Nutrition Research Reviews (2024), 37, 121–130 doi:10.1017/S0954422423000100

Re-assessing the role of peri-operative nutritional therapy in patients with pancreatic cancer undergoing surgery: a narrative review

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Abstract

Pancreatic cancer is the most common medical condition that requires pancreatic resection. Over the last three decades, significant improvements have been made in the conditions and procedures related to pancreatic surgery, resulting in mortality rates lower than 5%. However, it is important to note that the morbidity in pancreatic surgery remains r latively high, with a percentage range of 30–60%. Pre-operative malnutrition is considered to be an independent risk factor for post-operative complications in pancreatic surgery, such as impaired wound healing, higher infection rates, prolonged hospital stay, hospital readmission, poor prognosis, and increased morbidity and mortality. Regarding the post-operative period, it is crucial to provide the best possible management of gastrointestinal dysfunction and to handle the consequences of alterations in food digestion and nutrient absorption for those undergoing pancreatic surgery. The European Society for Clinical Nutrition and Metabolism (ESPEN) suggests that early oral feeding should be the preferred way to initiate nourishing surgical patients as it is associated with lower rates of complications. However, there is ongoing debate about the optimal post-operative feeding approach. Several studies have shown that enteral nutrition is associated with a shorter time to recovery, superior clinical outcomes and biomarkers. On the other hand, recent data suggest that nutritional goals are better achieved with parenteral feeding, either exclusively or as a supplement. The current review highlights recommendations from existing evidence, including nutritional screening and assessment and pre/post-operative nutrition support fundamentals to improve patient outcomes. Key areas for improvement and opportunities to enhance guideline implementation are also highlighted.

Keywords: **Pancreatic surgery: Pancreatoduodenectomy: Nutrition support: Nutrition therapy: Immunonutrition**

(Received 17 April 2022; revised 8 June 2023; accepted 9 June 2023; accepted manuscript published online 5 September 2023)

Introduction

Pancreatic surgery is the only established curative treatment for the majority of pancreatic cancers and involves several major procedures of pancreatectomy with multiple organ resection and reconstruction of the digestive system, which are associated with functional and metabolic alterations[(1)]. The most common type of pancreatic surgery is pancreaticoduodenectomy (PD) or Whipple surgery, while total pancreatectomy (TP) and distal pancreatectomy, including or not including splenectomy (DP), are also widely used[(2)]. During the last three decades, conditions and procedures during the peri-operative period of pancreatic surgery have significantly improved, resulting in mortality rates lower than 5%[(3)]. However, it is important to highlight that the morbidity range in pancreatic surgery remains relatively high, at 30–60%. Pre-operative nutritional disorders, post-operative surgical trauma and complications could negatively affect patient recovery and clinical outcomes and should always be considered and resolved without delay[(4)]. Malnutrition before surgery is extremely prevalent in patients with pancreatic cancer. A total of 80% of patients with pancreatic head cancer present with recent weight loss at the time of diagnosis, while almost up to 40% of patients have lost more than 10% of their body weight during the last 6 months before diagnosis. Recent data indicate that 52–88% of patients who underwent pancreatic resection for cancer were at moderate to severe risk of malnutrition before surgery[(3,5)].

Pre-operative malnutrition is considered an independent risk factor for post-operative pancreatic surgery complications such as impaired wound healing and higher infection rates, prolonged hospital stay, hospital readmission, poor prognosis and increased morbidity and mortality[(4)]. Several factors related to the disease itself, including inflammation, stress, cancer cachexia, chemotherapy/radiotherapy before surgery and mal-absorption due to pancreatic insufficiency, could lead to weight loss and malnutrition. In addition, reduced dietary intake due to abdominal pain, bloating, flatulence (provoked by delayed gastric emptying and/or ileus due to gastric outlet obstruction), anorexia, taste changes, and depression are common and important factors that could be related to the appearance of malnutrition[(6)].

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Table 1. Characteristics of currently used nutritional screening tools

