

Review Article

Pancreatic exocrine insufficiency in pancreatic cancer: A review of the literature

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ABSTRACT

Pancreatic exocrine insufficiency is a well-documented complication of chronic pancreatitis; however, study results of pancreatic exocrine insufficiency in pancreatic cancer are less consistent. This applies for patients who are treated non-surgically and those who undergo curative pancreatic cancer resection.

This review article summarizes relevant studies addressing pancreatic exocrine insufficiency in pancreatic cancer, with particular differentiation between non-surgically and surgically treated patients, as well as between the different surgeries. We also summarize studies addressing pancreatic enzyme replacement therapy in pancreatic cancer.

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1. Introduction

Pancreatic exocrine insufficiency (PEI) is a known complication of both benign and malignant pancreatic diseases, pancreatic resection, and post-surgical alteration of the anatomy of the foregut. It is defined as inadequate pancreatic enzyme activity for digestion caused by insufficient pancreatic enzyme production, insufficient activation, or disturbed enzyme deactivation [1].

1.1. Physiology of pancreatic enzyme release

Pancreatic enzyme release occurs in response to nutritional intake. The initial stimulus is seeing, smelling, and tasting of food which is vagal mediated and termed cephalic phase [2]. Next, gastric distension increases pancreatic enzyme secretion via the gastro-pancreatic reflex (gastric phase) [2,3]. The passage of chyme through the duodenum provides the most robust stimulation of exocrine pancreatic secretion, particularly the passage of hydrolysed triglycerides (free fatty acids). This is termed intestinal phase and is mostly cholecystikinin (CCK) mediated [4–6].

Following duodenal nutrient exposure in healthy volunteers, pancreatic lipase secretion peaks within 30 min at a fourfold higher level than its baseline and decreases to its baseline over 2–4 h in a

biphasic manner. Similar patterns were also found for amylase and trypsin [7–10].

Ultimately, pancreatic exocrine function is inhibited by a physiological feedback mechanism when nutrients reach the distal ileum. In this context, ileal lipid perfusion in 12 healthy volunteers resulted in dose-dependent inhibition of both pancreatic enzyme and bile secretion with unchanged intestinal motor activity [7,11,12].

1.2. Pathophysiology of pancreatic enzyme release in pancreatic cancer

The physiologic biphasic pattern of pancreatic enzyme release is lost in patients with pancreatic cancer, as shown by Ihse et al. A standard meal (Lundh test) prompted only a small peak or no peak in intraduodenal enzyme activity followed by a low plateau phase in 25 patients with pancreatic cancer [13]. Similar findings were demonstrated also in patients with chronic pancreatitis [13,14]. The bicarbonate secretion was decreased as well [15–18].

To our knowledge no pancreatic exocrine secretion studies were done in patients following pancreaticoduodenectomy (PD). However, one can speculate that a duodenal resection, which is the strongest pancreatic exocrine stimulator, further contributes to decreased postprandial pancreatic enzyme secretion in patients with pancreatic pathology.

It is also known that decreased pancreatic exocrine secretion shifts the site of maximal nutrient absorption from the proximal to the distal small intestine. Laver et al. demonstrated in patients with severe PEI due to chronic pancreatitis that, following

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a standard meal, 40% of nutrients were delivered to the terminal ileum whereas only 5% were physiologically malabsorbed in healthy volunteers [19]. In addition, the authors demonstrated that both gastroduodenal and small intestinal transit are accelerated in patients with PEI, which further increases the exposure of the distal ileum to nutrients [19]. Consequently, we can assume that in patients with PEI, pancreatic exocrine secretion is further diminished by a supraphysiologic nutrient exposure of the distal ileum triggering the above mentioned feedback mechanism, which might also affect patients with non-surgically and surgically treated pancreatic cancer.

2. PEI in pancreatic cancer

Despite an estimated incidence of 46,420 pancreatic cancer cases in 2014 in the US, the treatment of pancreatic cancer is often restricted to the oncological aspect whereas PEI is commonly disregarded in this cohort [20]. As of now, several mechanisms of PEI have been described in the context of pancreatic cancer. Pancreatic atrophy secondary to tumour-induced pancreatic duct obstruction and pancreatic fibrosis can lead to preoperative PEI whereas reduction of glandular tissue following pancreatic resection, impending postoperative pancreatic duct occlusion, extensive denervation following lymph node dissection, and surgically altered anatomy contribute further to PEI postoperatively [21].

