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Full Title:	Prediction of exocrine and endocrine insufficiency after pancreaticoduodenectomy using volumetry
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Article Type:	Original Article
Keywords:	pancreatic surgery; volumetry; exocrine insufficiency; endocrine insufficiency
Abstract:	<p>The aim of this study is to evaluate the use of pancreatic volumetric assessment to predict exocrine and endocrine insufficiency after pancreaticoduodenectomy. Thirty-seven patients who underwent pancreaticoduodenectomy were included in the study. Endocrine function was assessed in all patients without a history of diabetes using an oral glucose tolerance test. A 13C-labeled mixed triglyceride (MTG) breath test evaluated exocrine function before and after resection. Volumetric measurements were performed on CT or MRI.</p> <p>The volumetric measurements could not predict pre- or postoperative diabetes. Moreover, the resected volume was significantly lower in patients who developed diabetes after resection. Comparing patients with a normal and disturbed postoperative MTG, postoperative volumes and parenchymal thickness were significantly different. The parenchymal thickness on postoperative imaging is withheld as a predictive factor (OR = 0,85 [95%CI 0.71-1.01], p=0,049) and. The best cut-off value is a parenchymal thickness of less than 11,4 mm (AUC = 0,76, p =0,025, sensitivity= 88,9%, specificity = 70,0%).</p> <p>Pancreatic remnant volumetry and parenchymal thickness measurement after pancreaticoduodenectomy are correlated with exocrine insufficiency, but with a limited predictive value. None of the preoperative measurements are withheld to predict postoperative exocrine function. Pre- and postoperative volumetry appear to have no use in predicting postoperative diabetes.</p>
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Prediction of exocrine and endocrine insufficiency after pancreaticoduodenectomy using volumetry.

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The authors report no conflicts of interest

Prediction of exocrine and endocrine insufficiency after pancreaticoduodenectomy using volumetry.

Objectives

The aim of this study is to evaluate the use of pancreatic volumetric assessment to predict exocrine and endocrine insufficiency after pancreaticoduodenectomy.

Methods

Thirty-seven patients who underwent pancreaticoduodenectomy were included in the study. Endocrine function was assessed in all patients without a history of diabetes using an oral glucose tolerance test. A ^{13}C -labeled mixed triglyceride (MTG) breath test evaluated exocrine function before and after resection. Volumetric measurements were performed on CT or MRI.

Results

The volumetric measurements could not predict pre- or postoperative diabetes. Moreover, the resected volume was significantly lower in patients who developed diabetes after resection. Comparing patients with a normal and a disturbed postoperative MTG, postoperative volumes and parenchymal thickness were significantly different. The parenchymal thickness on postoperative imaging is withheld as a predictive factor (OR = 0,85 [95%CI 0.71-1.01], $p=0,049$) and. The best cut-off value is a parenchymal thickness of less than 11,4 mm (AUC = 0,76, $p=0,025$, sensitivity= 88,9%, specificity = 70,0%).

Conclusions

Pancreatic remnant volumetry and parenchymal thickness measurement after pancreaticoduodenectomy are correlated with exocrine insufficiency, but with a limited predictive value. None of the preoperative measurements are withheld to predict postoperative exocrine function. Pre- and postoperative volumetry appear to have no use in predicting postoperative diabetes.

Keywords: pancreatic surgery; volumetry; exocrine insufficiency; endocrine insufficiency

Introduction

Pancreaticoduodenectomy (PD) is the standard type of surgery for most malignant and some benign lesions of the pancreatic head and periampullary region. Improvements in both surgical technique and perioperative management have decreased postoperative mortality to around 2,5% [1] although postoperative morbidity remains high. In recent years, pancreatic surgery has been performed more frequently because of refined diagnostic tools that enable earlier detection benign or pre-malignant lesions before they transform to a malignancy, and because more patients with borderline resectable adenocarcinoma are referred for surgery after neoadjuvant treatment. These patients are at risk to develop both exocrine and endocrine insufficiency after resection which may have a significant influence on the long-term quality of life.

A decrease in endocrine function and subsequent development of diabetes is presumed after pancreatic resection and can be due to both pancreatogenic diabetes mellitus (DM), classified as type 3c DM according the American Diabetes Association, and further progression of underlying type 2 diabetes. The incidence of postoperative diabetes varies from 5% to 78% [2, 3, 4, 5, 6] and seems to differ depending on the site of resection [4, 7]. Measurement of the pancreatic remnant volume and percentage of resected volume has been described by several authors as an independent predictive factor for the development of new-onset DM after distal pancreatectomy[2]. After pancreaticoduodenectomy, the use of these volumetric measurements has not yet been evaluated [4].