Screening Tool	Components/scoring system
SGA	The Subjective Global Assessment (SGA) screening tool evaluates through a questionnaire certain clinical parameters, such as weight loss, changes in dietary intake, gastrointestinal symptoms, functional capacity. Additionally, through physical examination, it evaluates muscle, subcutaneous fat, sacral and ankle oedema and ascites. Clinician's overall judgment is also included in the assessment. The results are categorised in stages from A to C. Stage A is for well-nourished patients, stage B is for moderate or suspected malnutrition and stage C is for severe malnutrition.
PG-SGA	The Patient-Generated Subjective Assessment (PG-SGA) screening tool evaluates weight loss, condition and age, metabolic stress and includes physical examination. The results are categorised in stages from A to C. Stage A is for well-nourished patients, stage B is for moderate or suspected malnutrition and stage C is for severe malnutrition.
aPG-SGA	The abridged Patient-Generated Subjective Assessment (aPG-SGA) screening tool evaluates weight and weight change, food intake, symptoms, activities and functions. The results are classified in score 0–1 which indicates no nutrition problem, score 2–8 which indicates increasing nutrition problem, and score ≥9 which indicates critical need for improved symptom management and/or nutrition intervention.
MUST	The MUST screening tool evaluates BMI, weight loss and presence of acute disease. The score is categorised in score 0 meaning low risk, score 1 meaning medium risk and score 2 meaning high risk for malnutrition.
NRI	The NRI screening tool evaluates serum albumin level and ratio of actual to usual weight. The possible results of this screening tool are >100·0 meaning no risk, 97·5–100·0 meaning low risk, 83·5–97·5 meaning medium risk and ≤83·5 meaning high risk for malnutrition.
NRS 2002	The NRS 2002 screening tool evaluates age adjustment (≥70 years), nutritional score: weight loss and changes in food intake, BMI, general condition and severity of disease score. If score is <3 which means absent, mild or moderate risk, patient should be rescreened. If score is ≥3 which means severe risk, a nutrition care plan should be initiated.

Abbreviations: SGA, subjective global assessment; PG-SGA, patient-generated subjective assessment; aPG-SGA, abridged patient-generated subjective assessment; MUST, malnutrition universal screening tool; NRI, nutritional risk index; NRS 2002, nutritional risk screening

Peri-operative nutritional management is required to detect and correct malnutrition early and offer the patient the most appropriate personalised nutritional support. Considering all the above, this review aims to present up-to-date references regarding peri-operative nutritional management in pancreatic surgery specifically (and not abdominal surgery in general), including screening, assessment and intervention.

Search strategy

Current review strategy included an electronic search of the following online databases: PubMed, Scopus, Web of Science and Embase from inception to 10 December 2022. Search terms included key words such as "pancreatic surgery", "pancreatectomy", "pancreatoduodenectomy", "nutrition support", "nutrition therapy", "nutrition management", "perioperative", "postoperative", "immunonutrition" and "complications". We aimed to assess all relative papers regarding current practices, consensus statements and controversy of peri-operative nutrition management in pancreatic surgery patients and provide necessary guidance for clinical research and/or practice.

Pre-operative nutritional strategy

Nutritional screening

Nutrition screening refers to the quick and easy process of identifying patients who are at risk of malnutrition and could benefit from nutritional intervention. Malnutrition has been identified as an independent risk factor for surgical outcomes for almost 80 years, and therefore identifying patients at risk before surgery may be crucial to improving outcomes[7].

The routine pre-operative use of screening tools for malnutrition in surgical patients has been extensively explored. Several screening tools, including the Subjective Global Assessment (SGA), the Malnutrition Universal Screening Tool (MUST) and the Nutrition Risk Screening Questionnaire (NRS-2002)[8] (Table 1), have been developed and validated to identify patients at risk of malnutrition. All these tools have been validated for use in hospitalised patients and have high sensitivity and specificity for predicting post-operative morbidity[3]. The Enhanced Recovery after Surgery (ERAS) society and the European Society for Clinical Nutrition and Metabolism (ESPEN) recommend routine screening for patients with gastrointestinal (GI) cancer using validated tools to detect and treat malnutrition effectively. According to the ESPEN guidelines for clinical nutrition in surgery, malnutrition screening should be conducted for every hospitalised patient upon admission and before major surgery[9]. The importance of screening patients for malnutrition before pancreatectomy has also been recently emphasised in the position paper regarding nutritional support and therapy in pancreatic surgery by the International Study Group on Pancreatic Surgery (ISGPS)[10].

Although there is consensus in the literature that routine malnutrition screening before surgery is essential in patients with GI cancer, the best-performing tools have not been determined yet. Based on recent studies that indicate the importance of using screening tools validated in the patient population in which they are utilised[11], the current review only presents selected screening tools that have been studied in patients with pancreatic cancer before pancreatectomy and can predict post-operative complications such as pancreatic fistula, length of hospital stay, morbidity and survival.

The NRS 2002 tool remains the most widely used tool. Several studies have indicated that the NRS 2002 can identify patients at risk of malnutrition undergoing major abdominal and pancreatic surgery[12,13]. A retrospective study by Jing-Yong Xu *et al.* found that patients at high nutritional risk (NRS 2002 score ≥5) may benefit from pre-operative nutritional support by reducing the incidence of clinically relevant post-operative pancreatic fistulas

https://doi.org/10.1017/S0954422423000100 Published online by Cambridge University Press

(CR-POPF) after open pancreaticoduodenectomy in pancreatic surgery[6]. Another study showed that the pre-operative NRS 2002 score was the only independent prognostic factor for overall survival (OS) in patients undergoing surgery for pancreatic adenocarcinoma. Patients with a low pre-operative NRS-2002 score (<3) had significantly better 2-year OS compared with patients at high pre-operative nutritional risk[14].