2.1. PEI in patients with inoperable pancreatic cancer

Early studies by DiMaggio et al. demonstrated a lower trypsin, lipase, and bicarbonate secretion following CCK stimulation in 17 patients with non-resected pancreatic cancer and a pancreatic duct obstruction of 60% or more of its length [22]. Generally, a high prevalence of PEI in patients with unresectable pancreatic cancer was demonstrated in several studies. Perez et al. detected PEI in 75% of cases utilizing a 72-h faecal fat test, and Partelli et al. demonstrated extreme PEI (FE1 $\leq 20 \mu\text{g/g}$) in 25%, severe PEI (FE1 20–100 $\mu\text{g/g}$) in 14%, and moderate PEI (FE1 100–200 $\mu\text{g/g}$) in 11% [23,24]. Lower FE1 level was more frequently diagnosed in patients with pancreatic head cancer, jaundice, and clinical steatorrhea [23,24]. Acknowledging a high prevalence of PEI in this patient cohort, Sikkens et al. prospectively assessed the incidence of PEI in 32 patients with unresectable cancer of the pancreatic head [25]. Based on FE1 testing, 67% of patients had PEI at the time of pancreatic cancer diagnosis and 89% at the 2-month follow-up (median) [25].

These data indicate that PEI is common and progressive in unresectable pancreatic cancer, with a prevalence of 50–100%.

2.2. PEI in patients with resectable pancreatic cancer

Twenty percent of patients with pancreatic cancer undergo pancreatic resection with curative intent. Depending on the cancer location and extent, the PD (Whipple procedure), pylorus-preserving PD (PPPD), distal pancreatectomy (DP), or total pancreatectomy (TP) is offered. The majority of studies analysing PEI in patients with pancreatic cancer focused either on the preoperative and postoperative period or on a comparison between different surgical resection methods. However, most studies were biased by a very heterogeneous patient cohort that most of the time included a larger proportion of patients with benign pancreatic pathology and cystic neoplasms in relation to patients with pancreatic cancer.

2.2.1. PEI before and after pancreatic cancer surgery

Several studies addressed the prevalence of PEI prior to and after pancreatic surgery. Utilizing the secretin stimulation test as the

gold standard, Kato et al. detected PEI in 93% of 14 consecutive patients prior to PD, including 11 patients with pancreatic cancer [26]. Patients with obstructive jaundice tended to have more severe PEI. In comparison with the gold standard, ^{13}C -labelled Trioctanoin breath assay showed similar sensitivity for PEI; however, sensitivities of parallel tested para-aminobenzoic acid (PABA) excretion and faecal chymotrypsin dropped to 67% and 64%, respectively [26]. Comparable numbers were published by other groups. Sato et al. preoperatively detected PEI in 46% based on PABA (44 patients, including 11 with pancreatic cancer and 7 with ampullary adenocarcinoma), and Matsumoto et al. detected PEI with FE1 in 68% of patients with pancreatic cancer (31 patients), including 42% of cases of severe PEI (FE1 $<100 \mu\text{g/g}$) [27,28].

Postoperatively, the prevalence of PEI increased from 46% to 75% at 2 months in Sato et al.'s study (11 PD, 29 PPPD) and persisted in all patients with preoperative pancreatic duct diameter $\geq 10 \text{ mm}$ ($n=3$) at 12 months [27]. Matsumoto et al. only reported a significant drop of FE1 in patients with normal preoperative FE1, whereas low preoperative FE1 levels remained unchanged at the 1- and 2-year postoperative follow-ups (171 PPPD, 11 PD) [28]. These results were limited, however, by a substantial patient dropout [28]. Focusing on the postoperative long-term outcome, Nordback et al. detected PEI with FE1 in all patients with pancreatic cancer at a median follow-up of 52 months (pancreatic cancer in 6/26 patients, 6 PD, 15 PPPD, 5 duodenum-preserving pancreatic head resection [DPPHR]), although this study was limited as the majority ($n=20$) of patients had chronic pancreatitis and cystic neoplasms [29].

In contrast, a significant postoperative improvement of pancreatic exocrine function was documented by Kodama et al., though only in ampullary cancer following PD ($n=25$). Urinary PABA excretion rose from 35% prior to surgery ($n=9$) and 34% at 2 months ($n=25$) to 72.9% ($n=8$) at 12 months postoperatively, yielding the same level as a healthy control group (72.7%) [30]. Tanaka et al. confirmed these findings, yet again the study was limited to patients with ampullary cancer [31]. The authors speculated that pancreatic duct obstruction was the culprit of PEI which resolved postoperatively in patients with ampullary cancer [30,31]. Whether these data can be extrapolated to patients with pancreatic cancer remains unclear.

