ICCR IRB Protocol

Lauren Khanna, MD

April 10, 2009

Utility of 18-FDG PET Imaging to Distinguish Malignant from Benign Intrapapillary Mucinous Neoplasms

1. Study Purpose and Rationale

Intraductal papillary mucinous neoplasm (IPMN) is a cystic pancreatic neoplasm that is a precursor to invasive pancreatic cancer. It is characterized by intraductal proliferation of mucinous cells that secrete abundant mucin and cause cystic dilation of main and/or branch pancreatic ducts. IPMN is slower growing and less aggressive than pancreatic ductal adenocarcinoma, but it does progress from benign (adenoma or borderline) to malignant (in situ or invasive carcinoma), with 20 to 40% of lesions becoming invasive carcinoma. Due to improved quality and increased utilization of cross-sectional imaging modalities, IPMN is being increasingly identified in clinical practice. Such "incidental" findings of cysts are becoming an increasingly important clinical challenge, given the fact that IPMN has such a variable course and the majority of cysts, especially smaller lesions and ones found in elderly patients, will not cause significant morbidity or mortality. However, differentiating if a lesion is benign or malignant is critical, as the management differs drastically, ranging from surgical resection to observation by repeat imaging at varying intervals.

Currently, various radiological modalities such as computed tomography (CT) or magnetic resonance imaging (MRI) are utilized to characterize IPMN lesions. Radiological characteristics that appear to be associated with malignant disease include cyst size larger than 3 cm, location in the main pancreatic duct, dilation of the main pancreatic duct greater than 10 mm, and the presence of mural nodules.[1-3] Endoscopic ultrasound (EUS) is a more sensitive modality than traditional imaging and offers the advantage of fine needle aspiration (FNA) of cyst fluid for cytology or biochemical analysis.[4] However, EUS is invasive, operator-dependent, and offered only at select centers. Overall, even with the combined usage of the above modalities, it is estimated that about 30 to 40% of IPMN are incorrectly diagnosed preoperatively. Of the 112 patients who have undergone resection at Columbia University's Pancreas Center, 37% have been found to have malignant IPMN and 64% have been found to have benign IPMN on surgical pathology. The consequences of misdiagnosis are significant, since over-treatment involves the morbidity of pancreatic surgery, including possible diabetes and exocrine insufficiency, but under-treatment would lead to pancreatic cancer, an essentially incurable disease. Clearly, a more accurate and noninvasive test to identify malignant IPMN is needed.

Positron emission tomography (PET) is a type of three-dimensional imaging used to identify metabolically active cells, such as cancer cells, through the intravenous injection of radiolabeled glucose (most commonly 18-fluorodeoxyglucose) and its detection. It is a useful functional assay to identify malignant tissue, and is already being utilized in the evaluation, management, and follow-up surveillance of pancreatic ductal adenocarcinoma. Several small studies have demonstrated the potential utility of 18-FDG PET in IPMN. Yoshioka et al.[5] described the use of PET for IPMN in a 2003 case report from Japan, in which 2 patients with cystic pancreatic head lesions had no clear features concerning for malignancy on conventional imaging, but had FDG avid lesions (with SUV 6.0 and 2.6) and were found to have invasive carcinoma on resection.

In a study by Mansour et al.[6] in 2006 at Memorial Sloan-Kettering Cancer Center, the cases of 68 patients who had cystic pancreatic lesions and were evaluated by PET imaging were retrospectively analyzed. Of the 21 patients who underwent resection, 5 were found to have IPMN, 2 of which were malignant, although only 1 of the 2 had FDG avid uptake on PET imaging. Therefore 1 case of IPMN with carcinoma in situ was not identified by PET. In a 2007 study by Sperti et al.[7] assessing the ability of PET to distinguish benign IPMN from malignant IPMN, 64 patients were prospectively evaluated (including 26 patients previously reported by Sperti et al. in studies of PET for cystic pancreatic tumors[7],[8]). Of these, 42 patients underwent resection; 26 patients were found to have malignant IPMN, 24 of which had been FDG avid; 16 patients were found to have benign IPMN, of which only 1 patient was found to have an FDG avid pancreatic lesion, and this was in the setting of a concurrently discovered colon carcinoma. Therefore, the calculated sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of PET to detect malignant IPMN were reported as 92%, 97%, 96%, 95%, and 95%. In a 2008 study from Italy by Baiocchi et al.[9], 7 patients with IPMN were assessed by PET imaging. Two patients had FDG avid lesions (with SUV 6.7 and 9), 1 was found to have carcinoma in situ on resection, and 1 did not undergo resection due to high surgical risk, but died from disease within 5 months. The remaining 5 patients had PET showing no FDG avidity and were found to have benign disease on resection (2) despite high-risk features on MRCP or follow-up (3) at 21 to 34 months. Therefore, PET was found to correctly predict the presence or absence of malignancy.