The MUST screening tool is another widely used tool that is a well-validated, easy and a rapid malnutrition-screening tool that combines BMI, percentage of unintentional weight loss and presence of acute disease. A study among Italian patients[4] reported that MUST identified 83% of patients as being at nutritional risk (either medium or high risk) and more than one-third of the patients (41%) as being at high nutritional risk in relation to pancreatic surgical patients. The results of this study showed that patients identified at high risk of malnutrition using the MUST tool had a fourfold longer post-operative hospitalisation time, a fivefold higher surgical site infection (SSI) rate and a higher morbidity rate (53·2%) than those patients at low risk of malnutrition[4].

Although albumin is no longer used as a marker of nutritional status or as a parameter in the definition or assessment of malnutrition, it could be recognised as an inflammatory marker associated with "nutrition risk" rather than with malnutrition per se, according to the ASPEN position paper by Evans *et al.*[15]. Therefore, screening tools that include albumin as part of the pre-operative assessment of nutritional risk could possibly be used before pancreatic surgery. In this context, the Glasgow Prognostic Score (GPS) is an inflammation-based cancer-prognostic marker calculated based on serum C-reactive protein (CRP) and albumin concentration values, and it is considered a useful tool in identifying patients at high risk for malnutrition[3]. In two studies that evaluated inoperable patients with pancreatic cancer using GPS, the presence of systemic inflammation at diagnosis (as indicated by a high GPS score) could be a useful indicator of poor outcome, independent of TNM stage[16,17].

Finally, with regards to Controlling Nutritional Status (CONUT), PNI (Prognostic Nutritional Index) and NRI (Nutritional Risk Index), only a limited number of studies have utilised these screening scores in patients prior to pancreatic surgery. Based on the available studies, the CONUT score was found to be associated with survival and post-operative pancreatic fistula formation (POPF) after pancreatectomy, but not with post-operative complications, according to Masashi *et al.*[18]. On the other hand, PNI was associated with overall survival and post-operative complications, especially pancreatic fistula, among patients with pancreatic cancer, but its predictive usefulness and moderate accuracy limits its use[16]. Finally, NRI was found to be an independent factor in predicting he occurrence of surgical site infections after pancreaticoduodenectomy[19].

To conclude, firstly, it is crucial to note that while there may be ongoing discussions regarding the specific screening tool to be employed, the timing of screening holds paramount importance. We must consistently acknowledge and underscore the necessity of recognising nutritional risk at diagnosis and in a timely manner before surgery so that there is enough time for potential nutritional intervention and improvement of pre-operative nutritional status. If screening is postponed until the patient's admission to the surgical ward, it would result in the oversight of every single patient, rendering the screening outcome inconclusive. Instead, screening ought to be conducted in the pre-operative clinic setting, enabling the identification of patients who are at risk and potentially facilitating pre-operative nutritional support interventions.

Secondly, according to current literature, there is no evidence-based recommendation regarding the use of one of the aforementioned tools over another, and all may be used as long as they have been validated across the surgical population[8,11].

Nutritional assessment

After malnutrition screening, each patient at nutritional risk should undergo further assessment to diagnose and classify the severity of malnutrition. Pre-operative nutritional assessment is highly recommended by the ERAS protocols published in 2019[20]. Nutritional assessment includes the assessment of human subject body composition, which comprises lean body mass or muscle mass, and fat mass. Patients with pancreatic cancer often suffer from body composition derangement, such as sarcopenia, which is a serious syndrome characterised by progressive muscle loss and functional decline. Sarcopenia is significantly correlated with post-operative chemotherapy intolerance, pancreatic fistula, early post-operative recurrence, prolonged hospital stay, and short survival[21,22]. The prevalence of sarcopenia in patients with pancreatic cancer ranges between 21·3% and 86·3%[23]. Body composition assessment methods include dual-energy X-ray absorptiometry, bioelectrical impedance, computed tomography (CT) and MRI images, anthropometry such as calf circumference and upper limb circumference, and muscle strength measurement such as grip strength. These indices are significantly correlated with post-operative pancreatic fistula, mortality and readmission rate[23]. Similarly, in the retrospective study of Pecorelli *et al.*, the authors concluded that the total abdominal muscle area (TAMA), which combines visceral obesity and sarcopenia, was the best predictor of post-operative death, whereas visceral fat area (VFA) was an independent predictor of pancreatic fistula[24]. However, in the systematic review of Perra *et al.*, the relationship between sarcopenia and post-operative pancreatic fistula following pancreatic surgery remains unclear[24].

