Pancreatic Exocrine Insufficiency in Patients With Pancreatic or Periampullary Cancer

A Systematic Review

Dorine S.J. Tseng, MD, I. Quintus Molenaar, MD, PhD,* Marc G. Besselink, MD, PhD,† Casper H. van Eijck, MD, PhD,‡ Inne H. Borel Rinkes, MD, PhD,* and Hjalmar C. van Santvoort, MD, PhD**

Objectives: The aim of this study was to determine the prevalence of pancreatic exocrine insufficiency in patients with pancreatic or periampullary cancer, both before and after resection.

Methods: Systematic review according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA guidelines). We included studies reporting on pancreatic exocrine insufficiency in patients with pancreatic or periampullary cancer. Data on patient demographics, type of pancreatic resection, diagnostic test, and occurrence of pancreatic exocrine insufficiency were extracted. Prevalence of pancreatic exocrine insufficiency was calculated before and after pancreatic resections and in patients with locally advanced pancreatic cancer.

Results: Nine observational cohort studies with 693 patients were included. Median preoperative prevalence of pancreatic exocrine insufficiency was 44% (range, 42%–47%) before pancreatoduodenectomy, 20% (range, 16%–67%) before distal pancreatectomy, 63% before total pancreatectomy, and 25% to 50% in patients with locally advanced pancreatic cancer. The median prevalence of pancreatic exocrine insufficiency at least 6 months after pancreatoduodenectomy was 74% (range, 36%–100%) and 67% to 80% after distal pancreatectomy.

Conclusion: Pancreatic exocrine insufficiency is diagnosed in approximately half of all patients scheduled to undergo resection for pancreatic or periampullary cancer. The prevalence increases markedly after resection. These data highlight the need of pancreatic enzyme suppletion in these patients.

Key Words: pancreatic exocrine insufficiency, pancreatic cancer, pancreatic resection

(*Pancreas* 2016;45: 325–330)

Pancreatic acinar cells are responsible for the exocrine function and are evenly distributed throughout the pancreas, whereas the Langerhans cells responsible for the endocrine pancreatic function are mostly located in the pancreatic tail.[1] The pancreatic head constitutes approximately 50%, and the body and tail constitute the remaining 50% of the pancreatic parenchymal mass.[2] In pancreatic exocrine insufficiency (PEI), the pancreas is unable to deliver a sufficient quantity of pancreatic enzymes to the small intestine to digest nutrients. This may occur because of obstruction of the pancreatic duct or loss of functional parenchyma. As a result, maldigestion and malnutrition develop, and caloric intake due to fat and protein uptake decreases.

Typical symptoms of PEI include weight loss, steatorrhea, and nutritional deficiencies, especially of the fat-soluble vitamins A, D, E, and K.[3–5] It has been suggested that 5% to 10% of normal enzyme output is sufficient to prevent malabsorption and maintain a normal digestion.[6,7] In a study of patients with pancreatic cancer and their families, difficulties with gut symptoms and related dietary issues (ie, PEI) greatly influenced quality of life.[8]

In patients with pancreatic or periampullary cancer, tumor growth can cause both loss of pancreatic parenchyma and obstruction of the pancreatic duct and thereby PEI. Surgical resection is the only curative option.

Limited data on PEI exist in patients undergoing pancreatoduodenectomy (PD) for pancreatic or periampullary cancer. Most studies on PEI after pancreatic surgery have been performed in patients with chronic pancreatitis. These patients, however, are prone to develop PEI before surgery due to atrophy of acinar cells and replacement of the parenchyma by fibrous tissue due to chronic pancreatitis. Resection can further aggravate the pancreatic insufficiency in these patients.[9]

The aim of this review was to assess the prevalence of PEI in patients with pancreatic or periampullary carcinoma undergoing different types of pancreatic resections as well as patients who did not undergo resection because of locally advanced disease. These data are especially relevant because PEI can easily be treated with pancreatic enzyme replacement therapy (PERT).