2.2.2. PEI following PD versus PPPD for pancreatic cancer

Yamaguchi et al. compared postoperative prevalence of PEI in patients undergoing PD ($n=10$) and PPPD ($n=44$) [32]. Patients in the PD cohort had mostly pancreatic cancer, ampullary cancer and cystic neoplasms, whereas only half of PPPD were performed for pancreatic malignancy. Within 3 months postoperatively, mean PABA excretion decreased in both cohorts from 61.6% to 41.3% and 69% to 48.8%, respectively. Eventually, PABA excretion rose to 64.1% in the PPPD cohort, but remained low in the PD cohort at 6 months. These results were also limited by a substantial patient dropout (Fig. 1) [32].

2.2.3. PEI following pancreatic cancer resection utilizing pancreaticojejunostomy versus pancreaticogastrostomy

Pancreaticojejunostomy is the most common pancreaticoenteric anastomosis followed by pancreaticogastrostomy in the setting of PD and PPPD [33,34]. The initial study by Lemaire et al. detected PEI in 94% of patients based on a 72-h faecal fat excretion (median 28 g/24 h) and in 100% of patients based on FE1 at 32 months (median) following PD with pancreaticogastrostomy (14 benign pancreatic tumours, 5 pancreatic cancer) [35]. Nakamura et al. found PEI utilizing ^{13}C -labelled mixed triglyceride breath testing in 62.3% of 61 patients with a pancreaticogastrostomy following PPPD or PD (including 8 pancreatic cancer, 10 biliary cancer, 13 ampullary cancer, and 24 cystic neoplasms) with a postoperative follow-up range of 3–108 months [36]. Lastly, Jang et al. compared

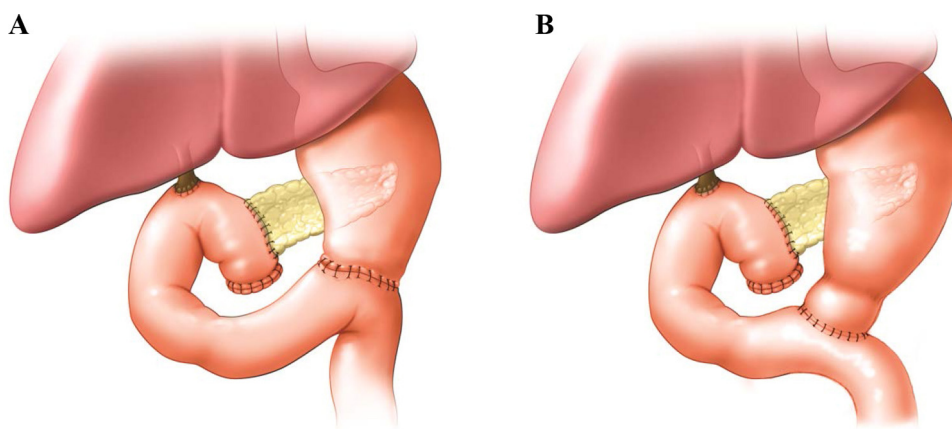


Fig. 1. Pancreaticoduodenectomy (Whipple procedure) (A) and pylorus-preserving pancreaticoduodenectomy (B). Patients with resectable pancreatic head cancer typically undergo the Whipple procedure or the pylorus-preserving pancreaticoduodenectomy. Both procedures are associated with pancreatic exocrine insufficiency (PEI). Beside the reduction of pancreatic parenchyma several mechanisms contributing to PEI have been proposed. Firstly, a derangement of antral grinding in combination with a distant proximal pancreas location results in poor mixture of chyme with pancreatic enzymes. Secondly, lymph node dissection and transection of the duodenum result in disruption of branches of the vagus nerve connections causing altered gastric emptying and decreased pancreatic exocrine function. Lastly, the resection of the duodenum which is the main production site of the two important exocrine pancreatic stimulants Secretin and CCK, results in declined pancreatic exocrine function.

the prevalence of PEI in 20 patients undergoing pancreaticojejunostomy with 14 patients undergoing pancreaticogastrostomy in the setting of PPPD (10 pancreatic cancer, 17 cholangiocarcinoma) [37]. Based on FE1 testing, 95% patients in the pancreaticojejunostomy cohort and 100% in the pancreaticogastrostomy cohort had PEI at 21.9 and 26.5 months, respectively, although most patients remained asymptomatic [37].

2.2.4. PEI following DP for pancreatic cancer

Speicher et al. studied 83 patients following DP with FE1 testing (56% pancreatic cystic neoplasms, 12% pancreatic cancer) [38]. Preoperatively, 30% patients with pancreatic cancer and 66% with chronic pancreatitis were diagnosed with PEI. Postoperatively, patients with normal preoperative FE1 only developed PEI when the resection extended to the right of the portal vein (12% at 3-month and 8% at 12-month follow-up). None of the patients had PEI at the 24-month follow-up. A subgroup analysis for pancreatic cancer was, however, not performed [38].

