Nutritional support and therapy in pancreatic surgery: A position paper of the International Study Group on Pancreatic Surgery (ISGPS)

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\textbf{ABSTRACT}

\textbf{Background:} The optimal nutritional therapy in the field of pancreatic surgery is still debated.
\textbf{Methods:} An international panel of recognized pancreatic surgeons and pancreatologists decided that the topic of nutritional support was of importance in pancreatic surgery. Thus, they reviewed the best contemporary literature and worked to develop a position paper to provide evidence supporting the integration of appropriate nutritional support into the overall management of patients undergoing pancreatic surgery.
resection. Strength of recommendation and quality of evidence were based on the approach of the grading of recommendations assessment, development and evaluation Working Group.

Results: The measurement of nutritional status should be part of routine preoperative assessment because malnutrition is a recognized risk factor for surgery-related complications. In addition to patient’s weight loss and body mass index, measurement of sarcopenia and sarcopenic obesity should be considered in the preoperative evaluation because they are strong predictors of poor short-term and long-term outcomes.

The available data do not show any definitive nutritional advantages for one specific type of gastrointestinal reconstruction technique after pancreatectoduodenectomy over the others. Postoperative early resumption of oral intake is safe and should be encouraged within enhanced recovery protocols, but in the case of severe postoperative complications or poor tolerance of oral food after the operation, supplementary artificial nutrition should be started at once. At present, there is not enough evidence to show the benefit of avoiding oral intake in clinically stable patients who are complicated by a clinically irrelevant postoperative pancreatic fistula (a so-called biochemical leak), while special caution should be given to feeding patients with clinically relevant postoperative pancreatic fistula orally. When an artificial nutritional support is needed, enteral nutrition is preferred whenever possible over parenteral nutrition.

After the operation, regardless of the type of pancreatic resection or technique of reconstruction, patients should be monitored carefully to assess for the presence of endocrine and exocrine pancreatic insufficiency. Although fecal elastase-1 is the most readily available clinical test for detection of pancreatic exocrine insufficiency, its sensitivity and specificity are low. Pancreatic enzyme replacement therapy should be initiated routinely after pancreatectoduodenectomy and in patients with locally advanced disease and continued for at least 6 months after surgery, because untreated pancreatic exocrine insufficiency may result in severe nutritional derangement.

Conclusion: The importance of this position paper is the consensus reached on the topic. Concentrating on nutritional support and therapy is of utmost value in pancreatic surgery for both short- and long-term outcomes.

Introduction

The metabolic stress response is a physiologic consequence of tissue damage and the resultant inflammatory response. Major surgery produces intense changes in metabolism and nutritional status through the activation of an inflammatory cascade and the release of stress hormones and cytokines; this response appears to be proportional to the extent of the operative trauma. Pancreatic resections are recognized as one of the most challenging operations because of the magnitude of the dissection and resection, the resultant global stress, and the relatively high rate of morbidity. Appropriate tissue healing and recovery/maintenance of organ function after such operations can lead to an effective and efficient metabolic response, which in turn necessitates adequate qualitative and quantitative nutritional substrates to be effective.

Malignant patients or those who experience major complications after surgery may exhaust their nutritional reserves rapidly and thereby compromise their functional recovery and healing. Moreover, other pre-existing comorbidities of many cancer patients, such as diabetes, subclinical organ dysfunction, a defective immune response, and consequences of neoadjuvant treatments, may impair the functional reserve and lead to loss of muscle mass (sarcopenia) and its effects on recovery.

The aim of the present position statement is to provide evidence supporting the integration of appropriate nutritional support into the overall management of patients undergoing pancreatic resection and to define when and how appropriate nutritional support should be prescribed to provide substrates for an optimal metabolic response to improve both the short- and long-term outcomes.

Methods

Given the paucity of specific guidelines on optimal nutritional in the field of pancreatic surgery, a group of internationally recognized surgeons and pancreatologists with confirmed experience in the treatment of pancreatic diseases decided that the topic of nutritional evaluation and support was of importance in pancreatic surgery; therefore, a review of the existing literature, best practices, and any evidence-based studies was undertaken to develop recommendations on perioperative and long-term nutritional care.

In May 2016, all members of the International Study Group of Pancreatic Surgery (ISGPS) were contacted via e-mail to explore their interest in the topic; the first meeting of this group was held in July 2016 at the European Pancreatic Club in Liverpool, UK. During the meeting, several key questions were formulated to acquire and address detailed answers to topics that were undefined or controversial in this particular area of research.

Open queries were assigned to small groups of the authors, who then performed an extensive, web-based literature search focused on specific areas that had been identified by the ISGPS. MEDLINE, Embase, PubMed, Cochrane, and Scopus libraries were queried, and all papers analyzing the relationship between nutrition and pancreatic operations or enzyme supplementation written in English and published since 1980 were considered for inclusion. The terms used for the literature search are reported in the supplementary Table 1. The process of inclusion and exclusion criteria according to the preferred reporting items for systematic reviews and meta-analyses statement1 is summarized in the Figure.

Several revised versions of the first draft of the manuscript were circulated through electronic mail for critical analysis and modification until the final version before submission was approved by all authors in February 2018.

The strength of recommendation and the quality of evidence of the proposed statements are described according to Guyatt et al2 and reported in Table 1.

Discussion

Is routine preoperative evaluation of the nutritional status and malnutrition risk indicated?