MATERIALS AND METHODS

Literature Search and Study Selection

A systematic literature search in Pubmed, Embase and the Cochrane Library was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA guidelines)[10] of studies published up to February 20th 2014. The search term was "exocrine pancreatic insufficiency." After removal of duplicates, title and abstract of all studies were screened to identify studies reporting on PEI in patients with pancreatic or periampullary cancer. Two authors (D.T. and H.v.S.) further assessed eligibility of selected studies through screening of full-text articles. Studies written in the English language, reporting on PEI in patients with pancreatic or periampullary cancer, were included. Exclusion criteria were (1) studies reporting on PEI due to other causes, (2) studies not reporting sufficient data to calculate the prevalence of PEI, (3) review articles, and (4) conference abstracts. The included studies were checked for cross-references to identify eligible additional studies that were not identified by our primary search. Any differences were resolved by mutual agreement.

Critical Appraisal of Methodology

All studies were graded according to the Oxford Centre for Evidence-Based Medicine levels of evidence, and the methodological quality of the studies was assessed based on the Oxford Centre for Evidence-Based Medicine Critical Appraisal Skills Programme appraisal sheets for cohort studies.[11]

From the *Department of Surgery, University Medical Center Utrecht, Utrecht; †Department of Surgery, Academic Medical Center, Amsterdam; and ‡Department of Surgery, Erasmus Medical Center, Rotterdam, The Netherlands.
Received for publication November 26, 2014; accepted June 4, 2015.
Reprints: I. Quintus Molenaar, MD, PhD, University Medical Center Utrecht, HP G04.228, PO Box 85500, 3508 GA, Utrecht, The Netherlands (e-mail: i.q.molenaar@umcutrecht.nl).
The authors declare no conflict of interest.

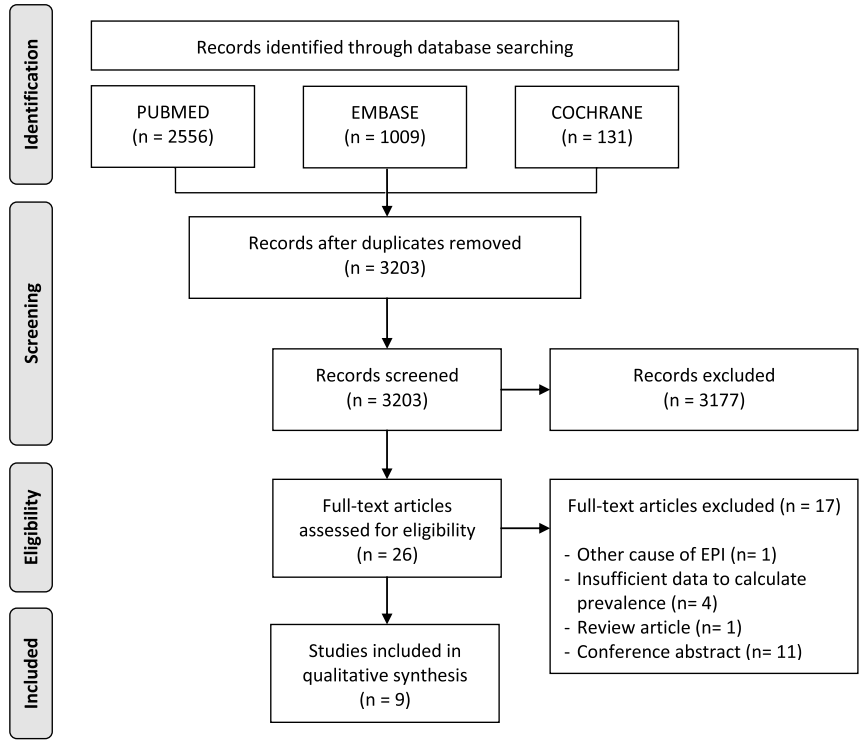

FIGURE 1. Flowchart of study selection and inclusion.

