tr>
<td>Cholangiocarcinoma</td>
<td>1 (0)</td>
</tr>
<tr>
<td>Malignant neuroendocrine tumor</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Non-Hodgkin malignant lymphoma</td>
<td>1 (0)</td>
</tr>
<tr>
<td>Treatments</td>
<td></td>
</tr>
<tr>
<td>Resection</td>
<td>10</td>
</tr>
<tr>
<td>Palliative surgery</td>
<td>4</td>
</tr>
<tr>
<td>Laparoscopy and non-surgical palliative care</td>
<td>5</td>
</tr>
<tr>
<td>Non-surgical palliative care</td>
<td>5</td>
</tr>
</tbody>
</table>

Number of tumors exhibiting 18FDG uptake in parentheses.

Results

The ultrasound, CT, endoscopic ultrasound, and PET-FDG results are summarized in table II. The sensitivity of PET-FDG to detect primary malignant pancreatic tumors was 64% (95% confidence interval (CI95) : 44 – 84%), i.e. 14 out of 22 patients. Uptake in a primary tumor was doubtful in one patient. All tumors in this series measured more than 10 mm. 18FDG uptake was identified in 7 of the 9 malignant tumors measuring > 40 mm (67%) and in 7 of the 13 measuring > 40 mm (56%). Endoscopic ultrasonography was the most sensitive exploration (82% [CI95 : 64-100%]) but was not significantly different from PET-FDG (P = 0.3). Two of the 4 diabetic patients with cancer exhibited 18FDG uptake in the primary tumor. 18FDG uptake was also identified in two cystadenocarcinomas and was not found in two mucinous cystadenomas.

Results of the different explorations performed to search for nodal metastasis are presented in table III. PET-FDG results were considered to be non-contributive for nodal invasion in the vicinity of the tumor because it was impossible to distinguish tumor uptake from satellite node uptake. One patient exhibited two uptake foci (figure 1) interpreted as a primary tumor and an metastasis (figure 2).

Results of the explorations performed to search for hepatic and peritoneal metastases are presented in table IV. The PET scan demonstrated liver metastasis in 3 out of 5 patients. Ultrasound or CT scan had identified the metastasis in all 3 of these patients. For the 2 others, the liver metastases which had gone undetected by all the explorations methods used, measured 8 and 3 mm. For peritoneal metastases 18FDG uptake was certain in one patient who had clinically palpable metastases and doubtful in a second. Finally, peritoneal metastasis suspected on the PET scan in 2 patients was not confirmed at surgery. None of these peritoneal metastases had been identified by the other morphology explo
rations (ultrasound, CT, endoscopic ultrasound) even in the patient with clinically palpable metastases. Four of the 5 perito
neal localizations were however identified at laparoscopy, subsequently contraindicating the scheduled surgery. Finally, in

Table II. – Results of radiological studies and PET-FDG for the detection of the primary tumor.

<table>
<thead>
<tr>
<th>Exploration</th>
<th>Number of patients</th>
<th>Detection of primary tumor n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultrasound</td>
<td>20</td>
<td>13 (65)</td>
</tr>
<tr>
<td>Computed tomography</td>
<td>15</td>
<td>10 (67)</td>
</tr>
<tr>
<td>Endoscopic ultrasound</td>
<td>17</td>
<td>14 (82)</td>
</tr>
<tr>
<td>PET-FDG</td>
<td>24</td>
<td>14 n (64 %)</td>
</tr>
</tbody>
</table>

The percentage of detected primary tumors (in parentheses) indicates the sensitivity of each exploration method. * Including one doubtful. ** Sensitivity was calculated for 22 benign tumors, 95% confidence interval : 44%-84%.

one patient, PET-FDG suggested a spinal bone metastasis that was not confirmed by bone scintigraphy nor clinical evolution.

PET-FDG influenced decision making in only one of the 24 patients. In this patient, a subclavian metastasis that had not been identified at physical examination was recognized on the PET scan (figure 2). This patient had been scheduled for surgery to remove the pancreatic tumor, but the biopsy results demonstrated malignant non-Hodgkin lymphoma that was treated medically. 18FDG uptake was observed in 5 of the 8 primary tumors that were resected (62%) and in 9 of the 14 which were not resected (64%).

**DISCUSSION**

For clinical applications in patients with pancreatic disease, PET-FDG has been tested to determine its value for diagnostic (differentiation between malignant and benign pancreatic tumors), monitoring (tumor recurrence or response to chemotherapy), and prognostic purposes, but there has been little work on its contribution to decision making processes.