2.2.5. PEI following PD and PPPD versus DP for pancreatic cancer

Differences of PEI magnitude and prevalence between pancreatic head and pancreatic tail resections were pointed out in several cohort studies. Sato et al. detected a significant drop in PABA excretion in all patients following PPPD (27 patients, including 7 pancreatic cancer and 5 ampullary cancer) from 72.9% preoperative to 47.3% 2 months postoperative [39]. In contrast, no significant change in PABA excretion was reported in the DP cohort ($n=12$) [39]. Similarly, Sikkens et al. reported a postoperative rise in the prevalence of PEI based on FE1 testing from 42% to 92% at 6 months (PPPD [$n=24$] and PD [$n=2$]), whereas the prevalence of PEI remained unchanged in the DP ($n=3$) cohort at 66% [40]. Of note, this study included only patients with malignant tumours (pancreatic head [$n=9$], body or tail [$n=3$], ampullary [$n=14$], and distal common bile duct [$n=3$]) [40]. The higher postoperative PEI prevalence following pancreatic head resection versus DP was also delineated by Yuasa et al. in 110 patients who underwent PD ($n=10$), PPPD ($n=70$), and DP ($n=30$) for intraductal papillary mucinous neoplasm (IPMN, $n=30$), pancreatic cancer ($n=26$), ampullary cancer ($n=15$), and cholangiocarcinoma ($n=10$) [41]. Based on ^{13}C -labelled mixed triglyceride breath test at 17 months (median) postoperative, 64% of patients had PEI in the pancreatic head resection cohort (PD and PPPD) and 30% in the DP cohort ($n=30$) [41].

2.2.6. Summary of PEI following pancreatic resection for pancreatic cancer and limitations of available data

In summary, the available data indicate that PEI occurs in 46–100% of patients with resectable pancreatic cancer. Following PD and PPPD prevalence of PEI remains high at a rate of 70–100%, irrespective of whether patients undergo PD or PPPD and whether a pancreaticogastrostomy or pancreaticojejunostomy is performed. A lower prevalence of PEI (30–66%) is found in patients with DP, which can be explained by preservation of the duodenum. Whether patients with pancreatic cancer experience long term improvement of pancreatic exocrine function following pancreatic surgery cannot be drawn at that point. These conclusions are limited by the heterogeneous and small cohorts, as well as the utilization of non-gold standard testing for PEI. A substantial limitation of FE1 as a non-gold standard test for PEI is highlighted in two recent studies which challenge the results of previously outlined publications. Halloran et al. found no correlation between the 72-h faecal fat excretion test and FE1 testing in 40 patients with pancreatic cancer, ampullary carcinoma, and cholangiocarcinoma following PPPD ($n=21$), PD ($n=16$), and DP ($n=3$) for which the authors questioned the reproducibility and accuracy of FE1 testing in postoperative patients [42]. Benini et al. tested parallel 72-h faecal fat excretion and FE1 in 42 patients with conservatively managed chronic pancreatitis and cystic fibrosis and in 40 patients following PPPD ($n=37$), PD ($n=1$), or TP ($n=2$) for cystic neoplasms ($n=25$), pancreatic cancer ($n=8$), and neuroendocrine tumour ($n=4$) [43]. The authors demonstrated good correlation between both tests only in conservatively managed patients, with FE1 $<100\text{ }\mu\text{g/g}$ achieving sensitivity and specificity of 93.3% and 81.5% respectively. However, in agreement with Halloran et al., FE1 did not correlate with the 72-h faecal fat assay in postoperative patients. The authors suspected that small bowel bacterial overgrowth, derangement of antral grinding, and poor mixing of digestive enzymes with chyme in postoperative anatomy cause PEI-independent steatorrhea [43]. These findings indicate to avoid FE1 and faecal chymotrypsin assays for postoperative assessment of steatorrhea.

3. Symptoms and quality of life in patient with pancreatic cancer and PEI

It is a common assumption that severe PEI is always associated with dyspepsia and steatorrhea as a result of fat malabsorption. This is based on early studies of DiMagno et al. demonstrating that

mild PEI with subtle changes on pancreatic function tests resulted in no significant clinical symptoms, whereas severe PEI, with loss of 90% of pancreatic exocrine function in chronic pancreatitis, caused maldigestion of fat and protein leading to dyspepsia and steatorrhea [44]. However, more recent studies of unresectable pancreatic cancer, including two trials with 12 and 194 patients, respectively, found no statistically significant correlation between subjective steatorrhea and the presence of fat malabsorption verified by stool testing [23,24]. In fact, only 16.7% of patients with very severe PEI had clinically evident steatorrhea in one trial. Whereas 5.2% of patients had subjective steatorrhea without objective PEI [24].