Although most patients undergo pancreatic surgery for cancer, the indications for pancreatic resection include a variety of benign and malignant diseases, each with a different impact on the pre-
operative nutritional status. In a retrospective analysis, the rate of patients with pancreatic ductal adenocarcinoma (PDAC) who experienced body weight loss (WL) or impaired functional status or had moderate to high risk of malnutrition at diagnosis was greater than 50%. Malnutrition has been defined classically as WL and low body mass index (BMI). The development and progression of malnutrition can be related to decreased food intake and increased catabolism. WL, a low value of BMI, and loss of muscle mass have been correlated with poor surgical and oncologic outcomes after operations for pancreatic cancer. Thus, all patients undergoing pancreatic surgery should receive a meticulous evaluation of their nutritional status and a screening of the risk of developing malnutrition after operation.

How should nutritional status and risk for postoperative malnutrition risk be assessed?

WL and BMI are easy-to-measure parameters that can be used for patient evaluation at the time of diagnosis and admission. Unfortunately, BMI and WL do not provide reliable information on the relative amount of body components (adipose tissue, the distribution of this adipose tissue visceral versus subcutaneous, and

Table 1
Strength of recommendation and quality of evidence of the statements.

<table>
<thead>
<tr>
<th>Chapter</th>
<th>Statement</th>
<th>Strength of recommendation</th>
<th>Quality of evidence</th>
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<tbody>
<tr>
<td>a</td>
<td>Current nutritional status and risk of postoperative malnutrition should be part of the routine preoperative assessment of patients who are to undergo pancreatic surgery.</td>
<td>1</td>
<td>B</td>
</tr>
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<td>b</td>
<td>Percent of body WL loss over time and BMI should be assessed routinely.</td>
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<td>c</td>
<td>The measurement of body composition and the ratio of the different body compartments should be integrated with WL and BMI estimation, and the assessment should be performed by quantitative abdominal CT. Sarcopenia and sarcopenic obesity are strong predictors of short-term and long-term outcomes.</td>
<td>1</td>
<td>B</td>
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<td>d</td>
<td>Because nutritional status and body composition may be markedly affected by neoadjuvant treatments, it is recommended to monitor these parameters carefully and regularly and to initiate nutritional counseling and support during the neoadjuvant treatment if needed.</td>
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<td>C</td>
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<td>e</td>
<td>Aggressive preoperative nutritional support by enteral or parenteral feeding is indicated only in case of severe preoperative malnutrition and should be continued after the operation regardless early resumption of oral food intake.</td>
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<td>C</td>
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<tr>
<td>f</td>
<td>Oral nutritional supplements and nutritional counseling are indicated in patients with moderate malnutrition with no gastric outlet obstruction or in patients with a moderate risk of developing malnutrition in the early postoperative period.</td>
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<td>g</td>
<td>There is no clear consensus regarding the better surgical procedure for pancreatic head resection that is, PPPD or standard PD, with some studies favoring the former and others the latter for different postoperative aspects. The available data do not show any definitive nutritional advantages for one specific type of gastrointestinal reconstruction technique over the others. The choice of the procedure should, therefore, be based on personal preference and expertise.</td>
<td>1</td>
<td>B</td>
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<td>h</td>
<td>Early resumption of oral intake is safe and should be encouraged within ERAS protocols. Malnourished patients, those at high risk of developing malnutrition, and those who develop severe postoperative complications early after operation should receive supplementary artificial nutrition at once.</td>
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<td>B</td>
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<td>i</td>
<td>Well-nourished patients not achieving at least 50% of the energy/protein requirement by oral intake within 7 days after the operation should receive nutritional support. At present, there is no evidence to show the benefit of avoiding oral intake in clinically stable patients who are complicated by biochemical leakage or mild POPF, while special caution should be given to critically ill patients with CR-POPF who may not tolerate oral food intake.</td>
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<td>C</td>
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<td>j</td>
<td>Oral food intake in patients with CR-POPF should be managed on a case-by-case basis. It is reasonable to place of a feeding tube for enteral nutrition in patients undergoing PD: 1. when the patient presents with severe preoperative malnutrition 2. when the FRS predicts a high risk for developing a POPF 3. in cases of reoperation for major abdominal complications.</td>
<td>2</td>
<td>C</td>
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<td>k</td>
<td>Enteral nutrition is preferred over parenteral nutrition when nutritional support is needed. Routine placement of a feeding tube in all patients during pancreatic surgery is not warranted. Nasojejunal feeding tubes can be placed by endoscopy or fluoroscopy or at the bedside under electromagnetic guidance, depending on availability of these techniques.</td>
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<td>l</td>
<td>Regardless of the type of pancreatic resection or technique of operative reconstruction, patients should be monitored carefully to assess for the presence of endocrine and exocrine pancreatic insufficiency. Taking an accurate patient history is vital, especially looking for any clinical signs of steatorrhea and unexplained WL. In asymptomatic patients with maintenance of adequate nutritional parameters, routine laboratory tests are not indicated.</td>
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<td>m</td>
<td>Fecal elastase-1 is the most readily available clinical test for detection of PEI, but its sensitivity and specificity are not always reliable in patients who have undergone a pancreatic resection. The main clinical consequence of PEI is fat malabsorption. Steatorrhea is the most common clinical manifestation.</td>
<td>1</td>
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<tr>
<td>n</td>
<td>PERT should probably be initiated routinely in patients after a PD and continued for at least 6 months after surgery. PERT should be initiated in patients after a DP who present with PEI symptoms. PERT should be considered for all patients with locally advanced pancreatic cancer.</td>
<td>1</td>
<td>C</td>
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<tr>
<td>o</td>
<td>How should nutritional status and risk for postoperative malnutrition risk be assessed?</td>
<td>1</td>
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muscle mass) and the quantity and quality of fat and muscle wasting.

Several nutritional assessment scores have been developed to determine the magnitude of malnutrition and the risk of developing it. The most popular scores were summarized in supplementary Table 2.