Data Extraction and Analysis

The following data were extracted from each included study: first author, year of publication, study period, patient selection, sample size, patient demographics, type of pancreatic resection, diagnostic test for PEI, and occurrence of PEI. The prevalence of PEI was calculated from these data both before and after operation for the various time points, as mentioned in individual studies. For pooled data, median prevalence of PEI was calculated.

RESULTS

Figure 1 summarizes the results of the literature search. After screening 3203 articles, a total of 26 articles reporting on PEI in patients with pancreatic or periampullary cancer were identified. Subsequently, 17 studies were excluded for the following reasons: studies focusing on other causes of PEI (n = 1), studies providing insufficient data to calculate prevalence of PEI (n = 4), review article (n = 1), and conference abstract (n = 11). No additional studies were included after screening the reference lists of included studies. A total of 9 studies were included in this meta-analysis.

Study Characteristics and Critical Appraisal of Methodology

Characteristics of the 9 studies are summarized in Table 1. Four of 9 studies were prospective observational cohort studies,[12,14,17,18] and 5 studies were retrospective observational cohort studies.[13,15,16,19,20] All but 1 study used fecal elastase-1 (FE-1) test to diagnose PEI. One study used fecal chymotrypsin (ChT) test.[16] One study also compared the results of FE-1 with the results of coefficient of fat absorption (CFA) test.[14] In 5 studies, only patients with PD were included; 1 study exclusively studied distal pancreatectomy (DP); 3 studies studied both; and 1 study only included patients with irresectable disease.

TABLE 1. Study Characteristics

Study	Country	Year	N	Design	Diagnosis PEI
Armstrong et al[12]	United Kingdom	2002	10	Prospective	FE-1
Belyaev et al[13]	Germany	2013	104	Retrospective	FE-1
Halloran et al[14]	United Kingdom	2011	40	Prospective	CFA, FE-1
Matsumoto and Traverso[15]	United States	2006	138	Retrospective	FE-1
Ong et al[16]	Singapore	2000	11	Retrospective	ChT
Partelli et al[17]	Italy	2012	194	Prospective	FE-1
Sikkens et al[18]	Netherlands	2014	29	Prospective	FE-1
Speicher and Traverso[19]	United States	2010	83	Retrospective	FE-1
Tran et al[20]	Netherlands	2008	55	Retrospective	FE-1

The results of the critical appraisal are given in Table 2. All studies were cohort studies and thus Oxford level of evidence 3. Lack of adequate follow-up was the biggest concern in the critical appraisal.

Patient Characteristics

Patient characteristics are summarized in Table 3. The studies reported on a total of 693 patients. Of these patients, 326 patients (47%) underwent PD, 19 patients (3%) underwent total pancreatectomy (TP), and 109 patients (16%) underwent DP. The remaining 239 patients (34%) did not undergo a pancreatic resection due to locally advanced disease. Three studies also reported on PEI in chronic pancreatitis; these patients were excluded in our analysis.[13,15,19]

Outcomes

The prevalence of PEI varied between different types of pancreatic resections. Before PD, median preoperative prevalence of PEI was 44% (range, 42%–47%). Postoperative follow-up varied among studies. Most studies assessed exocrine pancreatic function at least 6 months postoperatively (Table 4). After PD, the median prevalence of PEI at least 6 months postoperative was 74% (range, 36%–100%). Only 1 study reported the presence of new-onset PEI after PD. In this study, normal FE-1 at 3-month follow-up was seen in 39% of patients without preoperative PEI, 12% at 1 year, and 35% at 2 years.[15]

Data on symptoms reflecting PEI after PD were limited. Only 1 study reported the number of patients with steatorrhea-related complaints. This study described that the majority of patients with PEI according to FE-1 did not experience symptoms.[18]

Three studies reported on PEI in patients undergoing DP. Median preoperative prevalence was 20% (range, 16%–67%). Postoperative prevalences and timing of follow-up varied between studies. One study reported an increase in PEI from 20% preoperatively to 80% at 3-month follow-up.[13] In contrast, another study had an equal prevalence preoperatively and at 6-month follow-up (67%), but PEI was seen in only 33% at 1-month follow-up. Noteworthy is that this study only included 3 patients with DP in their analysis. The last study on PEI before and after DP had a preoperative prevalence of 16%, and PEI was present in 22% and 7% of patients at 3- and 12-month follow-up, respectively.