Exocrine insufficiency may be due to parenchymal volume loss after pancreatic surgery and may deteriorate further by ongoing atrophy of the pancreatic remnant. A previous study by Nakamura et al. has shown that the reduced postoperative parenchymal thickness is a reliable indicator of exocrine insufficiency following PD [8]. In 2016 a study by Okano found the pancreatic remnant volume to best predict exocrine insufficiency after pancreatic resection

[9]. There is no morphometric marker described that is correlated with pre-existing exocrine dysfunction.

The aim of this study is to evaluate the use of volumetry of the pancreas to help predict exocrine and endocrine insufficiency after PD. To our knowledge this is the first study that combines systematically performed function tests and volumetry on imaging before and after PD to try to diagnose and predict pre- and postoperative exocrine and endocrine function.

Material and methods

All patients that underwent a pancreaticoduodenectomy in our center between January 2013 and December 2015 were included in this retrospective observational cohort study. All patients underwent a pylorus-preserving PD and reconstruction was done by a single layer of interrupted PDS 4/0 sutures to the back side of the stomach. No stent was used.

Endocrine function was assessed in all patients without a history of diabetes at surgical intake (= known diabetes) with a glycated haemoglobin (HbA1c) measurement and an oral glucose tolerance test (OGTT) before and after surgery. Following overnight fasting, an oral glucose load of 75g (Glucomedics®, Lambra) was administered. Blood sampling for plasma glucose, plasma insulin and c-peptide was performed at fixed time intervals (0, 30, 60, 120 minutes). The results were interpreted according the American Diabetes Association's criteria for DM [10]. Postoperative OGTT was performed at a mean interval of $2,7 \pm 2,1$ months. In patients treated with adjuvant chemotherapy the test was performed before the start of the regimen.

Weight and height were measured by a qualified nurse on admission to the hospital and during follow-up at the outpatient clinic. Body mass index (BMI) was calculated. Bilirubin plasma levels were controlled on the same day as the OGTT because elevated

bilirubin levels may be an indicator for liver mediated insulin resistance and may therefore influence the OGTT results [11, 12].

Exocrine function was assessed using a ^{13}C -labeled mixed triglyceride (MTG) breath test. During this breath test, 250mg of the substrate 1,3-distearyl-(^{13}C -Carboxyl)octanol glycerol is mixed with a test meal and digested in the small bowel through lipase. The breath test analyses the cumulative recovery of $^{13}\text{-CO}_2$ (cumulative dose percentage) with isotope ratio mass spectrometry. A cut-off value of 23% $^{13}\text{-CO}_2$ after 6 hours was used (= MTG%): results were considered as disturbed if MTG% <23. There is an excellent correlation between bowel lipase activity and $^{13}\text{-CO}_2$ concentrations in the breath [13]. Postoperative testing was done at a mean interval of $3,4 \pm 6,4$ months.

Volumetry was performed retrospectively on all patients with adequate imaging both pre- and postoperative (Figure 1). Imaging was considered adequate if a scan with intravenous contrast was available. Preoperative imaging was considered when performed within 4 weeks of the operation. The timing of the postoperative imaging varied from 2-6 months after surgery. If both computed tomography (CT) and magnetic resonance imaging (MRI) were available, the volumetric assessment was done on the latter. Volumetry was performed by a single radiologist with extensive experience in this field. The pancreatic contours were manually traced on each of the consecutive slices containing the pancreas. Pancreatic volume was calculated by multiplying the areas of the traced surfaces in each slice by the slice thickness. The total pancreatic volume in each case was obtained by adding up the volumes in all slices. Special attention was given to subtract vascular structures, bile duct and peripancreatic fat tissue from the measured volume. The following measurements were done: preoperative volume of the head and neck (V^{head}), preoperative volume of the body and tail (V^{tail}), tumor volume (V^{tumor}), postoperative volume of the pancreatic remnant (V^{remnant}), the total pancreatic diameter and main pancreatic duct diameter. From these measurements the

total pancreatic volume minus the tumor volume (V^{total}), the parenchymal thickness is calculated by subtracting the main pancreatic duct diameter from the total pancreatic diameter on both pre- and postoperative imaging (PT^{pre} and PT^{post}) and the resected volume in percentage (Res%) were calculated ($(V^{\text{total}} - V^{\text{remant}} / V^{\text{total}}) * 100 = \text{Res\%}$)

