Pseudomyxoma Peritonei: Role of 18F-FDG PET in preoperative evaluation of pathological grade and potential for complete cytoreduction

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ABSTRACT:**INTRODUCTION:**

For pseudomyxoma peritonei (PMP), survival depends on pathological grade and completeness of cytoreductive surgery. The aim of the study was to assess the ability of preoperative 18F-FDG PET to determine those 2 prognosis indicators.

MATERIAL AND METHODS:

In this prospective monocentric study, all patients presenting PMP were included. They underwent a preoperative 18F-FDG PET with a double radiological evaluation and an explorative laparotomy with the objective of optimal cytoreduction followed by a hyperthermic intra-operative intraperitoneal chemotherapy (HIPEC). Patients with non resectable disease underwent debulking surgery without HIPEC. The Completeness of Cytoreduction was assessed by CCscore.

RESULTS:

Thirty-four patients were included. PET scanning was positive for 19 patients with grade II (hybrid form) or III (peritoneal mucinous cystadenocarcinoma) and for 2 patients with grade I (disseminated peritoneal adenomucinosi), and negative for 3 patients with grade II - III and for 10 patients with grade I. PET scanning was positive for 6 patients with CCscore 2 - 3 and for 16 patients with CCscore 0, and negative for 2 patients with CCscore 2 - 3 and for 10 patients with CCscore 0. The 18F-FDG PET interpretation distinguished 2 patients groups (grade I and grade II - III) with a sensibility of 90% and a specificity of 77%. Moreover, probability of complete cytoreduction when PET was negative was over 80%.

CONCLUSION:

Preoperative 18F-FDG PET may predict pathological grade and completeness of cytoreduction which are the two main prognostics factors in patient with PMP.

Key words: Pseudomyxoma peritonei, 18F-FDG PET, prognosis, preoperative assessment.

INTRODUCTION:

Pseudomyxoma peritonei (PMP) is an uncommon disease affecting 1 per million population with an estimated incidence of 2 cases per 10 000 laparotomies (1). In 1884, Werth (2) reported the first case of PMP, describing gelatinous material from an ovarian cyst in the peritoneal cavity. Developments in immunohistochemical techniques and genetic analysis now suggest the origin of PMP is the appendix (3) (4) in the majority of cases. As a result of the proliferation of mucin there is an increase in intra-abdominal pressure. This phenomenon causes intestinal obstruction and often leads to the patient's death. As suggested by Sugarbaker (5), the current standard of care with curative intent should be the combination of cytoreductive surgery (CRS) with hyperthermic intra-operative intraperitoneal chemotherapy (HIPEC).

A number of specialized teams involved in the management of PMP use three pathological grades for classification (6) (7), grade I or « disseminated peritoneal adenomucinosis » (DPAM), grade III or « peritoneal mucinous cystadenocarcinoma » (PMCA) and grade II or intermediate hybrid form. For patients treated by CRS combined with HIPEC, the 5 year survival rate varies from 74 to 100 % for grade I, and from 30 to 54 % for grade II and III with less favourable prognosis for PMCA (8) (9). Pathological grades, prior surgical score (PSS) (10) and residual disease measure by Completeness of Cytoreduction score (CCscore) (10) have been found to be the main prognostic factors in several prospective studies (7) (11) (12). It remains difficult to predict preoperatively the completeness of cytoreduction which is dependent on pathological grade and disease extent (12).

18 FluoroDeoxyGlycose Positron Emission Tomodensitometry (18 F-FDG PET) has shown promising results in preoperative assessment of peritoneal carcinomatosis (13) (14) (15).

The aim of the study was to assess the ability of preoperative ^{18}F -FDG PET to determine the pathological grade of PMP allowing prediction of completeness of cytoreduction and therefore prognosis.

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PATIENTS AND METHODS:

Protocol

Between March 2003 and January 2008, all patients with PMP scheduled for CRS at the Centre Hospitalier Lyon Sud were included in this prospective study. Prior to cytoreductive surgery, the diagnosis of PMP was suggested by the clinical presentation and biopsy.

All patients underwent a preoperative 18F-FDG PET with a double radiological evaluation, and pathologic analysis of operative samples. Prior Surgical Score (PSS) was estimated: PSS 0 for biopsy only, PSS 1 for only one abdominopelvic region dissected, PSS 2 for 2 to 5 abdominopelvic regions dissected, PSS 3 for more than 5 abdominopelvic regions dissected (8).