Regarding specific diagnostic criteria, the Subjective Global Assessment (SGA) was the most commonly used tool for malnutrition assessment until 2019 when ESPEN published a diagnostic consensus titled "Global Leadership Initiative on Malnutrition (GLIM)". The GLIM criteria for malnutrition diagnosis consists of two parts: the first part assesses phenotypic criteria such as body weight loss, BMI and muscle mass, while the second part assesses malnutrition etiologic criteria such as reductions in food intake or assimilation and disease burden or inflammation. Although most studies on GLIM criteria have focused on medical patients, there is an increasing amount of literature examining surgical patients as well[25].

https://doi.org/10.1017/S0954422423000100 Published online by Cambridge University Press

Table 2. Specific indications for nutritional support according to various international societies

Society	Criteria for nutrition support initiation
ERAS 2019	Weight loss >15% BMI <18·5 kg/m^2
ISGPS 2018	WL>15% within 6 months BMI <18·5 kg/m^2 SGA grade C NRS 2002 >5 Serum albumin level <30 g/l (with no evidence of hepatic or renal dysfunction)
ASER 2018	Any positive PONS result (for every major gastrointestinal surgery including pancreatectomy)
ESPEN 2021	At least one of the following: WL >15% within 6 months/BMI <18.5 kgr/m^2/SGA = C/serum albumin <30 g/l

Abbreviations: ERAS, enhanced recovery after surgery for PD; ISGPS, international study group on pancreatic surgery; ASER: American society for enhanced recovery; ESPEN: European society for clinical nutrition and metabolism WL, weight loss.

Nutritional support

Indications: who really needs it?

Many candidates for pancreatic surgery are at high risk of malnutrition, so pre-operative nutritional support may prove beneficial for them. In the following paragraphs, we present specific indications for nutritional support before pancreatic surgery, as recommended by international scientific societies (Table 2)[21,26]. The International Study Group of Pancreatic Surgery (ISGPS) indicates that nutritional support is necessary for patients with weight loss >15% within 6 months, BMI <18·5 kg/m^2, SGA Grade C, NRS 2002 >5 points, and albumin <30 g/l (with no evidence of hepatic or renal dysfunction). On the other hand, the American Society of Enhanced Recovery criteria require any positive preoperative nutrition score (PONS) result for every major gastrointestinal surgery, including pancreatectomy, and the Enhanced Recovery after Surgery Society (ERAS) for pancreatic disease (2019) criteria require weight loss >15% and BMI <18·5 kg/m^2. These indications are mostly derived from studies conducted among patients undergoing major abdominal surgery, as no data on pancreatic surgery have been published so far[10].

The majority of patients with pancreatic malignancy have significant weight loss before surgery[27]. This finding emphasises the need for supplemental nutrition to restore baseline nutritional status prior to complex operations. Nutritional interventions (parenteral, enteral or oral/sip feeds) are often recommended for patients with significant weight loss scheduled for major operations, and these interventions will usually result in weight gain[28]. According to the narrative review by Jingyong *et al.* on the current situation, consensus and controversy of peri-operative nutrition management in pancreatic surgery, most patients with pancreatic surgery at nutritional risk can start nutritional support with a fortified diet and oral nutritional supplements (ONS). However, for patients with high nutritional risk or malnutrition before PD, aggressive nutritional support should be considered if the oral target cannot be met. This recommendation is in accordance with the Consensus Statement and Recommendation of ASER, which recommends that all patients at nutritional risk before major surgery, including PD, should be considered for nutritional support.

In the quasi-experimental study by Park *et al.*, the administration of pre-operative nutritional support (PNSP) to malnourished patients with pancreatobiliary cancer improved nutritional status and clinical outcomes. The main conclusion of the study was that among patients undergoing major pancreatic operations, there was no significant difference in terms of nutritional indices, complications, and length of hospital stay between malnourished patients receiving PNSP and well-nourished patients[29].

In contrast, according to the updated ERAS recommendations for pancreatoduodenectomy (PD), it remains unproven whether pre-operative nutritional support reduces complication rates or enhances recovery[28]. Similarly, a systematic review by Takagi *et al.* supported that EN can be given only to patients with severe malnutrition, while definitive advantages of pre-operative aggressive EN remain unclear in patients with PD[30].

In conclusion, even though the evidence level is low, according to the ERAS guidelines and the ISGPS consensus, pre-operative nutritional support with enteral nutrition (EN) (tube feeding) and/or total parenteral nutrition (TPN) (supplementary or total) can mainly be provided to severely malnourished patients and not in general[10].

Intraoperative nutritional feeding access and support

There is a lack of specific evidence on the optimal feeding strategy or placement of an enteral feeding tube (FT) to initiate early enteral support during pancreatic surgery[31]. Systematic reviews conducted over the last decade did not reveal any major differences in outcome between different feeding systems such as nasojejunal tube (NJT), gastrojejunostomy tube (GJT), or jejunostomy tube (JT) after PD[32]; however, the quality of the included studies was low to moderate.