One study assessed PEI before and after TP. In this study, preoperative PEI was present in 63% of patients, whereas, by definition, all patients displayed PEI after the operation. The indication for TP was not clearly defined (eg, extensive tumor growth, intraductal papillary mucinous neoplasm [IPMN]), nor if patients were initially planned for TP or other resections.

The prevalence of PEI in patients with locally advanced pancreatic cancer who therefore did not undergo resection was reported in 2 studies. The first study only included patients who were scheduled for curative resection but found irresectable at laparotomy. Before surgery, PEI was present in 25% of patients. This increased to 37% 3 months after laparotomy.[13] The second study included both patients who were deemed irresectable based on preoperative imaging as patients after laparotomy. Preoperative prevalence of PEI was 50%. Strikingly, clinically evident steatorrhea was only reported in 10% of patients. This study did not report on the course of PEI during follow-up.[17]

DISCUSSION

This is the first systematic review evaluating the prevalence of PEI in patients with pancreatic or periampullary cancer. The main findings are that PEI is diagnosed in 1 in 2 patients preoperatively and that the prevalence markedly increases after surgery, regardless of the type of resection.

The prevalence of PEI after PD for malignant disease found in this review is higher as compared with pancreatic resection for benign disease. Stone et al[21] found that 53% of patients experienced PEI after PD for chronic pancreatitis. In a study on pancreatic resection for chronic pancreatitis, 63% of patients experienced PEI at the last follow-up (median, 56 months) of which 16% had new-onset PEI.[22] Another study found 29% new onset of steatorrhea after PD for chronic pancreatitis.[23] There is no clear explanation for the difference in PEI prevalence between benign and malignant disease. It may be caused by atrophy of the pancreatic tail/remnant due to prolonged obstruction of the pancreatic duct. Atrophy of the pancreatic tail has been described in 45% of patients with pancreatic or periampullary cancer.[24,25] The majority of patients develop severe PEI after PD. The extent of PEI is strongly correlated with preoperative fibrosis. Preoperative dilatation of the pancreatic duct per se does not predict PEI or endocrine pancreatic insufficiency postoperatively.[20]

Our review showed a mean preoperative prevalence before DP of 20% (range, 16%–67%). However, only 3 studies reported PEI before DP, and the upper limit was based on a study that only included 3 patients before DP. When we disregard this study, reported prevalences are comparable with prevalences reported for DP for benign disease. In a meta-analysis of 12 studies on middle

TABLE 2. Critical Appraisal of Methodology

Study	Level of Evidence*	Selection Bias	Measurement Bias	Follow-Up	Applicability
Armstrong et al[12]	3	†	‡/†	†	†
Belyaev et al[13]	3	‡	‡	†	‡
Halloran et al[14]	3	‡	‡	†	‡
Matsumoto and Traverso[15]	3	‡	‡	†	‡
Ong et al[16]	3	‡	‡	‡	‡
Partelli et al[17]	3	†	‡/†	†	†
Sikkens et al[18]	3	‡	‡	‡	‡
Speicher and Traverso[19]	3	‡	‡	‡	‡
Tran et al[20]	3	‡	‡	†	‡

*Level of evidence according to Oxford Centre for Evidence-Based Medicine.

†Partly consistent with criteria, unknown risk of bias.

‡Consistent with criteria, low risk of bias.