Despite that all these metrics are based primarily on subjective questionnaires, they are easy to calculate and practical to use. Indeed, some of these metrics have been validated recently in several cohorts of patients undergoing general surgery operations. It remains unclear, however, which of these tools or scores are the most relevant and accurate in predicting postoperative complications in patients undergoing pancreatic resections. In fact, the percentage of patients at high risk for malnutrition varies between the scores, and the patients assigned as high risk by these scores were not significantly prone to more postoperative complications. Because these high-risk patients should be candidates for perioperative nutritional support, the discrepancy in predicting poor outcomes with different nutritional screening tools might lead to either nutritional undertreatment or overtreatment with potential detrimental effects.

Serum biomarkers of the status of visceral proteins and liver function have been used traditionally as surrogates for nutritional status and as predictors of postoperative complications. Yet, the value of these markers also remains unclear, because patients may present with normal values of plasma biomarkers but still fulfill the definition of malnutrition by other, more objective parameters.

Does assessment of body composition add value to the evaluation of nutritional status?

Body composition, in particular the measurement of muscle mass and visceral fat, cannot be determined accurately by the more classic subjective evaluation of malnutrition because the proportions of these body compartments may be abnormal in malnourished as well as in normal-weight or even in obese patients. This consideration is important, because patients who have an increased BMI or are obese by measurements of weight alone can still be sarcopenic.

The prevalence of sarcopenia in these studies varied from 19% to 65% because of the heterogeneity of the populations studied, for example, cancer patients at different stages of the disease or non-cancer patients. Nevertheless, the data showed a strong association between preoperative muscle wasting and worse postoperative outcomes. Depletion of skeletal muscle was also an independent predictor of clinically relevant postoperative pancreatic fistula (POPF), increased duration of in-hospital stay, and discharge to a nonhome facility or “skilled nursing/rehabilitation facility” according to the local setting. The combination of excessive intra-abdominal adipose tissue (visceral fat) and loss of muscle mass, a syndrome called “sarcopenic obesity,” has been shown to be a major determinant of procedure-related morbidity and mortality (details of the studies evaluating sarcopenia and sarcopenic obesity are summarized in supplementary Table 3).

When considering long-term outcomes, sarcopenic patients had a decreased overall survival when compared with nonsarcopenic patients, and, for pancreatic cancer patients, sarcopenia was associated with poor tolerance to adjuvant chemotherapy and an earlier recurrence of disease.

Well-defined cutoffs for visceral fat and lean muscle mass have been validated extensively in cancer patients, and quantitative abdominal computed tomography (CT) allows quantitative evaluation of the various body compartments without supplementary investigations. Therefore, CT should be considered the gold standard in assessment of body composition for adipose tissue and muscle mass and their ratio.

Do patients undergoing neoadjuvant treatment need supplementary nutritional screening and support?

New data suggest that locally advanced pancreatic cancer can be treated successfully with neoadjuvant chemoradiation or chemoradiation to downstage the disease; although this approach delays the operative intervention, the resection can then often be done safely and with a less extensive resection and less operative risk of complications.

Because delaying surgery may not be advisable when there is a progressive decline in a patient’s clinical condition, the effects of neoadjuvant treatments on nutritional status and body composition and the importance of nutritional support during this treatment have gained considerable attention recently. Although some studies support the use of nutritional and physical interventions during the delivery of the neoadjuvant chemoradiation in selected cases, unfortunately, very few studies have addressed specifically the perioperative management of nutritional support in pancreatic cancer patients receiving multimodal treatments.

WL in pancreatic cancer patients often progresses synchronously with the disease, but WL can also result from the adverse effects of chemoradiation, including anorexia, nausea and vomiting, and diarrhea with a rapid worsening of the nutritional status and depletion of lean body mass. One study highlighted the adverse effects of neoadjuvant treatments on nutritional status, but also reported the encouraging increase in serum albumin levels after completion of the neoadjuvant chemotherapy in the interim before operative exploration. Dalal et al showed that neoadjuvant chemotherapy caused WL, but the body compartment affected the most was the fatty compartment, with preservation or even in some patients a gain in skeletal muscle mass. These contrasting results may be the consequence of different patient characteristics, cytotoxic regimens, response of the tumor to the treatment, supplemental nutritional support, or possibly methodology used to assess nutritional status and measure fat and muscle compartments.

In the last few years, FOLFIRINOX or gemcitabine/nab-paclitaxel chemotherapeutic regimens have shown encouraging results in oncologic outcomes and downstaging of the pancreatic cancer to allow operative resection in many cases. The pharmacologic effects of different cytotoxic agents and their combination may affect fat and nitrogen metabolism differently. Sandini et al, in a recent, large, multicenter, international study including patients with borderline or locally advanced PDAC who received neoadjuvant chemotherapy, showed a significant loss of adipose tissue during treatment, but there was minimal or no wasting of lean body mass. Moreover, an increase in muscle mass during neoadjuvant chemotherapy was a strong predictor of eventual operative respectability.

At present, body composition by quantitative CT seems the most appropriate tool for screening and follow-up purposes. Indeed, consultation and follow-up with a nutritionist or dietitian are strongly encouraged during the neoadjuvant therapy.

When is preoperative nutritional support indicated?

Currently, there are no objective data or guidelines specifically addressing the need for preoperative nutritional support for patients who are to undergo major pancreatic surgery. The guidelines of European and American societies developed for major abdominal surgery (which includes patients undergoing pancreatic resection) may be acceptable in this specific cohort.
Although benefits of nutritional support have been demonstrated in randomized controlled trials (RCTs), the benefit was only documented in patients with severe malnutrition—or with a high risk of developing malnutrition—who were fed parenterally or enterally for at least 7 days prior to surgery. In particular, the beneficial effects of this preoperative nutritional therapy were seen on the rate of major postoperative morbidity. These data have been confirmed in several meta-analyses and systematic reviews.