Our results, showing a 64% sensitivity of PET-FDG scans for detecting malignant tumors of the pancreas are rather disappointing compared with earlier reports showing a sensitivity of 90% [15, 16]. Two recent studies have however reported lower sensitivity, 71% [18] and 77% [19], more in line with our findings. One might speculate that the lower sensitivity found in our series could be related to the use of a non-dedicated camera, although there is no proof that this affects results. Indeed, there are few data on the comparative performance of different cameras used to detect pancreatic tumors. Martin et al. [19] used a dedicated camera which like our camera, was not equipped with an external source for attenuation correction, a method which provides better quantification and better anatomic precision. Unlike the other morphological explorations studied, PET-FDG results do not appear to depend on tumor size (for tumors measuring more than 1 cm) [13, 16, 20] because FDG uptake is essentially related to the number of glucose Gluc-1 transporters per tumor [8]. To achieve better sensitivity, quantitative studies have been conducted in order to establish a standard uptake value (SUV) for 18FDG [11, 12, 18] based on a threshold level set from ROC curves. As could be expected, these studies have shown that lowering the threshold of the SUV increases sensitivity but lowers specificity [16]. In fact, visual interpretation, as we used, has been found to be superior to SUV [21]. The other possible explanation of false negatives would be diabetes [12, 22], but diabetics without cancer can exhibit 18FDG uptake and non-diabetics do exhibit false negatives [11]. This was observed in 2 of our 4 diabetic patients. In one study using ROC curves and standard and corrected SUVs in diabetic patients, taking into account serum glucose level had so significant effect on either method of interpretation [17]. The important point is to perform the scan in patients who have been fasting for at least six hours, with well controlled glycemia for diabetic patients.

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**Table III.** Results of radiological studies and PET-FDG for the detection of metastatic lymph nodes in the 22 patients with malignant pancreatic tumor.

<table>
<thead>
<tr>
<th>Exploration</th>
<th>n</th>
<th>Invaded nodes (5 patients)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>True positives</td>
<td>False positives</td>
</tr>
<tr>
<td>Ultrasound</td>
<td>19</td>
<td>1</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Computed tomography</td>
<td>13</td>
<td>1</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Endoscopic ultrasound</td>
<td>15</td>
<td>2</td>
<td>0 (4)</td>
</tr>
<tr>
<td>PET-FDG</td>
<td>22</td>
<td>Non-contributive</td>
<td></td>
</tr>
</tbody>
</table>

The figures in parentheses indicate the number of patients who underwent the exploration and who had malignant nodes. * Uptake in the primary tumor could not be distinguished from uptake in satellite node. The only true positive concerned a subclavian node.

**Table IV.** Results of radiological studies and PET-FDG for the detection of liver and peritoneal metastases in the 22 patients with malignant pancreatic tumor.

<table>
<thead>
<tr>
<th>Explorations</th>
<th>n</th>
<th>Liver metastasis</th>
<th>Peritoneal metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>True positives</td>
<td>False positives</td>
</tr>
<tr>
<td>Ultrasound</td>
<td>19</td>
<td>2</td>
<td>0 (4)</td>
</tr>
<tr>
<td>To Computed tomography</td>
<td>13</td>
<td>3</td>
<td>0 (3)</td>
</tr>
<tr>
<td>Endoscopic ultrasound</td>
<td>15</td>
<td>1a</td>
<td>0</td>
</tr>
<tr>
<td>PET-FDG</td>
<td>22</td>
<td>3</td>
<td>2</td>
</tr>
</tbody>
</table>

The figures in parentheses indicate the number of patients who underwent the exploration and who had liver metastasis. * Doubtful diagnosis.

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**Fig. 1** – Carcinoma of the head of the pancreas (30 mm). PET scan shows two areas of FDG uptake. The largest area was the pancreatic tumor and the smaller one was found to be a pancreatic carcinoma on the surgical specimen.

**Fig. 2** – Pancreatic lymphoma. PET scan shows multiple areas of uptake in the abdomen and supraclavicular areas corresponding to lymph node metastases not visible on the ultrasonography and CT scan.
For lymph node invasion, one study demonstrated true positives on 13 of 17 PET scans while CT only recognized 3 [22]. There is however a practical problem because nodal metastases lying in close proximity to the primary tumor can not be distinguished with certainty on PET scans. Like others [17], we have found that an invaded node lying next to a tumor mass cannot be differentiated. Others have proposed coupling CT data with the functional PET data to overcome this problem [23].

The principal contribution of PET-FDG appears to be in identifying visceral metastases or distant nodal involvement. In a series of 49 patients, PET-FDG scans enabled identification of 7 metastases that went undetected on the CT scans [17]. In another series of 65 patients, PET-FDG detected metastases non-visualized on the CT scans in 5 patients and correctly ruled out CT-suspected metastases in 2 others [16]. In one of our 22 patients with a malignant tumor, the PET scan correctly identified an invaded subclavian node that could not be palpated clinically. In this type of situation, the PET scan provides not only diagnostic information but also influences decision-making, contraindicating surgery due to the short life expectancy of these patients with metastasis [24, 25]. There is however the risk of false positives [9], particularly in case of cholestasis [13].