Similar findings were described in the postoperative setting. Neoptolemos et al. detected PEI with 72-h faecal fat testing in 56% of patients following PD ($n=11$), PPPD ($n=6$), DPPHR ($n=5$), DP ($n=7$), necrosectomy ($n=4$), and TP ($n=6$), though the aetiology of pancreatic disease was not disclosed in this study [45]. The presence of PEI did not correlate with dyspepsia, only with stool volume and frequency. Of note, 60% of patients with a faecal fat content >15 g/24 h had no or only mild dyspepsia [45]. Also, Traverso et al. reported no dyspepsia in 7 out of 8 patients following PPPD (1 duodenal cancer, 1 pancreatic cancer, 8 chronic pancreatitis) despite the presence of severe PEI based on a 72-h faecal fat assay (mean 44 g/24 h) [46]. Altogether, these results demonstrate a lack of correlation between dyspepsia and PEI both in non-surgical patients with pancreatic cancer and patients following pancreatic surgery [23,24,45,46].

Weight loss is a well-known problem of patients with pancreatic cancer who do not qualify for curative resection, and furthermore, it is often the herald of the terminal disease stage. Yet, postoperative weight loss was also reported by multiple authors. van Berge Henegouwen et al. reported a mean body weight loss, in relation to the baseline body weight, of 7% following pancreatic cancer diagnosis and 15% at the 3-month postoperative follow-up in 125 patients who underwent PD ($n=56$) and PPPD ($n=69$) [47]. Huang et al. found a similar range of postoperative weight loss, averaging 24 pounds in patients with pancreatic cancer ($n=54$), but only 10 pounds in patients with chronic pancreatitis ($n=34$) and 1 pound in a control cohort (laparoscopic cholecystectomy, $n=37$) at a mean follow-up of 47 months [48]. It is unclear whether malabsorption, decreased caloric intake, or both are the culprit of postoperative weight loss following pancreatic cancer surgery. In regard to non-surgical patients with pancreatic cancer, Perez et al. proved that only fat and protein malabsorption, not calorie consumption, correlated significantly with weight loss [23]. Whether the data can be extrapolated to postoperative patients with pancreatic cancer remains unclear. In this context, a lower quality of life, which includes the presence of dyspepsia and weight loss, was shown by Halloran et al. in 40 patients following PD, PPPD, and DP for underlying malignancy when postoperative PEI was present [42].

4. Predictors for PEI following pancreatic surgery

The clinical impact of PEI, which was reviewed in the previous paragraph, stresses the importance to identify patients at risk for development of postoperative PEI. Multiple authors used the pancreatic main duct diameter, the pancreatic glandular diameter, and the degree of pancreatic fibrosis as predictors for postoperative PEI [41]. Focusing on the main pancreatic duct diameter, Sato et al. reported in 44 patients, including 11 with pancreatic cancer, that a preoperative duct diameter ≥ 10 mm was associated with a lower postoperative PABA excretion at 2 months in comparison with normal preoperative duct diameter (53% versus 89%) [27]. Addressing postoperative pancreatic main duct dilation, Matsumoto et al. failed to prove a correlation between postoperative duct dilation (>3 mm) and FE1 excretion [28]. Assuming anastomotic stricturing to be the

culprit of duct dilation in this study, the authors concluded that a reduction of pancreatic tissue contributed more than an anastomotic stricture to postoperative PEI [28].

Nakamura et al. compared postoperative ^{13}C -labelled mixed triglyceride breath testing in 52 patients who underwent PPPD mainly for IPMN, ampullary cancer, pancreatic cancer, and cholangiocarcinoma with pancreatic parenchymal thickness on computer tomography imaging [49]. A postoperative pancreatic parenchymal thickness cut-off of 13 mm identified PEI with a sensitivity and specificity of 88.2% and 88.9%, respectively [49].

In contrast to PD and its variants, DP does not alter the bowel anatomy, which implicates that postoperative changes in exocrine pancreatic function can be mainly attributed to decreased pancreatic parenchyma. In this context, Speicher et al. demonstrated that patients with normal preoperative pancreatic exocrine function developed PEI only when the DP extended to the right of the portal vein, which reflects a larger resection [38]. Additional studies confirmed that the magnitude of pancreatic glandular reduction correlates with postoperative PEI [50].