Positron Emission Tomodensitometry

18F-FDG PET' image acquisitions were performed in 3D mode, with a Philips Allegro PET scanner (Philips, detectors GSO) for the first eleven patients from March 2003 to October 2004. For the next 21 patients a Philips Gemini PET scanner (Philips) combining an Allegro PET and a computed tomography MX8000 D (4 frames per second) was used. Each examination was performed from the base of the cranium to the top of the thighs, (3 min per step), 60 minutes after intravenous injection of a 5MBq/kg dosage of 18F-FluoroDeoxyGlucose (18FDG). During this period, all patients were at rest. A fasting period of at least 6 hours was observed before the examination. The analysis of the 18 F-FDG PET's images, not corrected or softening corrected, was performed after reconstruction using special software (Syntegra and PET-CT viewer on an EBW Philips console) in three orthogonal planes (transverse, sagittal and coronal). These images were compiled with all available clinical information and images from corresponding anatomic imaging examinations

(Computed Tomography scan (CT scan) and/or Magnetic Resonance Imaging), for interpretation by two nuclear physicians prior to cytoreductive surgery. In case of disagreement between the two physicians, a new examination was performed by both of them. Qualitative and semi-quantitative analysis was based on the comparison of uptake of 18F-FDG between lesions and healthy tissues into three categories: absence of pathologic uptake (figure 1), moderate uptake (figure 2) and high uptake (Figure 3). If intensity of uptake of 18F-FDG correlates to the aggressiveness of the disease, the hypothesis was that absence of uptake would represent well differentiated lesions like DPAM, with high and moderate uptake representing PMCA and hybrid disease respectively. PET was considered positive in case of uptake of 18F-FDG and negative otherwise. Quantitative assessment of fixation of 18F-FDG was not performed by means of the SUV (Standardized Uptake Value) because of no possibility of optimally calibrating the system.

Surgery

All patients underwent an explorative laparotomy, beginning with a complete intraperitoneal exploration and with the evaluation of disease extent using Gilly's peritoneal carcinomatosis staging (16)(17), and Sugarbaker's Peritoneal Cancer Index (10). The surgical goal was to obtain a complete cytoreduction, with residual disease nodules no greater than 5 mm, followed by hyperthermic intraperitoneal chemotherapy (HIPEC) at 42 °C for 90 minutes, using mitomycin C (0.5 mg/kg) and cisplatin (0.7 mg/kg). Peritonectomy procedures and surgical resection were performed according to Sugarbaker (18). Patients with non resectable disease underwent debulking surgery. Peritoneal disease was considered non resectable in the presence of extensive small bowel or mesenteric involvement, extensive pelvic disease or severe co-morbidity precluding extensive surgery. The residual disease was assessed by the Completeness of Cytoreduction Score (CC Score): CC-0 for absence of visible residual

nodules, CC-1 for absence of residual nodules more than 0.25 cm, CC-2 for residual nodules from 0.25 cm to 2.5 cm and CC-3 for residual nodules greater than 2.5 cm. Resection was considered as complete when CC score was 0 or 1.

Pathological analysis

Analysis of operative samples were done by the same pathologist according to the Ronnett classification (7): disseminated peritoneal adenomucinosis (DPAM) or grade I corresponding to lesions made up of large mucinous pools, with no cellular atypia and a low mitotic activity (figure 4); peritoneal mucinous cystadenocarcinoma (PMCA) or grade III corresponding to lesions made up of mucinous cells with cellular atypia, signet ring morphology or invasion (figure 5); and hybrid form representing lesions containing the morphology of grades I and III with less than 5% of cells demonstrating features of adenocarcinoma.

Statistical analysis:

EXCEL 2000 software manufactured by Microsoft was used for analysis. Sensitivity, specificity, accuracy, positive predictive value (PPV) and negative predictive value (NPV) were calculated. Youden's index, which measures the effectiveness of the test (negative index: ineffective test; index close to 1: effective test), Yule's Q coefficient, which measures the relatedness of 2 variables (the closer the coefficient to 1, the stronger the relationship), and positive and negative likelihood ratio were used to assess PET validity.

RESULTS:

Thirty two patients were included in this study, 20 female and 12 male. The mean age of patients was 55 (range, 27-85). No patient had chemotherapy during the three months preceding 18F-FDG-PET and CRS. After a fasting period of at least 6 hours, patient's blood glucose levels were less than 6.1mmol/l before 18F-FDG PET except for those receiving parenteral nutrition. Two patients were evaluated twice during progression of their disease. One patient had initial grade III PMP treated by complete cytoreductive surgery combined with HIPEC and had grade III PMP recurrence 2 years later. Another had grade II PMP treated by complete cytoreductive surgery combined with HIPEC and had grade III recurrence 1 year later. Analysis was performed on 34 complete procedures including preoperative 18F-FDG PET, surgery and pathologic analysis.