Statistical analysis

Results were analysed using SPSS (version 24.0, Chicago, IL). Normality was checked using the Shapiro Wilk method and by visual inspection of Q-Q plots and histograms. Continuous data are expressed as mean (standard deviation) for normally distributed variables and as median (range) for non-normally distributed variables. Categorical variables are expressed as numbers (%). Results were considered statistically significant for a p-value <0.05 . Distribution of groups were compared using Mann-Whitney U test for non-normally distributed data. The unpaired t-test was used to compare means between groups for normally distributed data. Pearson correlation was used to find a correlation between continuous data. A binomial logistic regression or linear regression was performed to find a predictive model when appropriate.

Informed consent and approval of the local Ethical Committee was acquired (Belgian registration number: BE300201318590). This study is conducted according to the ethical principles stated in the ‘Declaration of Helsinki’ and stated in ‘Good Clinical Practice’.

Results

Patient characteristics

During the study period 68 patients underwent a pancreaticoduodenectomy, 31 patients were excluded from the analysis due to the lack of adequate pre- and postoperative imaging. Patient characteristics are summarized in table 1. Known DM, meaning history of diabetes at surgical intake, was present in 9/37 (24,5%) patient. With preoperative OGTT testing, 7/37

(19,0%) patients had a new diagnosis DM and in an additional 12/37 (32,0%) patients the glucose metabolism was disturbed and could be classified as pre-diabetes using the American Diabetes Association criteria. In 9/37 (24,5%) the OGTT results were normal. A preoperative MTG test was performed in 35/37 patients and revealed an underlying exocrine insufficiency in 6 patients (Figure 2). The median V^{head} was 39,0 ml (20,0- 109,0), median V^{tail} was 30 ml (2,3- 78,0), median V^{total} was 60,0 ml (25,0- 122,1). The tumor volume varied between 0 and 28ml with a median value of 7,0 ml. The median PT^{pre} was 13,9 mm (3,0- 23,5) and PT^{post} 11,0 mm (3,7- 25,0). An average of $75,7 \pm 10,8\%$ of the pancreas was resected.

In the patients screened with OGTT after surgery postoperative DM was present in 8/28 (29%) patients, 4/28 (14%) patients were classified as pre-diabetes. In 11/28 (39%) patients' glucose metabolism remained stable after resection and in 5/28 (18%) patients the OGTT improved after PD. Exocrine function deteriorated in 20/37 (54,1%) patients after resection but improved in 2/37 (5,4%) patients. (Figure 1)

Relationship between pancreatic volumetry, bilirubin and glucose metabolism before surgery.

Can a relationship between preoperative pancreatic volumetry, tumor mass, elevation of bilirubin levels and glucose metabolism be found? The volumetric measurements and bilirubin level before surgery are summarized in table 2. A Kruskal-Wallis test was conducted to determine if these parameters differed significantly between groups defined by preoperative endocrine function. Distributions of both V^{head} , V^{total} and PT^{pre} are statistically different ($p=0,018$, $0,040$ and $0,023$ resp.) and this due to the smaller V^{head} and V^{total} in the known DM group. Pairwise comparisons between groups however revealed no statistically significant difference.

Relationship between pancreatic volumetry and glucose metabolism after pancreaticoduodenectomy

As expected, endocrine function in all of the 9 patients with a known history of DM remained stable after PD. Therefore these patients were excluded from postoperative analysis. We compared patients who were diagnosed with postoperative DM to all other patients (normal OGTT and prediabetes) and found a significant difference between the Res%, V^{remnant} and PT^{post} (resp. $p = 0,025$, $p = 0,008$, $p = 0,008$). However the results are the opposite of what was expected: the Res% is lower in patients who develop DM and V^{remnant} and PT^{post} are higher in the postoperative DM group (Table 3).

Furthermore, preoperative BMI and age were not predictive for postoperative endocrine insufficiency. Patients with a normal OGTT had an average BMI of $25,1 \pm 3,7$ kg/m² and age of 64 ± 11 yrs. Patients with postoperative DM had a BMI of $24,7 \pm 5,1$ kg/m² and age of 63 ± 10 yrs.

