Nutritional Approach in Pancreaticoduodenectomy for Pancreatic Adenocarcinoma

Abordagem Nutricional na Duodenopancreatectomia para o Adenocarcinoma Pancreático

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Abstract

Pancreatic cancer is the 7th leading cause of cancer death worldwide. Most pancreatic cancers are adenocarcinomas and arise in the exocrine pancreas. There aren't any reliable forms of early detection and overall survival rates are low. Surgical resection, which most often is a pancreaticoduodenectomy, is the only treatment that offers a potential cure of pancreatic adenocarcinoma.

Malnutrition is common among pancreatic adenocarcinoma patients, which demonstrates the importance of nutritional monitoring. Furthermore, as a pancreaticoduodenectomy is an extensive and radical procedure, patients are predisposed to an even higher nutritional risk. Perioperative nutrition therapy is critical to facilitate patient recovery from surgical stress, the management of surgical complications and long-term patient outcomes after surgery.

Regarding nutritional approach, two guidelines can be used: Enhanced Recovery After Surgery Society guidelines for perioperative care for pancreaticoduodenectomy and the European Society for Clinical Nutrition and Metabolism practical guideline for clinical nutrition in surgery.

In this review, the recommendations for the nutritional management of patients undergoing pancreaticoduodenectomy due to pancreatic adenocarcinoma will be discussed. Three periods will be considered to understand the measures recommended for the different phases of the surgical process: preoperative, early postoperative and late postoperative.

As this is a challenging surgery in patients that may be weakened, nutritional therapy is useful and must be implemented, ideally since the preoperative period and extended even after discharge.

Key words: Pancreas, Adenocarcinoma, Pancreaticoduodenectomy, Recommendations, Nutrition

Resumo

O cancro pancreático é a sétima causa de morte por cancro em todo o mundo. A maioria são adenocarcinomas e surgem no pâncreas exócrino. Não existem formas de deteção precoce confiáveis e as taxas de sobrevivência são baixas. A ressecção cirúrgica, que mais comummente corresponde a uma duodenopancreatectomia, é o único tratamento com potencial de cura para o adenocarcinoma pancreático.

A desnutrição é comum nos doentes com cancro pancreático, o que demonstra a importância do acompanhamento nutricional. Para além disso, como a duodenopancreatectomia é um procedimento extenso e radical, os doentes estão predispostos a um risco de desnutrição ainda maior. A terapia nutricional perioperatória é fundamental para facilitar a recuperação dos doentes do *stress* cirúrgico, para a gestão das complicações cirúrgicas e os resultados do doente a longo termo.

Quanto à abordagem nutricional, duas *guidelines* podem ser usadas: as *guidelines* da Enhanced Recovery After Surgery Society para doentes submetidos a duodenopancreatectomia e as *guidelines* da European Society for Clinical Nutrition and Metabolism para doentes cirúrgicos.

Nesta revisão temática, serão discutidas as recomendações para a gestão nutricional dos doentes com adenocarcinoma pancreático submetidos a duodenopancreatectomia. Serão considerados 3 períodos de modo a serem abordadas as medidas recomendadas para as diferentes fases do processo cirúrgico: pré-operatório, pós-operatório imediato e pós-operatório tardio.

Como esta é uma cirurgia desafiante em doentes que poderão estar enfraquecidos, a terapia nutricional é útil e deve ser implementada idealmente desde o período pré-operatório e estendida até mesmo depois da alta hospitalar.

Palavras-chave: Pâncreas, Adenocarcinoma, Duodenopancreatectomia, Recomendações, Nutrição