Prior Surgery

PSS was 0 or 1 for 7 patients and 2 or 3 for 27 patients. No patient underwent surgery during the 30 days preceding 18F-FDG PET. The mean interval between previous surgery and 18F-FDG PET was 98 days. Sixteen patients underwent surgery in the 12 months before 18F-FDG PET: appendectomy for appendicitis in 8 patients, 1 right ovariectomy, ileocaecal resection in 3 patients, total hysterectomy combined with appendectomy and omentectomy in 3 patients and multiple peritoneal biopsies in 1 patient.

Extent of carcinomatosis

According to Gilly's peritoneal carcinomatosis staging peritoneal carcinomatosis was stage I or II for 9 patients and stage III or IV for 25 patients. PCI was between 0 and 14 for 15

patients and between 15 and 39 for 16 patients. For 3 patients, the surgical exploration did not provide a PCI assessment.

Pathological correlation with PET

Thirteen patients presented with grade I PMP and 21 with grade II or III PMP (11 grade II and 10 grade III). Preoperative PET scanning was negative for 10 out of 13 patients with grade I disease and positive for 19 of 21 patients with grade II or III disease. This resulted in a probability of 0.83 of a grade I lesion if PET was negative and a probability of 0.86 of a grade II-III lesion if PET was positive. Preoperative 18F-FDG PET predicted the pathological PMP grade with a sensitivity of 90%, a specificity of 77%, an accuracy of 85%, a PPV of 86% and NPV of 83%. According to Yule's Q coefficient, the strength of the connection between uptake of 18F-FDG and histological grading was very significant (0.94). Youden's index was 0.67. The Positive likelihood ratio was 3.92 and the negative likelihood ratio was 0.123.

Completeness of cytoreduction and correlation with PET

There were 26 complete cytoreductions (CC score 0 or 1) and 8 incomplete resections (CC score 2 or 3). Complete cytoreduction with HIPEC was performed in 25 patients, 1 patient underwent complete cytoreduction without HIPEC, and 2 patients uncomplete cytoreduction with HIPEC. Among the 8 patients with non resectable disease, 4 underwent debulking surgery and 4 underwent multiple peritoneal biopsies. Cytoreductive surgery was performed during the 30 days following the 18F-FDG PET, except in 3 patients who underwent surgery at 44, 68 and 114 days from scanning. The mean interval between 18F-FDG PET and surgery was 12 days (range, 1-114). Complete cytoreduction was performed in 11 of 13 patients with grade I PMP (85%) and in 15 of 21 patients with grade II or III PMP (71%). Two patients with grade I lesions who were treated with a CC-2 or 3 cytoreduction were over 80 years old.

Their age and co-morbidity prevented complete cytoreduction. Preoperative 18F-FDG PET was negative for 10 out of 26 patients with complete cytoreduction, and positive for 6 patients out of 8 with incomplete cytoreduction. When preoperative PET scanning was negative the probability of complete cytoreduction was 0.83. The probability of incomplete cytoreduction was 0.27 when PET scanning was positive. Predictive positive value of preoperative 18F-FDG PET to assess completeness of cytoreduction was 27%, predictive negative value was 83%, with 75% sensitivity and 38% specificity. According to Yule's Q coefficient, the strength of relationship between uptake of 18F-FDG and the CC score was significant (0.3). Youden's index was 0.13.

DISCUSSION:

Prognostic factors and preoperative evaluation of PMP

Cytoreductive surgery combined with perioperative intraperitoneal chemotherapy is currently considered the standard of care for the management of PMP and results in 20 years survival rates of 70% (12) (19). Surgical history represented by the Prior Surgical Score (PSS) (10), pathological grade (3) and completeness of cytoreduction (10) have all been reported as important prognostic factors. According to pathological grade as described by Ronnett, 2 broad groups exist: patients with DPAM who have 84 % 5 years survival and patients with PMCA or hybrid form with a 7 and 38 % 5 years survival, respectively (7) (6) .

CT (Computed Tomography) features such as presence of an appendiceal mucocele (20), low attenuation ascites, visceral scalloping, septae in mucinous material, calcification and omental cake may all suggest the diagnosis of PMP (21). Disease in dependent areas of the peritoneal cavity is described as the redistribution phenomenon (22). CT scan features of DPAM are typically calcification, and of PMCA, omental cake or lymph nodes (23). Absence of bowel obstruction with no tumor deposits on the jejunum and proximal ileum (24) and small volume disease on pre-operative CT scan (21) all suggest that complete cytoreduction may be possible.

¹⁸F-FDG PET is reported to have a sensitivity varying from 35.5 to 88% for detection of peritoneal carcinomatosis depending on origin (13) (25) (14). However, CT scan appears to have higher sensitivity for preoperative staging of peritoneal carcinomatosis (26), compared to PET which underestimates the extent of lesions, especially for nodes less than 5mm (13) (14) (15) (27). For preoperative assessment of PMP, PET scanning may have the additional benefit of identifying pathological grade pre-operatively and therefore allowing tailored treatment.