Relationship between pancreatic volumetry and exocrine insufficiency after pancreaticoduodenectomy

A preoperative MTG test was performed in 35/37 (94,6%) patients and revealed an underlying exocrine insufficiency in 6/37 (16,2%) patients. No correlation could be found between the preoperative volumetry and pre-existing exocrine insufficiency. The patients with a pre-existing exocrine insufficiency or without preoperative function test were excluded from further analysis. Subsequently the relationship between the measurements and the cumulative percentage ¹³-CO₂ (MTG%) at 6 hours was assessed. There was a moderate positive correlation between PT^{pre} and MTG% using Spearmans rank-order correlation, $r_s(29) = 0,525$, $p = 0,003$. The distribution of V^{tail} was significantly different between the group that developed exocrine insufficiency after the resection (25,5ml [2,9 – 78,0]) and the group with

normal MTG after surgery (35,0ml [17,0-49,0]) $p=0,045$, but both PT^{pre} and V^{tail} could not be withheld as predictive factors in multivariate analysis. In 20/29 (68,9%) patients exocrine function deteriorated after surgery.

The postoperative volumetric measurements, $V^{remnant}$, Res% and PT^{post} , were significantly different between the groups with postoperative disturbed and normal MTG (resp. $p = 0,015$, $p = 0,039$, $p = 0,023$) (Table 4). PT^{post} is withheld in multivariate analysis (OR = 0,85 [95%CI 0.71-1.01], $p=0,049$) as a predictive factor. The best cut-off value was defined by ROC curve analysis and a PT^{post} value of less than 11,4 mm could most accurately predict a disturbed MTG result after resection (AUC = 0,76, $p = 0,025$) with a sensitivity of 88,9% and specificity of 70,0%. Spearman's rank-order correlation coefficients for MTG% and $V^{remnant}$, Res% and PT^{post} are shown in table 5. Using linear regression PT^{post} could statistically significantly predict MTG% at 6 hours, $F(1,27)$, $p = 0,011$ and PT^{post} accounted for 21,4% of the explained variation in MTG%. When we used the linear regression equation $MTG\% = 3,392 + (1,27 * PT^{post})$, the value for PT^{post} that can best predict a MTG% result below 23% was 15 mm (95% CI: 16,5- 28,4).

Discussion

Endocrine insufficiency

The prevalence of pancreatogenic or type 3c DM in a general population is 8%. The major cause is chronic pancreatitis, pancreatic surgery accounts for 3% of all cases [10, 14].

In pancreatic adenocarcinoma, some tumor-related factor seems to influence the glucose metabolism. This is suggested by Pannala et al. who observed a resolution of preoperatively diagnosed DM after pancreatic resection in 57% of patients [15]. In the present study the glucose metabolism improved after PD in 6/28 (21,4%) patients with preoperative prediabetes or diabetes. Five of these patients were being treated for pancreatic adenocarcinoma and one

patient underwent resection for an ampulloma. Therefore the tumor volume was investigated in this report, but no relationship between tumor volume and presence of preoperative DM was found.

In chronic liver disease, markers for common bile duct obstruction are associated with the development of insulin resistance, metabolic syndrome and type 2 DM. However the influence of elevated serum bilirubin level before and after pancreaticoduodenectomy has not been clearly identified. Nagino et al. reported that the impaired insulin secretion caused by obstructive jaundice is not reversed until 4-6 weeks after biliary drainage[16]. In this series elevated bilirubin was found in 15/37 patients. There was no significant difference in bilirubin levels between the preoperative groups based on OGTT (table 2). The influence of neoadjuvant chemotherapy was not taken into account in this series but may also influence preoperative OGTT results, however only 3/37 (8,1%) patients were treated with neoadjuvant chemotherapy (table 1).

A possible correlation between the total pancreas volume, main pancreatic duct diameter and preoperative DM was suggested by Sakata et al. but he did not make a distinction between patients with a known history of DM and those diagnosed with DM during their preoperative tests [17]. Our data confirm this correlation between V^{total} and the presence of preoperative endocrine insufficiency but suggest that this is attributed to a smaller pancreas volume in patients with known DM, and no significant difference is seen between patients with newly diagnosed DM and normal OGTT.

The incidence of postoperative DM varies widely with reports of 5% to 78%[2, 3, 4, 5, 6] . This variance may be due to the wide spectrum of surgical indications (malignancy, chronic pancreatitis, pre-malignant lesions), due to the lack of systematically performing function test after resection or due to the varying demographics.