The need for placement of a feeding tube during pancreatic surgery is determined by specific intraoperative risk factors, such as the type of pancreatic surgery, existing malnutrition and the possibility of post-operative complications such as a POPF, which might severely affect the capability of oral feeding[31]. High-risk patients are more likely to require an FT compared with low-risk patients. In a retrospective review by Scaife *et al.*, selective intra-operative FT placement for at-risk patients may potentially benefit patients, as well as reduce costs. The authors concluded that surgeons should consider selective intra-operative enteral FT placement in all patients aged 80 years

https://doi.org/10.1017/S0954422423000100 Published online by Cambridge University Press

and in any patients with two or more of the pre-operative comorbidity risk factors (according to the National Surgical Quality Improvement Program (NSQIP) database)[31].

According to the ISGPS, (a) there is no evidence supporting the routine placement of feeding tubes during surgery because severe risk factors are rare in these patients, and (b) each of these techniques is associated with its own complications. NJT dislodge in up to 36% of patients within the first week, and percutaneous JT can cause potentially life-threatening torsion and bowel necrosis in 0·4% of patients. It is up to the surgeon to decide which enteral access or technique to utilise during surgery to feed the patient. Due to the ERAS protocol and the development of endoscopic technology, the majority of pancreatic surgeons prefer to place feeding tubes when necessary after operation and not routinely during operation[21].

Gastro versus jejunum feeding access

Feeding access is an important consideration for patients undergoing pancreatic surgery, and a key question is whether targeting the stomach or jejunum is more appropriate. According to the position paper of the ISGPS, nasogastric feeding may be appropriate for many patients, but in cases of increased risk of aspiration (such as in patients with delayed gastric emptying or gastric outlet obstruction), postpyloric and possibly intrajejunal placement of a feeding tube is strongly indicated[10].

Insertion of a nasogastric tube (NGT) has been associated with higher patient discomfort, nasal trauma, gastroesophageal reflux, respiratory complications, and a higher rate of dislodgement. Insertion of a gastrostomy tube (GT) has advantages over the NGT, particularly if prolonged gastric decompression is required, as is often the case, without the discomfort and complications associated with prolonged nasal intubation[33]. In addition, a recent literature review found that the incidence of gastroparesis was significantly lower in the gastrojejunum tube (GJT) group compared with the NGT group. Moreover, the duration of gastric decompression and length of hospital stay were significantly shorter in the GJT group compared with the NGT group[3].

Nasojejunal tube (NJT) versus jejunostomy tube (JT)

According to the guidelines of the European Society for Clinical Nutrition and Metabolism (ESPEN), in patients undergoing major upper gastrointestinal (GI) and pancreatic surgery who require tube feeding, placement of a nasojejunal tube (NJ) or needle catheter jejunostomy (NCJ) should be considered, especially in those who are malnourished[9].

The position paper of the International Study Group of Pancreatic Surgery (ISGPS) indicates that both techniques have their pros and cons. Nasojejunal tube withdrawal rates are reported to be higher than those of jejunostomy tubes, and it can dislodge in up to 36% of cases within the first week, which can reduce patient comfort[21]. Three studies that compared nasojejunal and jejunostomy tubes after pancreatic surgery favoured nasojejunal tubes when considering the severity of complications and recovery of digestive function. However, many studies have shown the feasibility, safety and clinical benefits of needle catheter jejunostomy (NCJ) as a long-lasting access for enteral nutrition[33]. On the other hand, percutaneous jejunostomy tubes inserted via an endoscopic gastrostomy could increase the risk of complications as the jejunal extension tube can flip back into the duodenum and stomach and may not be a good alternative for long-term enteral feeding.

Many clinical trials have concluded that nasojejunal feeding is safer than jejunostomy and associated with only minor complications. Nasojejunal feeding can significantly decrease the incidence of delayed gastric emptying and shorten the post-operative hospital stay[34]. On the contrary, routine placement of jejunostomy tube (JT) at the time of pancreaticoduodenectomy (PD) should be abandoned as it is related to a higher rate of delayed gastric emptying, morbidity, longer hospital stay and longer time to solid intake[35].

Finally, in the retrospective cohort study of Gerritsen *et al.*, none of the analysed feeding strategies, including nasojejunal tube (NJT), jejunostomy tube (JT) and total parenteral nutrition (TPN), was found to be superior with respect to timing of resumption of normal oral intake, morbidity and mortality, while each strategy was associated with specific complications[36]. According to the results of this study, nasojejunal tubes dislodged in one-third of patients, jejunostomy tubes caused few but potentially life-threatening bowel strangulations, and TPN doubled the risk of infections. The above research team came to similar conclusions in their systematic review 1 year later[32].

To conclude, the optimal tube for enteral feeding cannot be determined based on current data, and each method is associated with specific complications. As mentioned above, nasojejunal tubes commonly dislodge and retroflex into the stomach, while jejunostomies are associated with less frequent but more serious complications, like intestinal torsion and bowel necrosis[3]. According to the consensus statement of the International Study Group of Pancreatic Surgery (ISGPS), the need for routine use of percutaneous or operatively placed feeding tubes is questionable considering (a) the current routine fast-track-like strategy in major surgery, (b) the fact that only about 50% of patients will require nutritional support after pancreatic surgery, and (c) a nasojejunal tube can usually be placed post-operatively if needed[10].