Abbreviations

BMI – Body Mass Index

CBD - Common Bile Duct

DGE – Delayed Gastric Emptying

EN - Enteral Nutrition

ERAS - Enhanced Recovery After Surgery

ESPEN – European Society of Clinical Nutrition and Metabolism

h - Hours

IM – Immunonutrition

ISGPF - International Study Group Pancreatic Fistula

LOS – Length of Stay

NCJ - Needle Catheter Jejunostomy

NRS - Nutritional Risk Screening

ONS - Oral Nutritional Supplements

PA – Pancreatic Adenocarcinoma

PEG – Percutaneous Endoscopic Gastrostomy

PC – Pancreatic Cancer

PD – Pancreaticoduodenectomy

PN – Parenteral Nutrition

POPF - Postoperative Pancreatic Fistula

SGA - Subjective Global Assessment

Summary

Introduction

Pancreatic cancer (PC) is the seventh leading cause of cancer death worldwide[1]. PC incidence rates increase with age, being higher in men[2]. Most PCs arise in the exocrine pancreas (96%) and most of these are adenocarcinomas (95%)[2]. Pancreatic adenocarcinoma (PA) develops after a series of mutations that alter normal mucosa to precursor lesions and ultimately invasive malignancy[3]. Approximately 60 to 70% of PAs are located in the head of the pancreas with the remainder being found in the body (15%) and tail (15%)[4]. Currently, there aren't any reliable forms of early detection. Most patients do not show clinical symptoms until the disease is locally advanced or metastatic[5]. By the time of diagnosis, most cancers have spread beyond the pancreas[4]. Overall survival rates for all stages of PA are low, with 1- and 5-year rates of 29% and 7%, respectively[5]. The dismal prognosis means that more attention is needed for the prevention of this disease. Smoking, obesity, diabetes and chronic pancreatitis are well-established modifiable risk factors. Non-modifiable risk factors include age, race, family history and genetic susceptibility[2].

Surgical resection is the only treatment that offers a potential cure of PA. The addition of adjuvant chemotherapy has been shown to improve survival rates[6]. A pancreaticoduodenectomy (PD) or Whipple procedure is one of the most complex surgical operations. It's performed to remove benign and malignant tumors that involve the head of the pancreas, duodenum, periampullary region or distal common bile duct (CBD). It can also be indicated to remove cystic tumors of pancreas and in chronic pancreatitis[7].

Malnutrition characterized by weight loss and decreased dietary intake is common among PA patients[8], which already demonstrates the importance of nutritional monitoring in these patients. Furthermore, being PD an extensive and radical surgical procedure, patients are predisposed to an even higher nutritional risk due to the procedure on itself, its complexity and metabolic disruption due to pancreatic resection[5]. In addition, due to surgical complications, oral or enteral nutrition (EN) via tubes may not be adequate for the immediate postoperative period[9]. Therefore, perioperative nutrition therapy has been recognized as critical for facilitating patient recovery from surgical stress, the management of surgical complications and long-term patient outcomes after pancreatic surgery[10].

In this review, recommendations for the nutritional management of patients submitted to PD due to PA will be discussed.

Methods

To elaborate this review, an extensive search of the electronic databases PubMed and Embase was undertaken to identify studies published in the last 5 years that were relevant for the theme, considering the correspondent title/abstract. The heading terms included combinations of “nutrition” or “nutritional” with “status” or “intervention” or “guidelines” and with “pancreatic adenocarcinoma” or “pancreaticoduodenectomy” or “pancreaticoduodenectomy complications”. The bibliography of the selected articles in the initial search allowed the obtention of additional relevant articles. Electronic webpages of relevant institutions were also searched such as the European Society of Clinical Nutrition and Metabolism

(ESPEN) and Enhanced Recovery After Surgery (ERAS) Society. References were managed through EndNote 20 software.

Physiology of Pancreatic Adenocarcinoma

The pancreas has both endocrine and exocrine functions. The endocrine pancreas regulates metabolic pathways through the production of insulin and glucagon, while the exocrine pancreas produces digestive enzymes[5]. In the setting of cancer, both functions are affected. Pancreatic exocrine insufficiency manifests as weight loss and steatorrhea, while endocrine insufficiency may result in diabetes mellitus[5].

PC leads to malnutrition, particularly undernutrition, and altered glucose homeostasis. Malnutrition, due to physiologically induced anorexia, malabsorption and increased caloric requirements, results in weight loss. The inadequate nutritional intake associated to the pathological process of increased nutrient depletion due to tumor cytokine release results in a catabolic state[5]. Many of these patients then experience cachexia, a severe condition involving pathological weight loss related to the wasting of skeletal muscle and adipose tissue[11]. Ultimately, PC patients with malnutrition or cachexia have a lower quality of life, increased morbidity and mortality, longer hospital stays and a reduced response to treatment[5].

Pancreaticoduodenectomy Technique

The classic technique of PD consists of the *en-bloc* removal of the distal segment of the stomach (antrum), the first and second portions of the duodenum, the head

of the pancreas, the distal CBD and the gallbladder. Another approach to this procedure is known as a pylorus-sparing PD, in which a small segment of the duodenum is left *in situ* with the entire stomach to preserve the pylorus and prevent post–gastrectomy related symptoms and complications.[7] Current evidence suggests there is no difference between the pylorus-preserving PD and the classic PD in terms of long-term survival, postoperative mortality and morbidity. There might be a potential benefit for the classic PD regarding delayed gastric emptying (DGE). However, it seems that the pylorus-preserving PD may reduce operating time, intraoperative blood loss and red blood cell transfusion. Nevertheless, there is no relevant difference between the two procedures for the treatment of PC[12].

Postoperative Surgical Complications

Due to improved surgical techniques and postoperative care, the mortality rate of patients post-PD has decreased from 30 to 1% in high-volume institutions[9]. However, the morbidity rate remains at 30%[13].