Combining both pancreatic thickness and duct diameter, Sato et al. found a negative correlation of postoperative PABA excretion rate following PD and PPPD (39 patients, including 7 pancreatic cancer) and the preoperative ratio of pancreatic main duct and parenchymal diameter at the presumed surgical transection line on computer tomography images [39]. In summary, both dilated pancreatic duct and diminished pancreatic parenchymal thickness on pre- and postoperative assessment correlate with a higher rate of postoperative PEI.

Prediction of PEI by magnetic resonance imaging and endoscopic ultrasound is, as of now, limited to conservatively managed patients with chronic pancreatitis [51–54].

5. Overview of pancreatic enzyme replacement therapy for PEI

Indication for pancreatic enzyme replacement therapy (PERT), according to expert opinion, is progressive weight loss and steatorrhea defined as at least 7–15 g faecal fat per day on a 100 g fat per day diet [55,56]. However, there is no substantial data to support these guidelines [55]. To achieve optimal lipid digestion 25,000–50,000 international units (IU) of lipase (equals 75,000–150,000 United States Pharmacopoeia units [USP]) are required for a typical meal.

It is a general assumption that effective PERT requires optimal mixture of pancreatic enzymes and chyme as proximally as possible in order to optimize digestion. In patients who are managed conservatively, PERT needs to be taken during or after consumption of the meal. The optimal timing of postoperative PERT in relation to food intake is unclear [57,58].

A known limitation of PERT is that lipase is inactivated by gastric acid. Therefore, with the exception of Viokace® (Pancrelipase), current pancreatic enzyme replacement preparations consist of acid-resistant, pH-sensitive microspheres which prevent denaturation of lipase by gastric acid. Moreover, lipase is released from microspheres at a pH of 5.5–6, which is assumed to be in the duodenum.

Current available microsphere sizes are 1–2 mm. This is based on studies in healthy volunteers, which revealed that sphere sizes of 1 mm emptied faster than chyme into duodenum whereas spheres of 2.4–3.2 mm did slower. Both extremes result in dissociation of duodenal passage of enzymes and chyme [59–61]. By extrapolation, optimal sphere size was calculated to be 1.4 mm [59,60].

5.1. PERT in patients with inoperable pancreatic cancer

As of now, multiple studies showed improved fat absorption with pH-sensitive microsphere formulation in comparison to

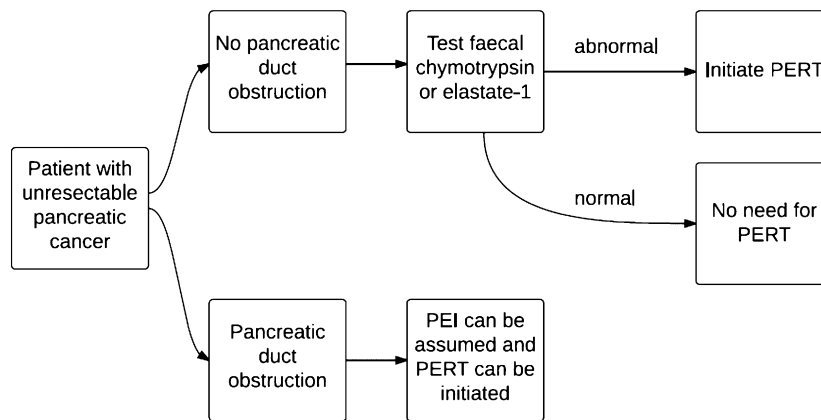


Fig. 2. Pancreatic enzyme replacement therapy in patients with unresectable pancreatic cancer. Patients without evidence of pancreatic duct obstruction are at risk for pancreatic exocrine insufficiency (PEI). PEI should be assessed with faecal chymotrypsin or FE1 in lieu of a 72-h faecal fat assay. A diagnosis of PEI warrants initiation of pancreatic enzyme replacement therapy (PERT), irrespective of the presence or absence of subjective PEI symptoms. In patients with evidence of pancreatic duct obstruction PEI can be assumed in practically all patients warranting initiation of PERT.

conventional pancreatic enzyme preparations or placebo in patients with chronic pancreatitis and PEI [62–68]. However, only a few studies addressed the utility of PERT for patients with inoperable pancreatic cancer. Bruno et al. randomly assigned 21 patients with pancreatic cancer following endoscopic biliary decompression into a placebo or PERT group. All patients experienced weight loss prior to the randomization [69]. At 4 weeks, patients in the PERT group ($n = 11$) regained 1.2% of their body weight, whereas patients in the placebo group ($n = 10$) lost 3.7% [69]. More recently, Domínguez-Muñoz et al. presented a retrospective, not randomized case series of 76 patients with inoperable pancreatic cancer [70]. The patients received either Creon® (Pancrelipase) replacement with nutritional counselling and palliative care ($n = 45$) or standard palliative care without PERT ($n = 21$). Although measurement of PEI was not mentioned in this study along with absence of randomization of treatment, the median survival of patients with PERT was longer than the survival of patient with standard palliative therapy alone (301 days versus 89 days) [70].