Based on these results, preoperative nutritional support should be seriously considered if at least one of the following criteria is met: (1) WL > 15% within 6 months, (2) BMI < 18.5 kg/m², (3) subjective global assessment grade C or nutritional risk score > 5, or (4) serum albumin < 30 g/L (with no evidence of hepatic or renal dysfunction).

These parameters reflect malnutrition as well as disease-associated catabolism. Hypoalbuminemia is a well-documented surgical risk factor and reflects more of a disease-associated catabolism and disease severity rather than just the lack of adequate nutritional intake.

Does the technique of gastrointestinal reconstruction after pancreateoduodenectomy affect gastric emptying, resumption of early oral feeding, and long-term nutritional status?

Pylorus-preserving pancreateoduodenectomy versus a classic pancreateoduodenectomy (Whipple procedure)

In the latest Cochrane review comparing pylorus-preserving pancreateoduodenectomy (PPPD) versus pancreateoduodenectomy (PD) for carcinoma (8 RCTs; 512 participants), the authors found no differences in postoperative morbidity except for delayed gastric emptying, which significantly favored the classic PD procedure. Only 3 studies reported long-term outcomes, and of these, found a statistically significant difference in favor of PPPD concerning weight gain but not overall quality of life. In 2011, a systematic review comparing PPPD versus PD by Diener et al. found no statistically significant difference in postoperative morbidity, but weight gain, exocrine insufficiency, and quality of life were significantly improved after PPPD.

No reliable data concerning the timing of resumption of early feeding or long-term nutritional status were included in these analyses. One retrospective study found that a pylorus-preserving total pancreatectomy was associated with better long-term nutritional status compared to a standard total pancreatectomy; this outcome was refuted by another study from Japan. Both of these studies, however, were small and monocenter studies and cannot be considered statistically robust.

Pancreaticojejunostomy versus pancreaticogastrostomy

In the latest systematic review and meta-analysis comparing the outcomes of pancreaticojejunostomy (PJ) with pancreaticogastrostomy (PG), the authors compared the outcomes of 10 RCTs involving 1,629 patients. They found no significant difference in the rate of morbidity nor in delayed gastric emptying. There was no mention of the timing of resumption of early feeding or long-term nutritional outcomes.

The potential long-term consequences of PG and PJ on pancreatic function should be taken into consideration, especially when a long survival is anticipated. In theory, a PG anastomosis should derange intraluminal digestion, because it diverts secretion both of pancreatic enzymes and of bicarbonate into the acid pH of the stomach. Available evidence is based mainly on results from small series of patients. Some evidence suggests that PG is associated with more changes in the pancreas than PJ. For example, Tomimaru et al. found that 2 years postoperatively after a PG, the main pancreatic duct dilates slightly more, and atrophy of the remnant pancreatic parenchyma is more severe than after PJ, suggesting the presence of some element of obstructive pancreatitis. In one series of 49 patients who underwent a PD and were evaluated 6 to 8 years postoperatively, Benini et al. estimated the remnant gland volume and found a more significant smaller pancreatic parenchyma volume after PG than after PJ.

Several studies with a short follow-up of 2 years or less found no difference in symptoms or in performance status after PG versus PJ. In contrast, in the long term, the group from the University of Verona reported significantly lower fecal elastase-1 levels after PG and more severe steatorrhea; in addition, in another study, the serum level of vitamin D was statistically significantly less after PG. Despite these differences, BMI was unaffected by the type of reconstruction, suggesting that the regimen of enzyme supplementation were largely effective in preventing severe malabsorption after both operations.

Single-limb versus dual Roux-en-Y limbs

In their systematic review and meta-analysis of differences in the type of gastrointestinal drainage after PD, Klaiber et al. found no statistically significant difference in postoperative morbidity nor in gastric emptying when comparing the outcomes of 3 RCTs and 4 cohort studies, which involved 802 patients. Unfortunately, there was no mention of the timing of postoperative feeding or the long-term nutritional outcome.

Antecolic versus retrocolic gastroenteric anastomosis

In the latest systematic review and meta-analysis, gastric emptying was found to be similar between the antecolic and retrocolic groups. No particular mention of the timing of postoperative feeding was given. Of note, the authors studied the subgroups of PPPD as well but again did not find any statistically significant difference of delayed gastric emptying. Although the study by Park et al. stated that the type of pancreatic surgery influenced the outcome in multivariate analysis, they did not provide any details or subgroup analyses as to which type of operation (PPPD or PD) or type of gastrointestinal reconstruction was used. Moreover, at 3 months postoperatively, all differences in global health status, quality of life, relative WL, and other functional scales had disappeared.

Is early oral feeding safe and effective after operation?