TABLE 3. Patient Characteristics

Study	N	Surgery	Diagnosis	Pancreatic Anastomosis
Armstrong et al[12]	10	PD (10)	Pancreatic ductal adenocarcinoma (n = 3) Duodenal cancer (n = 3) Ampullary cancer (n = 2) Cystadenocarcinoma (n = 1) Carcinoid tumor (n = 1)	End-to-side pancreaticogastrostomy
Belyaev et al[13]	133	PD (49) DP (20) TP (19) None/palliative (45)	Malignant (n = 76)* Benign (n = 19)† Chronic pancreatitis (n = 38)†	Unknown
Halloran et al[14]	40	PD (37) DP (3)	Pancreatic ductal adenocarcinoma (n = 17) Periampullary cancer (n = 8) Cholangiocarcinoma (n = 5) Neuroendocrine tumor (n = 5) Others (n = 5)	End-to-side pancreaticojejunostomy
Matsumoto and Traverso[15]	138	PD (138)	Pancreatic ductal adenocarcinoma (n = 31) Periampullary cancer (n = 22) IPMN (n = 41) Islet cell cancer (n = 1) Serous cystadenoma (n = 7) Mucinous cystadenoma (n = 1) Chronic pancreatitis (n = 27)† Other (n = 8)	End-to-side pancreaticojejunostomy
Ong et al[16]	11	PD (11)	Pancreatic ductal adenocarcinoma (n = 1) Duodenal cancer (n = 1) Ampullary cancer (n = 7) Cholangiocarcinoma (n = 1) Duodenal leiomyoma (n = 1)	Pancreaticogastrostomy
Partelli et al[17]	194	None/palliative (194)	Pancreatic ductal adenocarcinoma (n = 194)	Not applicable
Sikkens et al[18]	29	PD (26) DP (3)	Pancreatic ductal adenocarcinoma (n = 12) Ampullary cancer (n = 14) Cholangiocarcinoma (n = 3)	End-to-side pancreaticojejunostomy
Speicher and Traverso[19]	83	DP (83)	Pancreatic ductal adenocarcinoma (n = 10) IPMN (n = 18) Islet cell tumor (n = 14) Serous cystadenoma (n = 19) Mucinous cystadenoma (n = 9) Chronic pancreatitis (n = 6)† Other (n = 7)	Not applicable
Tran et al[20]	55	PD (55)	Pancreatic or periampullary carcinoma (n = 55)*	End-to-side pancreaticojejunostomy

*Not further specified.
†Excluded from analysis.

pancreatectomy versus DP, median prevalence of PEI was 16% after DP.[26] This is comparable with the prevalences of PEI in our review.

The main complaints of patients with PEI are foul smelling, loose stools, and flatulence. In addition, weight loss and muscle wasting can occur.[27] Management of PEI-related symptoms can be established with the use of PERT. Nevertheless, a recent study shows that patients experiencing symptoms of PEI at the time of diagnosis rarely receive treatment.[18] During follow-up, the percentage of patients with PEI receiving PERT increases, but still, not all patients receive PERT, and furthermore, replacement therapy seems suboptimal in up to a third of patients who continuously experience symptoms of PEI despite PERT.[18] Patients with PEI report a lower quality of life with regard to the physical component of validated questionnaires.[13] In addition, an open-label clinical trial on the efficacy of PERT showed significant improvement of quality of life after treatment with PERT, although this was studied in patients with chronic pancreatitis.[28] Given the high prevalence of PEI in patients with pancreatic or periampullary cancer and the increase in prevalence of PEI after pancreatic resection, more attention should be paid to adequate treatment and symptom relief, before and after surgery.