An important limitation of previous studies that have addressed PERT is the not well understood gastric emptying kinetics in patients with conservatively managed pancreatic pathology. In that context no data exist for pancreatic cancer and the information is extrapolated from studies in chronic pancreatitis and from healthy volunteers. Bruno et al. showed that 2 mm spheres emptied faster into the duodenum than a radioactive labelled solid meal in patients with chronic pancreatitis (50th percentile 24 min versus 52 min). Of note, the emptying rate into the duodenum in healthy volunteers showed opposing results (50th percentile 172 min and 77 min) [71]. In conjunction with these results, Domínguez-Muñoz et al. analysed the timing of PERT in relation to food intake in patients with chronic pancreatitis and documented PEI. Utilizing ^{13}C -labelled mixed triglyceride breath test, PERT given along with or following food intake resulted in better fat absorption than PERT administration before food intake, although the findings were not significant [57]. These results are in agreement with current PERT guidelines in conservatively managed pancreatic conditions in terms of timing of PERT administration in relation to food intake [1,55,72]. Similar studies do not exist for patients with inoperable pancreatic cancer and postoperative patients.

In summary, the available studies indicate that PEI is present in more than 50% of patients with inoperable pancreatic cancer. Further, PEI appears not to correlate with the presence of clinically evident steatorrhea. Obstruction of the pancreatic duct is not universally present in patients with unresectable pancreatic cancer. However, Bruno et al.'s results indicate that this subgroup of

patients with pancreatic cancer can benefit from PERT in terms of a decelerated weight loss (Fig. 2) [69].

5.2. PERT in patients following PD

Data on the utility of PERT for PEI following surgery for pancreatic cancer are limited as well. Braga et al. induced complete PEI by occluding the pancreatic duct with Neoprene following PD for mostly malignant conditions [73]. Although patients regained weight on PERT, they remained on average 7% under the preoperative weight. In addition, they had an elevated mean faecal fat excretion (10.7 g/24 h) at 2.5 years [73]. Even higher rates of steatorrhea and postoperative weight loss were reported in a recent study by Sikkens et al. Despite PERT in 37 patients with pancreatic cancer following PD (84%), 68% of patients had subjective steatorrhea and 46% of patients reported further weight loss [74]. The same authors demonstrated a comparable rate of subjective steatorrhea (40%) in 29 patients with mostly pancreatic cancer following PPPD ($n = 24$), PD ($n = 2$), and DP ($n = 3$) on PERT, although the BMI remained stable in this cohort between diagnosis and the 6-month follow-up [40]. These results were also confirmed by Huang et al. who reported abdominal pain in 41% of patients and presence of foul stools in 59% of patients on PERT for PEI following PPPD (80%) or PD (20%) for pancreatic cancer [48].

In summary, the limited data of patients with pancreatic cancer who underwent PD reveal persistence of subject steatorrhea in 40–68% of cases while receiving PERT. The body weight appears to stabilize on PERT postoperatively, although data from controlled studies are lacking (Fig. 3).

Whether a change in gastric emptying kinetics following pancreatic surgery alters the efficacy of PERT is currently unclear. Most available studies addressed acute postoperative gastric emptying changes, but long term changes are underreported [75–77]. In this context, Patti et al. measured gastric emptying in 10 patients 1–45 months post-PPPD for underlying malignancies [78]. Following PPPD, gastric emptying was normal in 6 patients, rapid in 3, and delayed in 1 [78]. The difference in gastric emptying following duodenectomy emphasizes the difficulty to achieve optimal synchronous release of PERT and chyme into the small bowel.