The studies evaluating the use of PET imaging to determine the malignancy of IPMN lesions are promising, but their significance and applicability is restricted by small sample sizes and lack of reproduction of results. We predict that 18-FDG PET may be an accurate modality in differentiating between malignant and benign IPMN lesions. We hypothesize that, in patients with findings sufficiently concerning for malignant IPMN such that resection is planned, 18-FDG PET imaging will have an

acceptable negative predictive value (>80%) to prevent unnecessary resections. In order to investigate this hypothesis, we will prospectively study the sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of 18-FDG PET in patients with IPMN who are undergoing surgical resection for their disease. Ten consecutive surgical patients recruited from the Columbia University Pancreas Center will undergo 18-FDG PET imaging, as well as CT, MRI, and/or EUS as clinically indicated. Nuclear radiologists will be blinded to the clinical outcomes of patients and surgical pathology will be utilized as the reference for histological determination.

2. Study Design and Statistical Analysis

This is a prospective study to investigate the sensitivity, specificity, positive predictive value, and negative predictive value of 18-FDG PET in patients with IPMN who are undergoing surgical resection for their disease. Columbia University's multidisciplinary Pancreas Center is a high-volume pancreatic surgical referral center, with 156 patients evaluated for surgical consultation for IPMN between 2002 and 2008, of which 112 underwent resection for IPMN.

From the Pancreas Center's surgical practice, ten consecutive patients with clinically-suspected IPMN who are undergoing surgical resection will be recruited. To ensure that lesions will be of a size sufficient for detection by 18-FDG PET, inclusion criteria will include overall cyst size and main duct involvement of at least 3 cm. To ensure that complete data is available to compare 18-FDG PET with conventional evaluation, only patients who have undergone EUS with cyst fluid aspiration which is sufficient for CEA fluid level analysis will be included. All patients will have undergone standard conventional imaging, either CT or MRI, as well as EUS.

Demographic, clinical, laboratory, and radiological data will be collected, including age, gender, history of smoking, symptoms, serum CA 19-9 and CEA levels, size and location of lesions, involvement of main or branch pancreatic ducts, presence of mural nodules, cyst fluid CEA and amylase, and cyst fluid cytology. Within one month of surgical resection, patients will undergo 18-FDG PET imaging and simultaneous CT scan per standard protocol. All scans will be reviewed by two experienced nuclear medicine radiologists who will be blinded to the clinical characteristics of study patients and who will reach a consensus. Areas of focally increased 18-FDG intake will be identified. Side-by-side reading with CT scan will be performed to evaluate whether the increased 18-FDG uptake corresponds to a pancreatic lesion. Mean and maximal SUV values, as well as differences in intensity between the region of interest and the remaining pancreas, will be calculated.

All scans will be performed at Columbia University's research PET center and funded by the CTSA Irving Institute Grant (UL1 RR024156 from the National Center for Research Resources). Patients nor their health insurance will be billed for the PET scans. The results from PET-CT scans will not be included in the patients' medical charts, nor utilized in the clinical management of patients, as PET scans have not been utilized as standard-of-care in the management of IPMN.

Surgical pathology will be referenced as the gold standard. Pathologic data for each IPMN lesion will be recorded, including size, duct involvement (main, side, or mixed), ductal dilatation, lesion location (head, neck, body, tail), and histologic grade (adenoma, borderline, carcinoma in situ, invasive carcinoma). In addition, any associated pancreatitis or any other non-IPMN neoplastic change will also be noted.

The primary outcome will be to determine the positive and negative predictive values of 18-FDG PET imaging for identifying malignant IPMN lesions. Based on the Sperti et al. study, in patients who would have had surgery based on conventional imaging findings, 93.75% with malignant IPMN had positive PET imaging and 0% with benign IPMN had positive PET imaging. To determine sample size, we will estimate based on chi-square testing to detect difference in proportion between these groups, with proportion of positive PET in patients with malignant IPMN to be 0.9375 and in patients with benign IPMN to be 0. To determine with 80% power that the proportion of patients with positive PET imaging is significantly different between patients with malignant and benign IPMN, a sample size of at least 10 patients is necessary for this initial pilot study. Secondary outcomes that we are interested in include the benefit of PET to other modalities, such as CT, MRI, and EUS. Finally, while the number of patients within this proposal is too small for subgroup analysis, we are interested in beginning analysis to determine if size, location, and branch involvement affect the accuracy of PET.

3. Study Procedures

Participants will undergo 18-FDG PET-CT imaging per standard protocol.

4. Study Drugs or Devices

There are no study drugs or devices being utilized in this study.

5. Study Questionnaires

There are no study questionnaires being utilized in this study.