One can only speculate on why PEI is undertreated and also why the presence of PEI is underestimated. Pancreatic exocrine insufficiency can easily be diagnosed by direct and indirect function tests. Direct tests include the CFA test and the test of Van de

TABLE 4. Prevalence of PEI After PD

Study	Preoperative PEI	Postoperative PEI			
		1 Mo	3 Mo	≥6 Mo	≥12 Mo
Armstrong et al[12]	—		—	10/10 (100%)	
Belyaev et al[13]	22/49 (44%)		48/49 (98%)	—	—
Halloran et al[14]	—		24/37 (65%)	17/29 (59%)	12/22 (55%)
Matsumoto and Traverso[15]	58/123 (47%)		—	—	—
Ong et al[16]	—			4/11 (36%)	
Sikkens et al[18]	11/26 (42%)	19/24 (79%)		22/24 (92%)	
Tran et al[20]	—			41/55 (74%)	
Overall, median (range)	44% (42%–47%)	79% (65%–98%)		74% (36%–100%)	

Kamer. These tests measure fat in patients' stools and require patients to maintain a high-fat diet for 5 days and collect their stools for 72 hours.[29] Although considered the reference standard, these tests impose a great burden on patients. Indirect tests are fecal ChT, FE-1 test, and other less often–used tests.[4,30] Chymotrypsin has been in use since the mid-1900s. The main disadvantage of this test is the interference with the enzyme replacement therapy. Fecal elastase-1 is commonly used as it is reliable with a sensitivity of 71% to 100% and a specificity of 80% to 100%, easy to perform without dietary restrictions, and independent of PERT and patients only need to collect a single stool sample.[31–34] In patients with chronic pancreatitis, a clear correlation is seen between low FE-1 and steatorrhea. Conversely, in patients after pancreatic resection, FE-1 can be normal or only slightly reduced despite steatorrhea.[31] However, patients without diarrhea can have reduced FE-1 levels, and the need for PERT in these patients can be debated.[35]

The main limitation of this systematic review is the limited number of prospective studies and the small sample sizes of the included studies. Only 3 of 8 studies on PEI after pancreatic resection were prospective studies, and these studies reported on 79 patients in total. Among these studies, the timing of follow-up also varied. Only 2 studies reported on multiple time points in the postoperative period, and given the limited data, no conclusions can be made on the natural course of PEI or the presence of new-onset PEI after pancreatic resection.[14,18] Nevertheless, these are the data available, and given the high prevalence, clinical relevant symptoms, and adequate treatment, which is frequently not given, we feel this systematic review is clinically very relevant.

Another limitation is that only 1 study used a CFA, the reference standard, to assess pancreatic function,[14] whereas all other studies used indirect tests to confirm PEI, and only 1 study reported on symptoms reflecting PEI.[18] In daily practice, the presence of PEI will regularly be a clinical diagnosis, and not all patients with steatorrhea will have a decreased FE-1 and vice versa.[31,35] However, because FE-1 test mostly underestimates PEI after pancreatic resection, one can consider the results of this review as a conservative estimation of the true prevalence of PEI.[31]

Furthermore, factors such as preoperative pancreatic duct obstruction, coexistence of chronic pancreatitis, volume of the remnant pancreas, and exposure to radiotherapy may influence the occurrence of PEI but were not mentioned in the included studies. Finally, 2 of 8 studies included in this systematic review performed a reconstruction with a pancreaticogastrostomy, whereas all other studies performed a pancreaticojejunostomy. It has been suggested that the pancreatic anastomosis (ie, pancreaticogastrostomy or pancreaticojejunostomy) may influence the occurrence of PEI.[36] However, in this systematic review, the 2 studies in which pancreaticogastrostomy was performed reported a prevalence of PEI that was the lower limit of the prevalence range in 1 study (36%) and the upper limit in the other (100%).[12,16] Thus, PEI seems to be unrelated to the type of reconstruction, and thus, attention should be paid on PEI-related symptoms, regardless of the type of pancreatic anastomosis.