Post-operative nutritional strategy

To combat the physiologic catabolism that is the hallmark of the post-surgical state and to promote wound healing, the initiation of nutrition and mainly of high protein intake during the immediate post-surgical period is essential, especially in patients with obesity and/or diabetes adequate protein is of utmost importance while caloric overfeeding is of no true benefit and has the risk of hyperglycaemia and associated complications[9,37].

This could be achieved through many different routes depending on patient's nutritional status and post-surgical complications (Table 3).

Oral route

In contrast to previous nutritional practices of "no feeding, fasting, and a full clear liquid diet" for the immediate post-operative period, current guidelines according to the

https://doi.org/10.1017/S0954422423000100 Published online by Cambridge University Press

Table 3. Recommendations for post-operative nutritional support in pancreatic surgery

Nutrition support strategy	Effects on outcome
Oral	Early resumption of oral intake without restriction is safe with no detrimental effect on complications and should be encouraged.
EN	Patients who are malnourished or have a high risk of developing malnutrition and/or severe post-operative complications or cannot meet nutritional goals (intake <50% of protein/energy target) through oral intake should receive supplementary artificial nutrition within 24 h.
ECPEN	When EN after PD is not well tolerated and caloric goal cannot be adequately achieved, EN combined with PN could be a safe choice to optimise clinical outcome without increasing morbidity.
PN	Supplemental parenteral nutrition (SPN) or TPN could be a choice when oral or enteral nutrition via tube feeding is not tolerated and/or fails to meet nutrient requirements or when post-operative complications affect gastrointestinal function or there is a high risk for peri-operative malnutrition or in already severely malnourished patients (pancreatic cachexia).

Abbreviations: EN, enteral nutrition; ECPEN, early combined parenteral and enteral nutrition; PN, parenteral nutrition.

Enhanced Recovery After Surgery (ERAS) protocol support Early Oral Feeding (EOF) after surgery from day 1 (during 12–24 h) without restrictions and increasing intake according to tolerance over 3–4 days[20,38]. The advantages of EOF are mainly focused on safety, physiology, fewer complications related to the tube and an earlier first bowel movement. In a recent observational, non-interventional, retrospective study of patients undergoing pancreaticoduodenectomy (PD), EOF was associated with a shorter hospital stay but not with severe post-operative morbidity or pancreatic fistula rate. However, EOF resulted in more chyle leaks and did not prevent delayed gastric emptying[39].

Immediate feeding after PD is the current recommendation of the ERAS protocol for PD and the International Study Group of Pancreatic Surgery (ISGPS), indicating that EOF is safe and should be encouraged. In addition, the American Society for Enhanced Recovery (ASER) recommends that a high-protein diet (via diet or high-protein oral nutritional supplements) can often start on the first day of surgery, except for patients without bowel continuity, with bowel ischemia, or persistent bowel obstruction[40].

Regarding the potential risks of EOF, a recent meta-analysis suggests that it is not associated with an increased risk of delayed gastric emptying (DGE), does not exacerbate post-operative pancreatic fistula (POPF), and appears to reduce the length of hospital stay. However, EOF may not be appropriate for patients with DGE. Similarly, a systematic review by Gianotti *et al.* found no evidence to support routine enteral or parenteral feeding after PD, while oral route diet could be considered the preferred routine feeding strategy[32]. The Clinical Practice Guidelines for Pancreatic Cancer 2019 by the Japan Pancreas Society also suggest avoiding enteral nutritional therapy via tube after pancreatic resection[41].

Enteral route

The routine use of enteral nutrition (EN) via feeding tube post-operatively is controversial. On one hand, full dependency on oral intake to meet nutritional needs may be impossible due to decreased appetite, nausea and gastro-intolerance. On the other hand, the use of EN in all patients could be considered as over-treatment and useless[42]. As a result, according to ASER and ISGPS recommendations, only patients who are malnourished or have a high risk of developing malnutrition and/or severe post-operative complications or cannot meet nutritional goals (intake <50% of protein/energy target) through oral intake should receive supplementary artificial nutrition within 24 h.

However, a recent meta-analysis suggests that routine supplementary enteral nutrition administration via a percutaneous enteral tube may improve post-operative outcomes (reduced infectious complications and post-operative length of hospital stay) after pancreatoduodenectomy compared with those not receiving enteral nutrition. The main advantage of this standard combination is better nutritional goal achievement and tolerance. Combining oral and tube feeding for all patients after PD, independently of pre-operational risk of malnutrition, is based primarily on findings from the NURIMAS Pancreas prospective study, where none of the existing nutritional assessment scores defining malnutrition was relevant to complications after pancreatic surgery. Secondly, in the case of pancreatic surgery, data on malnutrition's influence on post-surgical complications are limited by retrospective study design and come from malnutrition scores of moderate accuracy[16,43].