Many factors may influence the glucose metabolism after pancreatic surgery, such as several demographics (age, ethnicity, BMI, weight), surgical complications, changes in pancreatic hormones influencing glucose production and utilization, and changes in insulin sensitivity. Ongoing postoperative atrophy of the pancreatic remnant may significantly increase the risk of postoperative DM. A suggested mechanism of atrophy of the remnant is the loss of the gastrointestinal hormones cholecystokinin and gastrin due to resection of the duodenum and in some cases the distal stomach[18] or due to an obstruction of the pancreatic duct caused by stenosis of the pancreatico-enteric anastomosis.

Several authors have reported BMI at the time of surgery to be a predictive factor for developing DM postoperatively[19]. In this series however, BMI in patients with a normal OGTT after surgery was similar to those developing DM (resp. $25,1 \pm 3,7$ and $24,7 \pm 5,1$ kg/m²) and the present study could not confirm the role of this predictive factor.

The percentage of resected pancreas (Res%) and resection volume assessed with volumetry on CT has been used to predict development of DM postoperatively by several authors. King et al. estimated that no more than 20-25% of normal residual pancreas was required to maintain clinically normal glucose homeostasis after distal pancreatectomy[20]. Pancreatic volumetric assessment has been described by Shirakawa et al.[2] for patients undergoing distal pancreatectomy. They found a resection of more than 44% of the pancreas to be an independent risk factor for the development of postoperative DM. They did not however perform function tests systematically before and after resection which may cause an underestimation of the number of patients with DM. Kwon et al.[19] found that Res% was predictive for postoperative DM in patients that underwent a distal pancreatectomy for a benign lesion. He describes a resection volume of more than 21,21 ml as a predictive factor (AUC= 0,67, sensitivity= 61%, specificity= 69%, OR 3,75 [95%CI 1,35- 9,48]) and a Res%

greater than 35,6% (AUC 0,69, sensitivity= 55%, specificity= 69%, OR 5,18 [95%CI 1,80-14,88]).

A possible bias in using Res% is the preoperative measurement of the total pancreatic volume. In many patients there is some extent of swelling of the pancreas due to pancreatitis on the preoperative imaging, therefor overestimating the V^{total} and Res%.

Only a few reports have studied the relationship between the remnant volume and the development of DM after pancreaticoduodenectomy. In the report by Sakata a resection of 90% of the pancreas resulted in DM one year after PD, although this conclusion was based on only three patients and no OGTT was performed [17]. Both reports by Kwon et al. and Iizawa et al. found no relationship between resection volume in patients that underwent PD or central pancreatectomy and postoperative DM [3, 19]. A possible explanation for this discrepant finding in PD versus DP patients, is the reported two-fold higher islet cell distribution/density in the pancreatic tail compared with the pancreatic head and body[21].

On the other hand Yun et al. reported recently that the pancreatic volume reduction rate (current pancreas volume/ preoperative total pancreas volume) at 6 months after PD was predictive for new-onset DM compared to the measurements on imaging at 7 days, 12, 24 and 36 months[22]. This finding however deals more with the consequences of pancreatic remnant atrophy in the long term, than with the immediate effects resected volume and pre-existing atrophy before surgery.

In our analysis we find the opposite relationship between postoperative diabetes and the volumetric measurements after PD. Res% is lower and V^{remnant} and PT^{post} are higher in the postoperative DM group. Although patient groups are small and may be underpowered, it seems reasonable to conclude that there is no role for pancreatic volumetry in predicting

diabetes after PD. It also suggests that “parenchym-preserving techniques” as used in liver surgery may not be translated to pancreatic surgery.

Exocrine insufficiency

Several published studies have suggested that pancreatic exocrine function after pancreatectomy is associated with various factors such as underlying pancreatic diseases, patency of the pancreatico-enteric anastomosis and degree of fibrosis in the pancreatic remnant[23, 24]. In this study we have tried to exclude patients with underlying pancreatic disease by performing a preoperative MTG test. Obstruction of the pancreatic duct can lead to pancreatic fibrosis[25, 26] which results in atrophy of the pancreas[7]. Furthermore reports have shown that histologic loss of pancreatic exocrine cells in the pancreatic stump was associated closely with postoperative pancreatic exocrine dysfunction after pancreatectomy[25]. Therefore it can be expected that the remnant pancreas volume and the parenchymal thickness may be correlated with the occurrence of exocrine insufficiency.