This was also addressed by Bruno et al. who compared effectiveness of PERT in patients with PEI following PD ($n = 7$) or PPPD ($n = 5$) for pancreatic, biliary, or duodenal cancer [79]. Based on ^{14}C -labelled octanoate breath test and PABA excretion, PERT improved PEI in patients after PD to a greater extent than after PPPD [79]. Moreover, the authors found that pancreatic enzymes

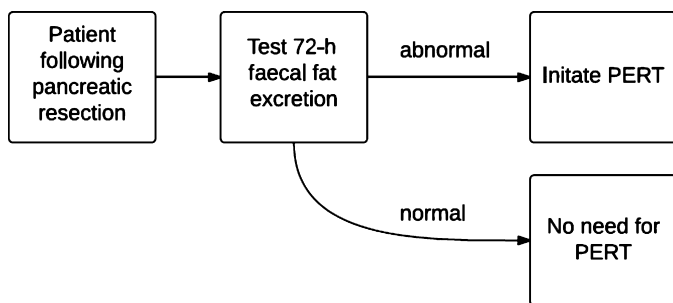


Fig. 3. Pancreatic enzyme replacement therapy in patients following resection of pancreatic cancer. Patients following pancreatic resection are at risk for pancreatic exocrine insufficiency (PEI), with a higher risk following pancreaticoduodenectomy versus distal pancreatectomy. Surgically altered anatomy, alterations of digestive hormones and disruption of nerve connections result in PEI despite significant remaining pancreatic parenchyma. In that case, PEI should be assessed with a 72-h faecal fat assay, warranting initiation of pancreatic enzyme replacement therapy (PERT) in case of PEI diagnosis, irrespective of the presence or absence of subjective PEI symptoms.

and solid food were released asynchronously into the jejunum only in patients after PPPD due to a prolonged gastric emptying time of pancreatic enzyme microspheres [79].

Based on the limited data, the optimal timing and formulation of PERT administration in relation to food intake post-PD and PPPD remains unknown.

6. Randomized controlled trials of PERT in patients with pancreatic cancer

Given the mixed results of PERT for PEI following PD in uncontrolled studies, randomized controlled trials are required to evaluate efficiency and optimal administration of PERT. The only placebo-controlled, randomized trial addressing PERT that included patients with pancreatic cancer was published by Seiler et al. [80]. The authors randomized 58 patients with severe PEI based on faecal fat testing, including 14 patients with pancreatic cancer, into a PERT ($n = 32$) or a placebo ($n = 26$) group 6 months following PD or PPPD ($n = 29$), DPPHR ($n = 13$), and other procedures ($n = 12$). In patients with underlying malignancy fat absorption improved with PERT from 54.8% to 69.4% whereas fat absorption decreased in the placebo group from 62.7% to 46.3%. Additionally, patients on PERT reported less frequent bowel movements; however, surprisingly, they had more adverse events, with flatulence being the most common one [80].

Similar findings were shown in several placebo-controlled, randomized trials of PERT for patients with chronic alcoholic pancreatitis who were treated conservatively or who underwent drainage procedures. Improvement, but incomplete resolution of subjective and objective steatorrhea was reported. In addition, PERT also had a higher incidence of adverse drug reactions like pain, dyspepsia, and flatulence [81–84].

6.1. Safety of PERT

Hyperuricosuria and especially colonic fibrosis are well described adverse drug reactions of long-term PERT, although limited to the paediatric literature in patients with cystic fibrosis [85–87]. Only few data exist on the prevalence of adverse outcomes of long-term PERT in adults. Gullo et al. reported 227 patients with chronic pancreatitis who received PERT from porcine pancreatic extract with a pH-sensitive polymer packed in gelatin capsules [88]. Ten capsules were administered daily, which reflects a dose of 135,000 USP units lipase and 105,000 USP units amylase. At a mean follow-up of 20.2 months, no adverse events were recorded beyond

occasional dyspepsia and heartburn. Fifteen patients who received PERT for 4 years had normal colonic thickness by ultrasound [88]. Most recent, open-labelled PERT trials lasting for 6–12 months did not report significant adverse drug reactions either [89,90].

7. Conclusion

Most of the current knowledge of pancreatic enzyme physiology relies on studies performed in healthy volunteers and patients with chronic pancreatitis. Available data on patients with pancreatic cancer suggest presence of fat malabsorption in a high proportion of patients at the time of the diagnosis. Progression of pancreatic cancer and pancreatic cancer surgery can additionally aggravate PEI.

PERT is the standard of care in patients with PEI in the setting of chronic pancreatitis. Studies that included non-surgical candidates and postoperative patients with pancreatic cancer tended to show an improvement of both subjective symptoms, like dyspepsia, as well as objective findings, including body weight and faecal fat excretion, with PERT. Confirmatory studies with randomized controlled protocols are paramount, but currently not available. New oncologic protocols (e.g., FOLFIRINOX) improved the survival of patients with pancreatic cancer. In this context, the optimization of the performance status of patients with pancreatic cancer is of the highest importance in order to make those patients eligible for new adjuvant or palliative options. We suspect that PERT plays a role here, but confirmatory studies are required. Further studies are required to determine optimal dose and timing of PERT in relation to meals in patients following PD.

Conflict of interest

None declared.

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