Strong support for early introduction of oral feeding after operations has been given by the introduction of protocols of enhanced recovery after surgery (ERAS) or so-called fast-track protocols in multiple types of gastrointestinal operations. One RCT, 20 case-control studies, prospective studies, and several meta-analyses and systematic reviews published on ERAS application in pancreatic surgery have demonstrated that early oral feeding after pancreatic surgery is both feasible and safe. Several different protocols involving early postoperative feeding starting on PODs 1 to 2 with a rapid increase to solid foods in some studies or a more gradual increase in intake of clear liquids to full liquids and solid food by days 3 to 4 have made direct comparisons of these different protocols difficult. More challenging to establish is whether early oral feeding is associated with improved outcomes. In the only available RCT, Deng et al reported a statistically significant decrease in delayed gastric emptying (DGE) in the ERAS group, while the incidence of postoperative pancreatic fistula (POPF), mortality, and 30-day readmission were not affected by ERAS. Some studies with a lower level of evidence reported a statistically significant decrease in overall morbidity and delayed gastric emptying with the use of an ERAS protocol but others did not find any differences. A recent meta-analysis concluded...
that the incidence of delayed gastric emptying and overall morbidity was less in the ERAS group, but this finding was not confirmed by another meta-analysis by Coolsen et al. 120

Despite that earlier feeding after pancreatic surgery seems well tolerated, there are no convincing data on whether the goal of attaining adequate nutritional needs is speeded by ERAS. Only 1 study has specifically addressed this issue101; in this study, the mean daily calorie and protein intakes in the first 2 weeks were similar in the ERAS group and the other group managed conventionally, despite that during the first 5 PODs, the mean daily intakes of calories and protein favored the ERAS group. Overall, the authors showed that the total energy goals through oral feeding were quite low in both groups.

Many of the published studies did not analyze the compliance with ERAS protocols and reported incomplete data, particularly on early oral feeding.95,97,99 Robertson et al110 reported compliance rates of 82% for resumption of oral fluids and 86% for tolerance of the diet. In a large Italian trial,100 postoperative oral liquids were tolerated by 55% of the patients and solid food in 53%, but compliance decreased substantially in patients with major complications.

The available evidence suggests that nutritional intake using only early oral feeding within an ERAS protocol after pancreatic surgery may be only partially adequate. Therefore, according to international guidelines,108,109 artificial nutritional support should be implemented early postoperatively in malnourished patients or those patients at high risk of developing malnutrition, in those who develop severe postoperative complications early after operation, and in well-nourished patients who do not tolerate at least 50% of their caloric and protein requirement by POD 7 for any reason.

At present, there is insufficient evidence to suggest the routine use of prokinetic gastric agents for the prevention of DGE or the superiority of one drug over others for its treatment.123,124

Is oral feeding safe in the presence of a clinically relevant postoperative pancreatic fistula (CR-POPF)?

Oral intake increases production of pancreatic juice and activation of trypsinogen, which may in theory exacerbate a clinically relevant postoperative pancreatic fistula (CR-POPF). In contrast, early provision of oral intake may decrease catabolism and morbidity.125 In addition to the nutritional aspects of early oral intake, physiologic passage of a food or liquid through the gastrointestinal tract could induce secretion of incretin, resulting in a more normal glucose metabolism.126 Presently, there is no specific operative technique that can prevent the development of a POPF completely.127 Several studies have addressed the safety of early oral feeding in the context of ERAS after PD,128,129 but the majority of these studies have not clarified how they managed the patient's nutritional needs after diagnosing a CR-POPF. Fuji et al130 analyzed the effect of oral food intake on the healing process of a POPF. In this multicenter RCT, they compared a group of 30 patients who were treated with oral dietary intake versus another group of 29 patients who had no oral dietary intake but were maintained on total parenteral nutrition after occurrence of POPF. There were no significant differences between groups in terms of the nutritional indexes when measured on POD 5, 12, and 21. As expected, the amount of pancreatic juice from the external drainage tube was greater in oral dietary intake group. Despite this difference in volume of pancreatic drain output, the progression to more a clinically relevant POPF or the development of an intra-abdominal hemorrhage or POPF-related complications were not statistically different. These data support the concept that oral feeding does not exacerbate POPF in this subset of patients.

One must carefully interpret this finding, however, because the majority of these patients had a biochemical leak without clinical symptoms, which is classified as a grade A POPF of no clinical relevance according to the present ISGSP definition.131 Recent studies have shown that infections with certain micro-organisms, such as Enterococcus, Pseudomonas, and Candida, can increase the development and severity of a POPF.123,133 Because long-term fasting alters the enteral flora, resulting in the growth of such microorganisms,134 nil-by-mouth may theoretically induce or exacerbate POPF by increasing the chance of infection by the above microorganisms.

Regarding enteric drainage of pancreatic secretions via PG, Pillai et al investigated the feasibility of fast-track protocols.102 Patients in the fast-track group were able to tolerate a liquid and solid diet earlier, while delayed gastric emptying was statistically less common in the fast-track group. There was no difference in the rates of POPF, postsurgical hemorrhage, and mortality between groups. Because foods or liquids may directly influence the anastomosis involving the gastric wall, Fuji et al excluded patients with PG from their study on the oral food intake and POPF.130

In the case of distal pancreatectomy (DP), there is another albeit small study by Fujii et al carried out in 15 patients who had oral dietary intake and 15 patients who had total parenteral nutrition.135 There was no significant difference in the natural history of POPF or biochemical leakage in these patients between the oral dietary intake and non-oral dietary intake groups, but the study lacked any robust statistical support.

At present, there is no evidence to show the benefit of avoiding oral intake in patients who are complicated by a CR-POPF after PD or DP, and there are no criteria for who can and who should not be fed orally. As previous studies have demonstrated, stable patients with a grade A or B POPF may well tolerate oral diets. Accordingly, nutritional support in patients with a CR-POPF should be managed on a case-by-case basis after a PD or DP, after a PJ or PG, or when there is evidence of bacterial or fungal infection.

Are there preoperative and intraoperative risk factors to suggest the need for placement of a feeding tube during pancreatic surgery?

