

## Predicting Diabetes after Partial Pancreatectomy

IRB Protocol

Irun Bhan

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### 1. Study Purpose and Rationale

Intraductal papillary mucinous neoplasms (IPMN) are precancerous lesions of the pancreas with a slow rate of progression (15-20 years). Their incidence is increasing with the increased use of cross-sectional imaging.<sup>1,2</sup> These lesions can be asymptomatic but patients often present with acute or chronic pancreatitis secondary to intermittent pancreatic duct obstruction by mucus; patients can also present with back pain, weight loss, anorexia, steatorrhea, and diabetes.<sup>3</sup>

Diagnosis of IPMN is multimodal, often using endoscopic retrograde cholangiopancreatography (ERCP), endoscopic ultrasound (EUS), pancreatoscopy, magnetic resonance pancreatography (MRP). Interventional procedures allow for cytologic analysis of the pancreatic fluid which shows characteristic molecular markers.<sup>4</sup>

The only treatment is surgical resection, but the indications for surgery are not clear. One group of experts proposed the Sendai Consensus Guidelines, which delineate that resection is indicated if at least one of these features are present: symptoms attributable to the cyst, dilation of the main pancreatic duct, cyst size  $\geq 3$ cm, presence of intramural nodules, cyst fluid cytology indicative of malignancy. Studies indicate these criteria are sensitive but not specific for malignancy and further data and guideline refinement are necessary.<sup>5</sup>

One important consideration for pancreatic resection is whether the patient will develop diabetes mellitus after resection. Previous studies have examined the association of post-operative diabetes and type of partial pancreatectomy. However, there is not good data for assessing post-op risk of diabetes.<sup>6</sup> A possible metric for assessing this risk would be beta cell mass removed as opposed to pancreatic mass removed, since islet cell distribution is not homogenous and patients may have differing starting proportions beta cell mass to total pancreatic mass.

A new technique for evaluating beta cell mass has emerged that uses positron emission tomography (PET). The radioligand used in this technique is called <sup>11</sup>C-(1)dihydratetrabenazine (DTBZ). This radiolabeled molecule targets the vesicular monoamine transporter 2 (VMAT2) of the pancreatic beta cells and the signal from this molecule allows for measurement of beta cell mass.

DTBZ was previously used as a marker of dopaminergic neurons in the brain.<sup>7</sup> DTBZ PET was subsequently used to study the pancreas in mice studies, which showed that measured beta cell mass correlated well with glucose control in rodent models of type 1 diabetes.<sup>8</sup> A follow up study used the technique in humans and showed that in comparison to a healthy group, type 1 diabetics had a ~40% decrease in functional VMAT2 binding capacity (a calculated metric based on PET data).<sup>9</sup> A clinical trial is now underway examining beta cell mass in healthy, type 1 diabetic, and obese participants to test the ability to distinguish between people with normal, decreased, and increased beta cell mass respectively.<sup>10</sup>

This study aims to correlate beta cell mass resected during surgery and the onset on diabetes after the operation. This data will help predict the risk of post-operative diabetes for prospective partial pancreatectomy patients. A physician would be able to perform a pre-operative PET scan, estimate the beta cell mass to be removed by a potential procedure, and then estimate the risk for post-operative diabetes. This information would be useful for counseling patients on the risks of surgery. It may also be useful for determining whether surgery is indicated in borderline cases, especially considering no firm guidelines for indications are yet in place and that these pre-malignant lesions progress slowly. Furthermore, this study would serve as a reference for future studies that examine beta cell mass: it could allow us to correlate calculated metrics established by PET scan and actual beta cell mass. These data will further contribute to our understanding of how beta cell mass plays a role in the development of diabetes.

## **2. Study Design and Statistical Analysis**

This is a case-control study in which cases are participants who become diabetic after pancreatectomy and the controls are those who do not. The outcome, percent functional VMAT2 binding capacity decrease (pre- vs. post-operatively) will be measured as a continuous variable as a metric for beta cell mass. The average percent beta cell mass resected in the diabetic and non-diabetic group will be compared.

Patients will be enrolled from the New York Presbyterian Pancreas Center after the diagnosis of intraductal papillary mucinous neoplasm. Approximately 150 patients per year undergo partial pancreatectomy at the Pancreas Center, approximately 100 of which are for premalignant or malignant exocrine tumors. Based on this data a sample size of 100 was selected so that patients could be enrolled over 3 years (assuming 1/3 of the patients with exocrine tumors have pre-malignant lesions). Partial pancreatectomy typically results in removal of 20-60% of the pancreatic tissues so a conservative standard deviation of 10% was used for each group (diabetic and non-diabetic). Using an unpaired t-test with a power of 0.8, an alpha of 0.05, sample size 50 per group, standard deviation of 10%, the study is powered to detect an effect size of 5.7%. By comparison the effect size was 40% in a study of beta cell mass of healthy subjects and those with type 1 diabetes as mentioned above.

## **3. Study Procedure**

After the patient and the surgeon determine that partial pancreatectomy is appropriate, the patient will be offered enrollment into the study. The patient will undergo HbA1c testing to evaluate for diabetes. Diabetics will be excluded from the study. The patient will then undergo a DTBZ PET study, which is not part of routine medical care. The patient will be injected with a bolus of DTBZ and then undergo a 90-minute PET scan. The precise settings will be as previously described.<sup>9</sup> MRI is also needed for anatomical calibration of the PET scan. Patients will likely already have these completed as part of their diagnostic work up. If not, then MRI will be completed.

Patients will then undergo partial pancreatectomy as otherwise planned by their surgeon. At discharge, patients will be given supplies and education regarding home glucose monitoring. Patients will be instructed to inform their physician about their fasting and post-prandial levels so that they can receive appropriate treatment. At 6 months post-operation, patients will be undergo repeat DTBZ PET, MRI and HbA1c testing to determine presence or absence of diabetes. HbA1c cutoff of 6.5 will be used

as this is now recommended by the American Diabetes Association <sup>11</sup> and it would be beneficial to avoid instructing patients with possible brittle diabetes to fast for a fasting glucose level.

#### **4. Study Drugs**

No new medical devices or drugs are being tested in this study.

#### **5. Study Questionnaires**

No study questionnaires will be used.

#### **6. Study Subjects**

100 patients will be enrolled at the Pancreas Center after the diagnosis of suspected IPMN.

Inclusion criteria: diagnosis of suspected IPMN; surgery deemed appropriate treatment.

Exclusion criteria: pre-operative HbA1c > 6.5, prior diagnosis of diabetes mellitus.

#### **7. Recruitment**

Patients will be informed of the study by their physician at the Pancreas Center after diagnosis of suspected IPMN. If interested, the patient will be recruited by a representative from the study investigator group.

#### **8. Confidentiality of Study Data**

Data will be depersonalized and stored in a secure location that is only accessible to the study investigators.

#### **9. Potential Risks**

DTBZ PET has been shown to be safe in previous studies of humans as cited above. The dose of radiation of similar PET scans is on the order of 10 mSv <sup>12</sup>. For comparison, an adult abdominal CT delivers approximately 10 mSv and a screening mammogram delivers approximately 3 mSv. <sup>13</sup>

#### **10. Potential Benefits**

Patients will receive evaluation for diabetes before and after the operation. The largest benefits will be for future patients whose care may be improved from the data acquired in this study.

#### **11. Alternatives**

No therapy is being given as part of this study.

#### **12. References**

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