During the period of this study, we did not have any situations where there was a real problem of differential diagnosis between pancreatic cancer and chronic pancreatitis. Theoretically, PET scan would be normal in chronic pancreatitis and show strong uptake in malignant tumors [9, 17]. In comparative studies on ultrasound, CT, and PET used to differentiate between chronic pancreatitis, benign tumors, and malignant tumors, PET has been found to be the most sensitive and most specific exploration [7, 16, 18, 26, 27]. This is a logical finding since a purely morphological exploration cannot be expected to provide information on the nature of a tissue mass. False-positive PET scans are reported to occur in about 10% of patients with chronic pancreatitis [11, 26]. Inversely, false-negative PET scans in cancer patients have ranged from 5% in other studies [11, 17, 26] to 35% in our series. Those reporting the most disappointing experience with PET scans have seen 18FDG uptake as often in chronic pancreatitis as in cancer patients [21, 28]. In one series where 75% of the patients had pancreatic cancer, the positive predictive value was 85% and the negative predictive value was 44% [18]. This level of certainty is incompatible with appropriate decision making [18].

It has been suggested that PET-FDG scans could have prognostic value. One study demonstrated that mean survival was 5 months in patients with a high SUV (> 3) compared with 14 months in those with a low SUV (≤ 3) (P < 0.05) [20]. In our series, the presence or absence of 18FDG uptake was not related to resectability, the principle prognostic factor for pancreatic tumors.

More generally, authors prescribing and performing any new exploration technique are intrigued and have a natural tendency to promote the new method. A critical attitude is however required in order to assess the real decisional impact of any exploration method prior to its integration to the diagnostic process [30]. This attitude, which avoids unnecessary examinations, is particularly important for PET scans which are costly, time consuming and difficult to access. In case of cancer of the head of the pancreas, the clinical presentation and standard ultrasound are usually enough to obtain a sufficiently strong probability of diagnosis. This would of course not be the case in exceptional situations with atypical symptoms. Differentiating between cancer of the head of the pancreas, cholangiocarcinoma or ampulloma has an impact on prognosis but not on decision making. A pathological examination is required for final proof of diagnosis but should be ordered only when really useful, that is for non-operated patients entering a chemotherapy and/or radiotherapy protocol. For the diagnosis of hepatic metastasis of pancreatic cancer, ultrasonography, CT scan, and PET scan all have about the same level of sensitivity. The morphological explorations are less sensitive for peritoneal metastasis; here, the PET scan is more sensitive but with a significant risk of false positives. As confirmed in our series, the best performance is obtained with laparoscopy [29]. Morphological explorations are warranted preoperatively to determine resectability; here the best performance is obtained with helical CT and magnetic resonance imaging [30-33].

In everyday practice, the exploration attitude depends directly on which decision has to be made [34]. For patients with no operative risk and no detectable metastasis, laparotomy is the only way to be sure not to miss a chance to resect a tumor [30]. If the tumor cannot be resected, a biliary and digestive by-pass can be performed with celiac plexus neurolysis. In this type of situation, searching for preoperative signs of resectability can add nothing to the decision-making process [34]. Inversely, if a palliative non-surgical intervention (biliary endoprosthesis, duodenal stent) would be preferable for a patient with no operative risk and no detectable metastasis, searching for signs of resectability might modify the therapeutic attitude [35], although this remains to be proven and depends greatly on experience.

In our series, the PET-FDG results obtained in 4 patients with cystic tumors are remarkable: neither of the 2 mucinous cystadenomas exhibited uptake but both of the cystadenocarcinomas did. It would be useful to examine the contribution of PET scan to the exploration of mucinous cysts of the pancreas in a larger series.

In conclusion, the discordant data available on PET-FDG of the pancreas can be explained by different reference standards used by the different teams. In our prospective series, precise external references suggested that PET scans contribute little to the initial staging of patients with pancreatic tumors. PET scans might be helpful in distinguishing between mucinous cystic tumors, cystadenomas, and cystadenocarcinomas, but this remains to be demonstrated. In other situations, the contribution of PET-FDG to decision-making is limited when the objective is to identify metastases contraindicating surgery, a rare situation observed in only 1 of our 24 patients. It can thus be concluded that in 90% of the cases, PET-FDG does not contribute to decision making. This must be kept in mind when determining the cost effectiveness of prescriptions. Further assessments conducted with a dedicated camera and attenuation correction would be useful.

REFERENCES