Parenteral route

EN versus TPN. Over the past few decades, total parenteral nutrition (TPN) has been the preferred nutritional treatment for every patient undergoing gastrointestinal cancer surgery. However, despite guidelines recommending oral feeding on the first day after surgery, TPN remains the most common support route after surgery for the majority of clinicians. Recent meta-analyses support the use of the enteral nutrition (EN) route over TPN, mainly because of the significant reduction in length of stay, improved outcomes in bowel function and reduced complication rates after pancreaticoduodenectomy in patients with pancreatic cancer[44]. Furthermore, there was no difference in the risk of post-operative complications, including delayed gastric emptying, post-operative pancreatic fistula, post-pancreatectomy haemorrhage, infections and mortality between the EN and TPN groups[45].

In conclusion, the International Study Group of Pancreatic Surgery (ISGPS) recommends enteral nutrition over parenteral nutrition when nutritional support is needed. Parenteral nutrition is only recommended in patients in whom adequate amounts of enteral nutrition are not feasible or not tolerated[10].

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EN+TPN. As mentioned above, recent literature indicates the benefits of post-operative oral or enteral nutrition (EN) over the parenteral route in improving post-operative outcomes. However, in some cases, EN after PD may not be well tolerated, and the caloric goal may not be achieved adequately. To optimise clinical outcomes by providing maximum calories post-operatively, the strategy of early combined parenteral and enteral nutrition (ECPEN) was introduced. The prospective study by Probst *et al.* found ECPEN to be safe after pancreaticoduodenectomy, and especially in combination with nasojejunal feeding tube (NJT), ECPEN adequately covered caloric requirements during the post-operative phase[43].

Moreover, early EN combined with PN was found to greatly improve liver function, reduce infectious complications, prevent delayed gastric emptying, and shorten post-operative hospital stays in patients undergoing PD[46]. Similarly, in a recent narrative review, Xu *et al.* concluded that EN combined with PN can be used as a choice of nutritional support after pancreatic surgery for at least 4 d[21], and does not significantly impact morbidity in patients post-operatively[5]. In addition, a recent meta-analysis proved that PN combined with EEN was a safe strategy for patients after pancreaticoduodenectomy[47].

Total parenteral nutrition. Total parenteral nutrition (TPN) has historically been used conservatively in the management of patients after pancreaticoduodenectomy (PD). Although routine post-operative PN as a first-line treatment is not recommended or encouraged according to ASER, ASPEN, ESPEN and ERAS after pancreatic resections, there is no clear consensus on the ideal nutritional route for post-PD patients. Current literature suggests that supplemental SPN or TPN could be an option when oral or tube feeding is intolerant or fails to meet nutrient requirements, or when post-operative complications affect gastrointestinal function[21,28,40]. In particular, Cullen *et al.*, who studied the effect of TPN in 1184 patients, concluded that TPN administration should only take place in patients who have additional PD-associated complications such as deep surgical site infections or PF and be avoided in cases of isolated grade A DGE[48]. TPN is considered a safe choice and may benefit patients at high risk for peri-operative malnutrition or severely malnourished patients (pancreatic cachexia) by covering energy and protein requirements[5].

Immunonutrition (IN). Pancreatic surgery is associated with both infectious and non-infectious complications, which can lead to prolonged hospital stays and poor clinical outcomes. Patients with pancreatic cancer often experience elevated levels of pro-inflammatory cytokines, malnutrition, cachexia and immunosuppression induced by cancer, chemotherapy and surgical stress, all of which are considered to be major causes of peri-operative morbidity. Immunonutrition (IN) enriched with arginine, glutamine, omega-3 fatty acids and nucleotides is thought to positively impact immune system regulation through various mechanisms, including reducing inflammatory responses and accelerating wound healing in patients undergoing major gastrointestinal surgery, including pancreatoduodenectomy (PD)[49]. Evidence-based data on the role of IN before and after PD primarily comes from recent meta-analyses, the latest ERAS guidelines for Perioperative Care for Pancreatoduodenectomy, and ESPEN recommendations for major gastrointestinal surgery, including pancreas[50]. However, the role of IN in patients undergoing PD is still unclear, doubtful and contradictory.

Regarding the relationship between immunonutrition and survival in pancreatic surgery, results from a randomised controlled study among 108 patients with oesophagogastric and pancreaticobiliary cancer showed no significant difference in short- or long-term survival[51]. According to the meta-analysis by Fu-An Yang *et al.*, immunonutrition could reduce infectious complications, wound infection rates and length of hospital stay only in the pre-operative period, whereas no impact was observed during the post-operative period[52]. Similarly, in the recent systematic review and meta-analysis of Adiamah *et al.*, the authors concluded that pre-operative IN should be encouraged in routine practice in patients undergoing surgery for gastrointestinal cancer, given its significant impact on infectious complications and its tendency to shorten length of stay[53].