6. Study Subjects

Inclusion criteria:

1. Patient is seen in consultation for IPMN at Columbia-Presbyterian Medical Center and scheduled for surgical resection.
2. Patient has radiological evidence, by CT or MRI, suspicious for IPMN, with lesion involving main duct with size equal to or greater than 4 cm and/or involvement of at least a 4cm segment of the main pancreatic duct.
3. Patient has undergone EUS with aspiration of cyst fluid with sufficient fluid for CEA level.
4. Patient is at least 18 years of age.
5. Patient is able to provide written, informed consent

Exclusion criteria:

1. Active pancreatitis within 30 days of recruitment.
2. Uncontrolled diabetes mellitus.
3. Pregnancy or breastfeeding (urine beta-HCG will be performed on all women of child-bearing age prior to enrollment in study)
4. Unwillingness or inability to sign informed consent.

7. Recruitment

Patients who meet the inclusion criteria will be informed of the study by their physician in the Columbia-Presbyterian Medical Center faculty practices. If the patient is willing to discuss the study, patients will be referred to study investigators by their physician. A study investigator will obtain informed consent prior to enrollment, using Columbia University Medical Center IRB approved consent forms, which will be signed to indicate the participants' consent.

8. Confidentiality of Study Data

The demographic, clinical, radiological, pathologic, and follow-up data on these patients will be collected into a database maintained by the Pancreas Center. All patient identifiers will be removed from the database. Each subject will be given a unique study number, such that it will not be possible to link this number back to the patient chart from which the data is taken. The results of the study will be presented as an analysis of the entire study population and not as an individual participant. The study coordinator

and the PI will have a list of the participant's name, medical record number and the corresponding study ID which will be kept elsewhere to maintain confidentiality.

9. Potential Risks

The risks to participation in this study are minimal and are related only to the PET and CT scans. The use of the 18-FDG radioisotope and of spiral CT generally expose the patient to approximately 1000 millirem, which is approximately 1/5 of the annual radiation exposure limit allowed to radiation workers. The long-term risks of such levels of exposure are low. Allergic reactions to the contrast utilized in CT scan occur in approximately 2% and are <1% with 18-FDG. Reactions can be minor, such as skin rashes or itching, but can also be major, including laryngeal edema or anaphylactic reactions. Other non-allergic reactions can include flushing or minor pain at the injection site.

10. Potential Benefits

There is no anticipated direct benefit to the patients in this study. Results of PET-CT scans will not be included in patients' medical chart nor utilized for clinical management, given the unclear diagnostic benefit that PET-CT scan has for IPMN. However, the outcomes from this study may benefit the treatment of future patients, as the goals are to improve the ability to distinguish between benign and malignant IPMN prior to surgical resection.

11. Alternatives

The alternative to participation in this research is to not participate in this study. Any patients who opt to not participate will simply receive the current standard pre-operative evaluation for IPMN.

References

1. Sugiyama M, Izumisato Y, Abe, Masaki T, Mori T, Atomi Y. Predictive factors for malignancy in intraductal papillary-mucinous tumours of the pancreas. British Journal of Surgery 2003;90:1244-9.

2. Rodriguez JR, Roberto S, Stefano C, et al. Branch-Duct Intraductal Papillary Mucinous Neoplasms: Observations in 145 Patients Who Underwent Resection. Gastroenterology 2007;133:72-9.

3. Tanaka M, Chari S, Adsay V, et al. International Consensus Guidelines for Management of Intraductal Papillary Mucinous Neoplasms and Mucinous Cystic Neoplasms of the Pancreas. Pancreatology 2006;6:17-32.

4. Baba T, Yamaguchi T, Ishihara T, al. e. Distinguishing benign from malignant intraductal papillary mucinous tumors of the pancreas by imaging techniques. Pancreas 2004;29:212–7.

5. Yoshioka M, Sato T, Furuya T. Positron emission tomography with 2-deoxy-2-[(18)F] fluoro-d-glucose for diagnosis of intraductal papillary mucinous tumor of the pancreas with parenchymal invasion. J Gastroenterol 2003;38:1189 - 93.

6. Sperti C, Bissoli S, Pasquali C, et al. 18-Fluorodeoxyglucose Positron Emission Tomography Enhances Computed Tomography Diagnosis of Malignant Intraductal Papillary Mucinous Neoplasms of the Pancreas. Ann of Surg 2007;246.

7. Mansour JC, Schwartz L, Pandit-Taskar N. The utility of F-18 fluorodeoxyglucose whole body PET imaging for determining malignancy in cystic lesions of the pancreas. J Gastrointest Surg 2006;10:1354 - 60.

8. Baiocchi G, Portolani N, Bertagna F, et al. Possible additional value of 18FDG-PET in managing pancreas intraductal papillary mucinous neoplasms: Preliminary results. Journal of Experimental & Clinical Cancer Research 2008;27:10.

9. Herrmann K, Eckel F, Schmidt S, et al. In Vivo Characterization of Proliferation for Discriminating Cancer from Pancreatic Pseudotumors. J Nucl Med 2008;49:1437-44.