The rationale supporting the placement of a feeding tube in patients undergoing a pancreatic resection is based on 2 main concerns. First, PDAC is associated with a well-known and severe metabolic derangement referred to as the cancer anorexia-cachexia syndrome.136,137 Second, the peculiar pattern of postoperative complications occurring after pancreatectomy such as a POPF might severely affect the patient capability to be fed orally.130,138,139

To use nutritional support via a feeding tube appropriately, it is critically important to identify which patients are at risk for nutritionally related complications. Severe malnutrition is well-recognized as an important predisposing factor in the morbidity and mortality of patients undergoing pancreatic resection, particularly in patients with tumors occurring in the head of the pancreas. Obstructive jaundice is invariably associated with impairment of absorption, the nutritional state of the patient, and overall nutritional homeostasis.140

The main intra-operative risk factors supporting a role for placing a feeding tube involve the type of pancreatic resection itself. PD results in loss of the small intestinal pacemaker in the duodenum, with a consequent increased risk of symptomatic postoperative gastric stasis.141 Moreover, the dissection of the nerve plexus around the superior mesenteric artery during the lymphadenectomy can result in severe diarrhea and malnutrition because of the loss of the small bowel extrinsic nerve supply regulating its motility and its absorptive and secretory functions.142 These postoperative rearrangements, in addition to the effects of the relative “apaneotropic state” (exocrine as well endocrine), which are even more pertinent after a total pancreatectomy, are not present in most resections of the distal pancreas unless the celiac artery is resected. Because the occurrence of these severe alterations in gas-
trointestinal function after a routine DP is extremely rare, there is no evidence supporting the routine placement of feeding tubes in these patients.

The surgeon can effectively assess the leading factors that play a role in determining the likelihood of developing pancreas-specific complications in the intra-operative setting. Specific factors can be then integrated into a scoring system able to stratify patients into classes of different risk of developing a POPF and related complications.43,44 It seems reasonable to suggest placement of a feeding tube in patients with a high risk of POPF (using a Fistula Risk Score at least 7). Other scores have been assessed to predict the occurrence of postoperative complications, such as the Preoperative Pancreatic Resection score45 and the Accordian Severity Grading System,46 but the Fistula Risk Score appears to be the most accurate.

A further scenario that can affect the decision to place a feeding tube is relaparotomy. Reoperation after pancreatic resection can be necessary to control postoperative major bleeding, to drain intra-abdominal collections, and, on occasion, to redo or further drain the pancreaticoenteric anastomosis. In patients suffering such life-threatening complications, protein catabolism and severe alterations of carbohydrate and lipid metabolism are often present or may very well develop without nutritional support. Moreover, reoperation may be associated with long interruption of oral feeding and may compromise its early resumption.

When the need for postoperative nutritional support is determined, which form is best?

There are several options for nutritional support. Oral nutritional supplements are the least invasive option but are inefficient in patients not tolerating oral intake, such as in the case of DGE. Total parenteral nutrition is successful in providing adequate and complete nutritional needs, but this form of nutritional support is associated with many potential complications.47 Because of the high glucose load needed to deliver an adequate amount of calories, hyperglycemia, metabolic acidosis, and fluid overload can occur if not monitored carefully.48,49

In contrast, enteral nutrition is more “physiologic,” because the nutrition is delivered directly into the stomach, duodenum, or jejunum. In doing so, enteral nutrition stimulates the release of pancreatic biliary secretions, which in combination with the luminal nutrients stimulate the release of metabolic and regulatory gastrointestinal hormones and maintain a more normal gut contractility and blood flow.73,149-152; moreover, enteral nutrition preserves the gut mucosal barrier function, thereby helping to prevent bacterial translocation when compared to total parenteral nutrition. But enteral nutrition also has its potential complications related to the feeding tube.153 Other concerns about enteral feeding are that it may be more difficult to deliver an adequate number of calories and protein because the patient may not tolerate the feeding because of bloating or diarrhea. Parenteral nutrition is only recommended in patients in whom adequate amounts of enteral nutrition are not feasible or not tolerated.19,68

Although the majority of surgery on the pancreas is for cancer, there are other indications for operative intervention in patients with nonmalignant pancreatic disorders who are often malnourished (chronic pancreatitis or necrotizing pancreatitis) and may need nutritional support even more.

Several studies have compared the use of enteral and parenteral nutrition after pancreatic surgery. In all trials, early enteral nutrition and parenteral nutrition after surgery was given routinely instead of on demand when early oral feeding was unsuccessful within the currently recommended ERAS strategy.54-160 All but 1 study161 favored enteral nutrition because of a lesser incidence of infection and overall complications and a faster recovery of digestive function, nutritional status, and liver and kidney function; moreover, the cost was considerably less.

Some investigators have claimed that the composition of the enteral formulas may affect outcome after pancreatic resection. A recent meta-analysis on immunonutrition after major abdominal surgery suggests that this approach may statistically decrease postoperative morbidity, infection rate, and duration of hospitalization in malnourished patients who underwent hepatobiliary and pancreatic operations.62 This topic, however, needs more investigation to robustly support the use of these more expensive feeds.

Which techniques are best for placement of an enteral feeding tube?

Enteral nutrition can be delivered via various routes. Nasogastric feeding may be appropriate in many patients, but in cases of increased risk of aspiration (eg, in patients with DGE or gastric outlet obstruction), postpyloric and possibly intrajejunual placement of the feeding tube is strongly indicated,163-165

Postpyloric access can be obtained via insertion of a nasojejunal feeding tube or through more invasive operative, laparoscopic, percutaneous, or endoscopic options, such as the operative insertion of a feeding jejunostomy at the time of pancreatic surgery or via a percutaneous or endoscopic gastrostomy with a jejunal extension. Each of these techniques is associated with its own complications:169,170,177,178 (Supplementary Table IV).