Sato et al. showed that exocrine function after pancreatic resection was significantly influenced by the morphology of the pancreas at the presumed transection line and suggested the PT^{pre} as a predictive factor [27]. In 2016 Okano et al. reported that pancreatic enzyme replacement therapy should be considered for patients who have remnant pancreatic volume < 24.1 ml by CT volumetry [9]. In 2011 Nakamura reported that PT^{pre} was predictive for developing exocrine insufficiency using a cut-off value of 14,5 mm (AUC = 0,70) with a sensitivity of 67,6% and a specificity of 69,2%. This finding could not be validated in this study, although there was a significant, but moderate correlation between MTG% and PT^{pre} ($r_s(29) = 0,525$, $p = 0,003$). Perhaps this can be explained by the fact that all patients with preoperative exocrine insufficiency were excluded in our data, whereas in Nakamura’s study, no preoperative function test was performed and it can be presumed that patients with

preoperative exocrine dysfunction may have biased his analysis. Furthermore Nakamura et al. also found PT^{post} to be a predictive factor for exocrine insufficiency after PD, suggesting a cut-off value of 13mm (AUC = 0,90) with corresponding sensitivity of 88,2% and specificity of 88,9% [8]. Similarly in the present study PT^{post} was the most accurate predictor for exocrine insufficiency: a PT^{post} of less than 11,4 mm could most accurately predict a disturbed MTG result after resection (AUC = 0,76, $p = 0,025$) with a sensitivity of 88,9% and specificity of 70,0%. A moderate to good correlation was found between $V^{remnant}$, Res%, PT^{post} and MTG%.

This difference in predictive value of the preoperative and postoperative parenchymal thickness suggests that there are postoperative factors that cause ongoing changes to the pancreatic remnant and further influence exocrine function besides the reduction in pancreatic volume. For instance outflow obstruction to the pancreatic duct because of stenosis at the pancreaticogastrostomy or pancreatitis in the postoperative period resulting in acinar cell loss.

Limitations / future perspectives

The strength of this study is the thorough documentation of both exocrine and endocrine function before and after pancreatic resection. It helps to exclude several confounding factors, such as pre-existing exocrine insufficiency and underlying glycemic disturbances. The study is limited by the number of included patients, the variety of underlying pathology and its retrospective study design.

Conclusion

Volumetry of the pancreatic remnant and measurement of the parenchymal thickness after pancreaticoduodenectomy are correlated with exocrine insufficiency. However, these measurements are difficult to use in daily practice and have only a limited predictive value. A systematic postoperative function test, such as a ^{13}C -labeled mixed triglyceride (MTG) breath test, remains much more accurate and is easier to perform. None of the preoperative

measurements are withheld to predict postoperative exocrine function. Pre- and postoperative volumetry appears to have no use in predicting postoperative DM after pancreaticoduodenectomy.

Figures

Figure 1. Example of volumetric measurements on CT

Total pancreatic diameter = 12,5mm; main pancreatic duct diameter = 6,0mm; surface area head = 2,85cm²; surface area tail = 12,36cm²

Figure 2. Endocrine and exocrine function before and after surgery

Figure 3. Postoperative diabetes and $V^{\text{remnant}}(\text{a})$, $\text{Res}\%(\text{b})$ and $\text{PT}^{\text{post}}(\text{c})$

Figure 4. Postoperative exocrine function and $V^{\text{remnant}}(\text{a})$, $\text{Res}\%(\text{b})$ and $\text{PT}^{\text{post}}(\text{c})$

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Submission to the Acta Chirurgica Belgica

Dear Editor-in-Chief

We would like you to consider our manuscript entitled “Prediction of exocrine and endocrine insufficiency after pancreaticoduodenectomy using volumetry.” for publication.

As HBP surgeons we have tried to identify risk factors for the development of exocrine and endocrine insufficiency after Whipple’s procedure. In particular we tried to assess if the amount of resected volume is linked to development of these insufficiencies.

Although the volumetry on CT and MRI was performed in a retrospective manner, all patients underwent prospective testing of endocrine and exocrine function before and after surgery using an oral glucose tolerance test and mixed triglyceride breath test.