Future studies on PEI in pancreatic cancer should ideally investigate the course of pancreatic insufficiency over time. In addition, it should clearly distinguish between benign and (pre)malignant disease, different types of pancreatic resection, and type of pancreatic anastomosis. This information can then be used to design interventional studies to treat PEI and hopefully improve quality of life in patients with pancreatic or periampullary cancer.

Until more details are elucidated on the natural course of pancreatic insufficiency, especially after PD, high prevalences of PEI suggest that standard postoperative PERT might be a good option.

REFERENCES

1. Neoptolemos JP, Urrutia R, Abbruzzese JL, et al. *Pancreatic Cancer*. New York, NY: Springer Science; 2010.
2. Medline. Available at: http://emedicine.medscape.com/article/1948885-overview-aw2aab6b3. Accessed September 5, 2014.
3. Perez MM, Newcomer AD, Moertel CG, et al. Assessment of weight loss, food intake, fat metabolism, malabsorption, and treatment of pancreatic insufficiency in pancreatic cancer. *Cancer*. 1983;52:346–352.
4. Friess H, Michalski CW. Diagnosing exocrine pancreatic insufficiency after surgery: when and which patients to treat. *HPB (Oxford)*. 2009;11 (suppl 3):7–10.
5. Shamseddine AI, Mukherji D, Melki C, et al. Lymph node ratio is an independent prognostic factor after resection of periampullary malignancies: data from a tertiary referral center in the middle East. *Am J Clin Oncol*. 2014;37:13–18.
6. DiMagno EP. Medical treatment of pancreatic insufficiency. *Mayo Clin Proc*. 1979;54:435–442.
7. Bruno MJ. Maldigestion and exocrine pancreatic insufficiency after pancreatic resection for malignant disease. pathophysiology and treatment. *Pancreatology*. 2001;1:55–61.
8. Gooden HM, White KJ. Pancreatic cancer and supportive care—pancreatic exocrine insufficiency negatively impacts on quality of life. *Support Care Cancer*. 2013;21:1835–1841.
9. Ahmed Ali U, Nieuwenhuijs VB, van Eijck CH, et al. Clinical outcome in relation to timing of surgery in chronic pancreatitis: a nomogram to predict pain relief. *Arch Surg*. 2012;147:925–932.
10. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol*. 2009;62:1006–1012.