Pathological grade assessment

In this study, preoperative 18F-FDG PET distinguished DPAM from PMCA or hybrid forms, with a sensitivity of 90% and a specificity of 77%. Positive and negative predictive values were 86% and 83% respectively. This suggests that preoperative 18F-FDG PET may be useful in differentiating between pathological grades based on uptake of 18F-FDG. The combination of 18F-FDG PET with CT scan improves evaluation of peritoneal spread.

Completeness of cytoreduction assessment

When 18 F-FDG PET was negative, macroscopic complete cytoreduction (CC score 0-1) was achieved in 83% (10/12) of patients. Two patients aged over 80 years old were treated by debulking surgery only because of extensive co-morbidity. They both had grade I PMP and preoperative PET scanning was negative. If these 2 patients are excluded from analysis, all patients with PMP who had negative PET scanning underwent a complete cytoreduction, and all patients with CC score 2 or 3 had positive PET scanning. For patients fit for CRS with HIPEC, the absence of uptake of 18F-FDG on preoperative PET scanning may predict the possibility of complete cytoreduction. But because of the low positive predictive value and low specificity, preoperative positive PET scanning was not able to predict the possibility of cytoreduction.

Limitations of PET

Prior surgery may cause residual inflammatory changes that can lead to uptake of 18F-FDG in resection areas. In this trial, 16 patients (8 with a grade I and 8 with grade II or III) underwent surgery during the 12 months preceding PET scanning, with a minimum time of 33 days between 18F-FDG PET and the last surgery. PET scanning was positive for 3 patients out of 8

with grade I PMP. The uptake area was always located outside the previous surgical resection sites. Of the 8 patients with grade II or III PMP, 6 had uptake in more than 2 abdominal quadrants, one had uptake in the right iliac fossa 124 days after an appendicectomy and the other had low uptake throughout the abdomen. Previous surgery had no impact on ^{18}F -FDG PET interpretation in 15 of these 16 patients with PMP, because fixation areas were located outside the previous surgical resection sites.

PMP disease progression may affect correlation of ^{18}F -FDG PET with operative pathology specimens. However, in this study, the time interval between PET scanning and cytoreductive surgery was less than one month apart from 3 patients. Pathological specimens obtained at surgery were therefore likely to represent the disease process assessed by preoperative PET scanning. The three patients who had an interval between PET scanning and surgery of more than 30 days (44, 68 and 114 days) may have had higher levels of uptake if disease had progressed. This phenomenon would have strengthened the negative predictive value of our results.

Preoperative chemotherapy is another potential confounding factor, but no patient received preoperative systemic chemotherapy in the three months preceding ^{18}F -FDG PET in our study. Therefore it is unlikely that our findings were affected by this.

The purpose of this study was to assess the ability of ^{18}F -FDG PET to aid preoperative assessment of patients with PMP by identifying patients in whom complete cytoreduction was likely to be achieved. PET scanning seems to be effective in differentiating between patients who have absence of uptake of ^{18}F -FDG and are likely to have DPAM, and those who have uptake of ^{18}F -FDG with a probable PMCA or hybrid form. ^{18}F -FDG PET may also be effective in the pre-operative evaluation of completeness of cytoreduction.

By ^{18}F -FDG uptake, PET scanning allows to distinguish 2 groups with different prognosis before surgery. It could offer a neoadjuvant treatment for patients with poor prognosis and adapt care according to general status of patients. Moreover, ^{18}F -FDG PET may be interesting for the follow up of patients with PMP.

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CONCLUSION:

These results suggest that preoperative 18F-FDG PET may predict pathological grade and the completeness of cytoreduction in patients with PMP. In light of the high morbidity and mortality associated with CRS and HIPEC it is important that we refine our operative selection criteria (28) (29) (30). Several studies display an improvement in sensitivity and specificity when PET scanning is combined with CT (13) (15) combining the functional information of 18F-FDG PET with the morphologic information of CT scan. Combining 18F-FDG PET with CT may provide the optimal imaging modality for identifying those patients most likely to benefit from CRS with HIPEC.

Absence of pathologic uptake for acellular mucinous ascites.

Figure 2: PET and fusion PET-CT images with moderate uptake for a hybrid form (grade II)

Figure 3: PET and fusion PET-CT images of a PMCA (grade III)

Intense uptake for lesions of PMCA on anterior mesentery.

Figure 4: Histological appearance of Disseminated Peritoneal Adenomucinosi s (DPAM)

Mucinous epithelium within extracellular mucin colored in blue by alcian blue.

Figure 5: Histological appearance of peritoneal mucinous cystadenocarcinoma (PMCA).

Abundant mucinous glang with cellular atypia.

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