In addition, there was no significant relationship between immunonutrition and non-infectious complications such as pancreatic fistula development, delayed gastric emptying and mortality. Two additional meta-analyses came to the same conclusions, but there were some major methodological issues, such as a small number of studies, different times of administration, no subgroup analysis (pre or post), and a high risk of bias[20,54].

More recently, in a systematic review by Shang-Yu Wang *et al.*, the authors attempted to investigate whether any specific nutritional therapy was superior in terms of complications associated with pancreaticoduodenectomy (PD). The authors concluded that pre-operative IN in addition to post-operative IN was associated with a decrease in infectious complications and the occurrence of post-operative pancreatic fistula (POPF), and that peri-operative administration of IN could provide the best clinical benefit for patients undergoing PD. However, it should be noted that in the above meta-analysis, nutritional status or malnutrition risk was not included as a confounding factor in the subgroup analysis[55].

Finally, the ESPEN guidelines for the general surgical patient recommend peri- or post-operative administration of IN for malnourished patients undergoing major cancer surgery. However, current data support the pre-operative use of IN. On the other hand, the current updated ERAS recommendations for PD (2019) state that peri-operative immunonutrition is not recommended. This is because there is a lack of high-quality data on IN administration in pancreatic surgery and studies that have supported its favourable impact have had methodological issues, such as high heterogeneity and bias. Therefore, unrestricted use of immunonutrition is not recommended on the basis of the existing literature, and further high-quality randomised controlled trials are needed[56].

Strengths and limitations

The current literature comprises systematic or critical reviews that focus on the nutritional needs of surgical patients in general. However, this review specifically focuses on studies regarding

https://doi.org/10.1017/S0954422423000100 Published online by Cambridge University Press

nutritional support among patients undergoing pancreatectomies. Our approach involved a search strategy across all citation databases to include all sources available to date and was oriented in three directions: pre-operative nutritional risk screening, nutritional assessment and peri-operative nutritional support. There are several limitations to this review. Initially, we did not apply a systematic review approach due to the relatively limited available data and low evidence level. However, we made a thorough effort to gather all available citations from major databases with contributions from authors from different specialties (doctors, dieticians, nurses) and consulted with a librarian. The search was limited to articles written in the English language, so it is possible that published data available in other languages were omitted. Two additional disadvantages of the present review are that no data were presented regarding post-discharge nutrition, and no reference was made to the recent field of personalised nutrition support in the surgical patient. Surgical trauma along with malnutrition presents a unique combination that causes muscle loss, which requires significant time to recover. Although some data exist on the use of oral nutritional supplements (ONS) during the post-discharge period, these data are neither of high quality nor specific to patients undergoing pancreatectomies[57]. Finally, some data show that the use of specific biomarkers and metabolic signatures can help distinguish between patients who may or may not benefit from nutritional support, or which nutritional support is optimal. However, to date, there is a lack of literature regarding personalised nutrition for patients with pancreatic cancer undergoing surgery.

Conclusion

The nutritional approach for patients suffering from pancreatic cancer during the peri-operative period is a critical factor that should always be adequately evaluated and optimised throughout the patient's journey. Despite the progress made in diagnosis, evaluation and nutritional intervention, most patients are not adequately and thoroughly evaluated.

Concerning pre-operative nutritional support in pancreatic surgery, the following points should be considered:

a. Patients with good nutritional status do not need special nutritional intervention.
b. Patients at low or medium nutritional risk could benefit from oral supplements intake.
c. For patients with high nutritional risk or malnutrition before PD, if the oral target route cannot be met, aggressive nutritional support could be recommended (artificial EN via tube feeding and/or supplementary or total PN).
d. PN is recommended only in severely malnourished patients.

Regarding post-operative feeding options, contrary to previous nutritional practices of no feeding, fasting, and full clear liquid diets for the immediate post-operative period, early resumption of oral intake without restriction is safe and should be encouraged with no detrimental effect on complications. Supplementary artificial nutrition should be administered within 24 h among patients who are malnourished present a high risk of developing malnutrition, not meeting nutritional goals (>50% of protein/kcal) through oral intake, or developing severe post-operative complications early after the operation. Although not fully supported by incontrovertible evidence, major societies recommend enteral nutrition over parenteral nutrition when nutritional support is needed, while parenteral nutrition is only recommended in patients for whom adequate amounts of enteral nutrition are not feasible or not tolerated.

In addition to the optimal feeding route, future research should focus particularly on post-discharge nutrition. Simultaneously, new data will emerge in the field of providing personalised nutritional instructions in the surgical patient.

Author's contributions

Z.B. and D.K. designed and conceptualised this review. Z.P., D.K., K.N. and A.A. completed the literature search. Z.B. wrote the first draft. D.K., V.V., G.L. and G.S. edited and reviewed the final version.

Financial support

This research was mainly conducted by the Department of Clinical Nutrition, Evaggelismos General Hospital and received no specific grant from any funding agency, commercial or not-for-profit sectors.

Competing interests

There are no conflicts of interest.

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