In general, in the literature, nasojejunal feeding tubes are reported to dislodge in up to 36% of the cases within the first week. Percutaneous jejunostomy tubes inserted via an endoscopic gastrostomy also can “flip back” into the duodenum and stomach and are not good alternatives for long-term enteral feeding. Albeit very rare, operatively placed jejunal feeding tubes can cause potentially life-threatening torsion and bowel necrosis in a very small percentage of patients.151,171-174

Three studies compared nasojejunal and transgastric jejunostomy tubes after pancreatic surgery,158,174,175 all favored nasojejunal tubes when considering severity of complications and recovery of digestive function. Others, however, suggest that the use of nasojejunal tubes may contribute to the development of POPF,176 but current literature does not support this assumption. In fact, nasojejunal feeding is to be preferred over parenteral nutrition, because enteral feeding is associated with significantly greater closure rates and a shorter time to closure of POPF.177 With the current interest and use of a fast-track–like strategy, it is questionable whether the routine use of percutaneous or operatively placed feeding tubes is warranted, given that only about 50% of patients will require nutritional support after pancreatic surgery, and a nasojejunal tube can usually be placed postoperatively if needed.98,129,178

The various techniques for placement of a nasojejunal feeding tube all have their specific disadvantages. Blind placement of feeding tubes beyond the pylorus is frequently unsuccessful and may lead to complications such as pneumonia due to inadvertent placement in the bronchus.178,179 Therefore, nasojejunal feeding tubes should be placed with the aid of endoscopic, fluoroscopic, or bedside electromagnetic guidance. A systematic review showed no differences in success and reinserter rates or complications between these 3 techniques.180 Data on the feasibility of these techniques in patients with an altered upper gastrointestinal anatomy after pancreatic surgery are, however, scarce. One study compared endoscopic to bedside electromagnetic-guided placement after PD, and concluded that success rates of both techniques were comparable and equally low.181 The decision on the preferred technique can, therefore, be made on logistics, costs, and preference of patients or the health care providers.
Is routine postoperative evaluation of exocrine and endocrine pancreatic functions indicated?

Pancreatic exocrine insufficiency (PEI) after pancreatic surgery has been defined by evidence-based guidelines published recently as a “...condition in which the amount of secreted pancreatic enzymes is not enough to maintain normal digestion...”. PEI after pancreatic surgery for cancer or chronic pancreatitis (CP) is quite common. The prevalence is increased after PD and in patients with pre-existing pancreatic disease, but only a limited number of studies have been published, and the definition of PEI varied across studies. When evaluated within a range of 6 to 12 months after PPPD, steatorrhea or other clinical symptoms can be observed in up to 32% of patients, and altered pancreatic function tests are present in up to 80% of patients. The long-term outcome of patients suffering from CP after resective operations seems to show that the incidence of PEI is as great as 93% when measured 15 years postoperatively. The incidence of PEI is greater in patients with CP after PD compared to DP, possibly related to either the resection of the duodenum with enteric drainage into the jejunum or stenosis of the pancreaticoenterostomy.

Considering patients who underwent PD for pancreatic cancer, some element of PEI was present in 64% to 100% after 12 months. PEI was present in 45% at the time of diagnosis, increasing to 89% after 6 months postoperatively and to 73% after 1 year. The incidence of PEI is greater in patients with malignancy undergoing PD compared to DP, similar to that observed for CP. The onset of postsurgical maldigestion (lack of quantity or mixing of digestive secretions) may be secondary to the following potential mechanisms: (1) loss of pancreatic tissue; (2) loss of hormonal regulation of pancreatic and biliary secretion secondary to the duodenectomy; (3) altered mixing of pancreatic and biliary secretions and gastric emptying; (4) altered intestinal pH; (5) upper gastrointestinal dysmotility; and (6) intestinal bacterial overgrowth. This maldigestion after pancreatic surgery is not a true “malabsorption” as such, but may be related in part to the type of operation, the technique of gastrointestinal and pancreatic reconstruction, the extent of pancreatic resection, and also the original pancreatic disease.

Patients with pancreatic cancer who undergo treatment of curative intent should receive long-term nutritional monitoring in the same manner as for patients with CP with PEI. There are many centers that routinely put patients who have undergone a pancreatectomy for pancreatic cancer on pancreatic enzyme replacement therapy for at least 6 months postoperatively.

Which is the optimal test to evaluate PEI?

The most frequent clinical sign of PEI after surgery is steatorrhea, defined as presence of more than 7 g/day of fat in the stool, leading clinically to WL and associated generally with flatulence, bloating, urgency to stool, and cramping abdominal pain. WL may be secondary also to the onset of postsurgical diabetes, particularly after extended resections of the pancreas or in patients with underlying CP. Steatorrhea generally appears when greater than 90% of the typical secretion of pancreatic enzymes is lost. After PD, the combination of loss of pancreatic tissue and asynchronous mixing of pancreato-biliary secretions with the meal can lead to the onset of steatorrhea also in the presence of a more limited decrease in pancreatic enzyme secretion.

Diagnosis of PEI can be difficult in practice. Pancreatic function and secretion are not solely reliant on the quantity or quality of pancreatic tissue but also depend on complex pancreatic stimulatory mechanisms.

The 72-hour fecal fat collection with a standard intake of fat allows the calculation of the coefficient of fat absorption; this is the gold-standard test to diagnose fat malabsorption but because this test is not available routinely, the fecal elastase-1 may be the only pancreatic function test available in clinical practice. It must be remembered that the sensitivity and the specificity of fecal elastase-1 for steatorrhea in patients after pancreatectomy is low. Benini et al showed that steatorrhea may be present in operated patients even if the fecal elastase-1 is only mildly decreased, suggesting that steatorrhea is only partially related to an absolute decrease in digestive enzyme production and may be secondary to other mechanisms reported above. None of the above tests measure protein and carbohydrate malabsorption or discriminate between extrapancreatic factors.