11. Oxford Centre for Evidence-Based Medicine. *The Oxford Levels of Evidence 2*. Available at: http://www.cebm.net/index.aspx?o=5653. Accessed September 5, 2014.
12. Armstrong T, Walters E, Varshney S, et al. Deficiencies of micronutrients, altered bowel function, and quality of life during late follow-up after pancreaticoduodenectomy for malignancy. *Pancreatology*. 2002;2: 528–534.
13. Belyaev O, Herzog T, Chromik AM, et al. Early and late postoperative changes in the quality of life after pancreatic surgery. *Langenbecks Arch Surg*. 2013;398:547–555.
14. Halloran CM, Cox TF, Chauhan S, et al. Partial pancreatic resection for pancreatic malignancy is associated with sustained pancreatic exocrine failure and reduced quality of life: a prospective study. *Pancreatology*. 2011;11:535–545.
15. Matsumoto J, Traverso LW. Exocrine function following the Whipple operation as assessed by stool elastase. *J Gastrointest Surg*. 2006;10: 1225–1229.
16. Ong HS, Ng EH, Heng G, et al. Pancreaticoduodenectomy with pancreaticogastrostomy: assessment of patients' nutritional status, quality of life and pancreatic exocrine function. *Aust N Z J Surg*. 2000;70:199–203.
17. Partelli S, Frulloni L, Minniti C, et al. Faecal elastase-1 is an independent predictor of survival in advanced pancreatic cancer. *Dig Liver Dis*. 2012;44: 945–951.
18. Sikkens EC, Cahen DL, de Wit J, et al. Prospective assessment of the influence of pancreatic cancer resection on exocrine pancreatic function. *Br J Surg*. 2014;101:109–113.
19. Speicher JE, Traverso LW. Pancreatic exocrine function is preserved after distal pancreatectomy. *J Gastrointest Surg*. 2010;14:1006–1011.
20. Tran TC, van 't Hof G, Kazemier G, et al. Pancreatic fibrosis correlates with exocrine pancreatic insufficiency after pancreatoduodenectomy. *Dig Surg*. 2008;25:311–318.
21. Stone WM, Sarr MG, Nagorney DM, et al. Chronic pancreatitis. Results of Whipple's resection and total pancreatectomy. *Arch Surg*. 1988;123: 815–819.
22. Riediger H, Adam U, Fischer E, et al. Long-term outcome after resection for chronic pancreatitis in 224 patients. *J Gastrointest Surg*. 2007;11: 949–959.
23. Schnelldorfer T, Lewin DN, Adams DB. Operative management of chronic pancreatitis: long-term results in 372 patients. *J Am Coll Surg*. 2007;204: 1039–1045.
24. Ahn SS, Kim MJ, Choi JY, et al. Indicative findings of pancreatic cancer in prediagnostic CT. *Eur Radiol*. 2009;19:2448–2455.
25. Chang WI, Kim BJ, Lee JK, et al. The clinical and radiological characteristics of focal mass-forming autoimmune pancreatitis: comparison with chronic pancreatitis and pancreatic cancer. *Pancreas*. 2009;38: 401–408.
26. Iacono C, Verlato G, Ruzzenente A, et al. Systematic review of central pancreatectomy and meta-analysis of central versus distal pancreatectomy. *Br J Surg*. 2013;100:873–885.
27. Lindkvist B. Diagnosis and treatment of pancreatic exocrine insufficiency. *World J Gastroenterol*. 2013;19:7258–7266.
28. Ramesh H, Reddy N, Bhatia S, et al. A 51-week, open-label clinical trial in India to assess the efficacy and safety of pancreatin 40000 enteric-coated minimicrospheres in patients with pancreatic exocrine insufficiency due to chronic pancreatitis. *Pancreatology*. 2013;13:133–139.
29. Van de Kamer J. Total fatty acids in stool. In: Seligson D, ed. *Standard Methods of Clinical Chemistry*. vol. 2. New York, NY: Academic Press; 1958:34–39.
30. Hammer HF. Pancreatic exocrine insufficiency: diagnostic evaluation and replacement therapy with pancreatic enzymes. *Dig Dis*. 2010;28:339–343.
31. Benini L, Amodio A, Campagnola P, et al. Fecal elastase-1 is useful in the detection of steatorrhea in patients with pancreatic diseases but not after pancreatic resection. *Pancreatology*. 2013;13:38–42.
32. Gullo L, Ventrucci M, Tomassetti P, et al. Fecal elastase 1 determination in chronic pancreatitis. *Dig Dis Sci*. 1999;44:210–213.
33. Carroccio A, Verghi F, Santini B, et al. Diagnostic accuracy of fecal elastase 1 assay in patients with pancreatic maldigestion or intestinal malabsorption: a collaborative study of the Italian Society of Pediatric Gastroenterology and Hepatology. *Dig Dis Sci*. 2001;46:1335–1342.
34. Löser C, Möllgaard A, Fölsch UR. Faecal elastase 1: a novel, highly sensitive, and specific tubeless pancreatic function test. *Gut*. 1996;39: 580–586.
35. Lemaire E, O'Toole D, Sauvanet A, et al. Functional and morphological changes in the pancreatic remnant following pancreaticoduodenectomy with pancreaticogastric anastomosis. *Br J Surg*. 2000;87:434–438.
36. Rault A, SaCunha A, Klopfenstein D, et al. Pancreaticojejunal anastomosis is preferable to pancreaticogastrostomy after pancreaticoduodenectomy for longterm outcomes of pancreatic exocrine function. *J Am Coll Surg*. 2005;201:239–244.