The patient population is rather small and our manuscript can be considered to be a pilot study. However, we find it worth reporting due to the surprising fact that the volume of resected pancreas is not related to the development of postoperative diabetes. Instead we found that the larger the resected volume, the lower the risk. This supports the idea that there are different factors that influence endocrine function besides pancreatic mass.

A strong relationship with the resected volume and development of exocrine insufficiency was not found and we therefore believe that there is no role for volumetry. This suggests that “parenchym-preserving techniques” used in liver surgery may not be translated to pancreatic surgery.

We confirm that this manuscript has not been published elsewhere and is not under consideration by another journal.

All authors have approved the manuscript and agree with its submission to the Acta Chirurgica Belgica. There are no conflicts of interest or sources of funding to declare.

Sincerely yours,

Vera Hartman, M.D.

Table 1. Clinical characteristics

	n	% - range
Male	16	43%
Age (years)	66	38-86
Weight (kg)	72	49-101
Body mass index (BMI)	25,2	18,7-35,6
Indication for surgery		
Suspected malignancy	31	84%
Pre-malignancy	6	16%
Histology resection specimen		
Adenocarcinoma	27	73%
No malignancy	2	5%
IPMN	3	8%
Neuroendocrine tumor	3	8%
Duodenal carcinoma	2	5%
Neoadjuvant therapy	3	8,1%
Preoperative endocrine function		
Normal	9	24,3%
Pre-diabetes	12	32,4%
Newly diagnosed diabetes	7	18,9%
Known diabetes	9	24,3%
Preoperative exocrine function		
Normal	29	78,4%
Low	6	16,2%
No test performed	2	5,4%

Table. 2 Volumetric assessment and bilirubin levels according to preoperative endocrine function

Preoperative	Normal OGTT (9/37)	Pre-diabetes (12/37)	Newly diagnosed diabetes (7/37)	Known diabetes (9/37)	Kruskal- Wallis (p-value)
V ^{tumor}	10,0 (1,3- 28,0)	7,1 (0- 20,0)	5,2 (1,5- 12,2)	7,2 (0,8- 20,0)	ns
V ^{head}	46,0 (35,0-73,0)	36,0 (26,0- 109,0)	42,5 (29,0- 45,0)	27,0 (20,0- 57,0)	0,018
V ^{tail}	34,0 (18,0- 52,0)	25,5 (2,3- 78,0)	38,5 (16,0- 49,0)	19,0 (10,6- 55,0)	ns
V ^{total}	67,1 (53,6- 94,6)	52,8 (25,0- 122,1)	68,2 (54,9- 83,5)	41,3 (26,9- 92,0)	0,040
Bilirubin	0,52 (0,3- 7,5)	0,99 (0,4- 10,0)	2,60 (0,5- 14,0)	0,89 (0,3- 13,0)	ns
PT ^{pre}	14,8 (7,6- 20,0)	9,6 (6,0- 22,0)	17,0 (9,3- 19,7)	8,3 (3,0- 23,5)	0,023

Table 3 Volumetric assessment according to postoperative endocrine function

Postoperative (excl. known diabetes)	No diabetes (20/28)	Diabetes (8/28)	Mann-Whitney U (p-value)
Vremnant	12,5 (3,3- 37,0)	20,4 (8,7- 35,0)	0,008
Res%	80,1 (68,2- 93,3)	74,1 (63,0- 82,0)	0,025
PT ^{post}	10,7 (5,2- 18,7)	14,1 (8,7- 19,6)	0,008

Table 4. Volumetric assessment according to postoperative exocrine insufficiency

Postoperative (excl. preop disturbed MTG)	MTG normal (9/29)	MTG disturbed (20/29)	Mann-Whitney U test (p-value)
V _{remnant}	21,0 (8,9- 36,0)	10,2 (3,3- 53,0)	0,015
Res%	67,2 (51,6- 85,6)	79,6 (42,4- 93,3)	0,039
PT ^{post}	14,2 (5,2- 20,0)	8,05 (3,7- 25,0)	0,023

Table 5. Correlation between $V^{remnant}$, Res%, PT^{post} and MTG% after surgery

	Spearman correlation	p-value
$V^{remnant}$	0,568	0,001
Res%	-0,470	0,012
PT^{post}	0,610	<0,001

Figure (High Resolution)

Figure (High Resolution)

Exocrine function stable = 9

Exocrine function improved = 2

Exocrine function worsened = 20

Figure (High Resolution)

Figure (High Resolution)