When and how should pancreatic enzyme replacement therapy (PERT) be prescribed?

Awareness of PEI by many physicians is poor outside of high-volume HPB centers and especially among physicians in primary care; consequentially, patients who present with symptoms of PEI may be overlooked or advised to adopt inappropriate dietary restrictions in an attempt to control the symptoms. A study of pancreatic cancer patients and bereaved caregivers identified that their primary unmet need was the difficulty in managing gastrointestinal problems, diet, and digestion; indeed, many of these patients and caregivers cited delays in dietary assessment and initiation of PERT as causing additional distress that could have been prevented.

PERT has been shown to stabilize weight, improve dietary intake, and decrease daily stool frequency in patients with inoperable pancreatic cancer. PERT use appeared to improve survival in patients postresection in a post hoc subgroup analysis, predominantly in those with pancreatic ductal dilation. A prospective, placebo-controlled study evaluating the impact of PERT on WL in patients with unresectable pancreatic cancer did not show any benefit, however, these patients were prescribed a fixed dose of PERT with no alteration for individualized portion size or food type. A prospective study evaluating patients with unresectable pancreatic cancer undergoing chemotherapy found less decrease in BMI in patients who received PERT.

Management of PEI involves replacing the lack of adequate pancreatic enzymes, which should be used to maintain weight and improve the symptoms of malabsorption. Therapy should start with doses of 40,000 to 50,000 units of lipase with meals, and 10,000 to 25,000 units with every snack. Dose escalation and inhibition of gastric acid secretion may be warranted according to response; in patients who fail to respond to treatment, extrapancreatic causes should be evaluated (Supplementary Fig. 1). Dietary intake and nutritional status should be monitored regularly to maximize patient compliance and specialist dietetic assessment sought in patients with underlying malnutrition. Although I study evaluating the impact of the scheduling of PERT administration on fat malabsorption suggested the optimal timing of administration was during or after meals, no significant difference was observed when patients took the PERT immediately before meals. In practice, although many patients prefer to take PERT at the beginning of meals, they should probably be encouraged to spread the capsules out over a meal when using multiple capsules or with larger meals. If the patient is taking the older preparations of pancreas powder, they should take about one-third of the dose immediately before, one-third during, and one-third immediately after the meal. If the patient does not respond to the dosage used, the dosage should be increased except in children in whom colonic strictures have been described with the coated, delayed-release preparations when given in too high a dose; in contrast, adults cannot take too much PERT but certainly can take too little PERT.
There are multiple pancreatic enzyme replacement preparations that are now licensed in the United States and European Union. All are of porcine origin and contain pancrelipase with varying concentrations of the enzymes lipase, amylase, and protease. There is limited comparative data available. Taylor and colleagues compared 2 different preparations in patients with cystic fibrosis demonstrating comparable efficacy. As part of a recent systematic review or meta-analysis examining the efficacy of PERT, the authors examined enteric-coated microspheres versus noncoated microspheres regarding the coefficient of fat absorption, and noted that while a higher coefficient of fat absorption was seen with coated microspheres, it was not statistically significant.

The choice of preparation depends on physician choice. The dosage recommended depends on the patient’s clinical response, but the dosage and dosing will need to be carefully monitored, as well as altered, depending on patient’s food intake or pattern of eating, method of cooking, and portion sizes, and this will require repeated education of the patient concerning alteration of the dosage and timing of administration. The absence of overt steatorrhea is not always an indicator of adequate absorption or optimal PERT.

**What are the long-term consequences of PEI after pancreatic surgery?**

PEI after pancreatic surgery is associated with symptoms related to the presence of undigested food within the intestinal lumen and to loss of the absorption of necessary nutrients (fat-soluble vitamins) with subsequent progressive WL or selective vitamin and mineral deficiencies. Patients with PEI often experience debilitating steatorrhea, urgency to stool, dyspepsia, flatulence, abdominal pain, and nausea; however, overt malabsorptive symptoms are not always apparent in patients with mild or moderate insufficiency.

Steatorrhea is the most obvious clinical manifestation of fat malabsorption. In patients with untreated PEI, complications such as WL, poor wound healing, deficiencies of the fat-soluble vitamins (A, D, E, K), osteomalacia, and electrolyte imbalance can occur. Vitamin A deficiency may cause xerophthalmia and night blindness. Vitamin E deficiency may lead to the appearance of neurologic symptoms (cerebellar ataxia, areflexia, loss of the sense of touch and pain), ophthalmoplegia, ptosis, and muscle weakness. Abnormal bleeding is the main outcome of vitamin K deficiency, leading to a tendency to easy bruising and mucosal bleeding. Because vita-
min D deficiency may lead to osteopenia and metabolic bone disease, it is crucial to start supplementation of vitamin D parenterally and maintain vitamin D supplementation indefinitely.

Non-alcoholic fatty liver disease (NAFLD) is also a poorly recognized complication of PEI after PD. The mechanisms underlying NAFLD after PD are different from NAFLD associated with metabolic syndrome, because it is mainly due to malabsorption of essential amino acids such as choline, which leads to a decrease in plasma levels of apoprotein B, a major component of very-low-density lipoprotein. In addition, insufficient secretion of insulin related to the pancreaticoduodenal resection or the diversion of nutrients away from the duodenum can enhance peripheral lipolysis and increase hepatic free fatty acid uptake, and the subsequent hepatic deposits of fat. Abnormal pancreatic exocrine function as evaluated by fecal elastase (<20 vs >20 µg/g of stools) has been reported as an independent predictor of survival in advanced pancreatic cancer.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.surg.2018.05.040.

References