Complications after PD generally result in prolonged hospital stay, delayed adjuvant therapy, lower quality of life or death. Common complications are gastroparesis, wound infection, hemorrhage, pancreatitis and postoperative pancreatic fistula (POPF), which is the most common one[7]. The incidence of PD-related complications ranges from 20 to 30% and 14 to 20% when it comes to POPF[14]. In the setting of POPF, the release of autolytic digestion enzymes in the peritoneal cavity is a source of other complications, such as peripancreatic collections, abscess and hemorrhage[7]. Currently, the International Study Group Pancreatic Fistula's (ISGPF) definition of POPF is the most useful for diagnosis. A

pancreatic fistula is defined as an abnormal communication between the pancreatic ductal system and other epithelial surface containing pancreas-derived, enzyme-rich fluid. It is diagnosed with any measurable volume of drain fluid on postoperative day 3 or after with an amylase level greater than 3 times the upper limit of normal amylase for the considered institution. However, to be defined as a POPF, clinical relevance is also necessary. The ISGPF also defines subcategories based on the grade of severity of the fistula[15]. Independent risk factors for the development of a clinically relevant POPF include small diameter of the main pancreatic duct, visceral fat area, soft pancreatic texture and large operative time[16].

Nutritional Approach Guidelines

Regarding nutritional approach in PD due to PA, two guidelines can be used: ERAS guidelines for perioperative care for pancreaticoduodenectomy[17] and the ESPEN practical guideline for clinical nutrition in surgery[18].

ERAS is a multimodal pathway that has been widely introduced to reduce surgical stress and improve recovery after major surgery. It is now validated in many types of surgery since it reduces postoperative medical complications, hospital stay and costs[17]. First guidelines for PD were published in 2012[19]. The most updated ERAS guidelines for PD refer to 2019[17].

ESPEN is a non-profit organization that is dedicated to all issues relevant to the field of clinical nutrition and metabolism, promoting basic and clinical research, basic and advanced education and organization of consensus statements about

clinical care and care quality control[20]. The most updated ESPEN guidelines for clinical nutrition in surgery refer to 2021[18].

In this review, three periods will be considered for the nutritional management in PD in order to understand the measures recommended for the different phases of the surgical process: preoperative, early postoperative and late postoperative.

Preoperative Period

Before scheduling surgery, it is important that the patients are assessed regarding their nutritional status[18]. As PD predisposes patients to a high nutritional risk[5], avoiding sarcopenia and loss of visceral adipose tissue before surgery may contribute to improved postoperative outcomes[17]. According to ESPEN, in the surgical patient, severe nutritional risk has been defined as the presence of at least one of the following criteria[18]:

- Weight loss > 10-15% within 6 months;
- Body Mass Index (BMI) < 18,5kg/m^2;
- Subjective Global Assessment (SGA) Grade C or Nutritional Risk Screening (NRS) > 5;
- Serum albumin < 30 g/l (with no evidence of hepatic or renal dysfunction).

<u>Prehabilitation</u>

Prehabilitation is the process of enhancing an individual's functional capacity before major elective surgery to improve tolerance to the physiological stress induced by surgery[21]. If nutritional risk is high, prehabilitation before surgery is recommended by both ERAS and ESPEN guidelines in order to optimize the patient's nutritional status[17, 18]. According to the ERAS guideline, it involves three

components: nutrition therapy, physical exercise and psychological support[17]. It is recommended to be initiated at least two to six weeks before surgery[17, 18]. Prehabilitation may contribute to decreased postoperative complication rates and shortened hospital length of stay (LOS) in patients undergoing major abdominal surgery[22-24]. However, more data is needed to confirm its benefit in PD patients[17].

Preoperative nutrition

Most patients with PC have a significant weight loss before surgery[5, 25]. For patients undergoing surgery for cancer, undernutrition is an independent risk factor for the incidence of complications, increased mortality, LOS and costs[18]. Also, the extreme surgical stress and trauma associated with PD will induce more catabolism[5, 18]. This emphasizes the need for nutritional supplementation, in order to restore the patient's nutritional status prior to surgery[17].

Nutritional support (parenteral, enteral or oral supplements) is often recommended for patients with severe nutritional risk, according to ESPEN criteria[18]. ERAS only recommends nutritional support for patients with weight loss > 15% within 6 months based on self-reported pre-morbid weight or BMI drop to < 18.5 kg/m^2 [10, 17]. These patients shall receive nutritional therapy prior to surgery, which may be postponed to obtain adequate nutritional status[17, 18]. Duration of preoperative nutritional therapy should vary according to nutritional risk, but a period of 7 to 14 days may be appropriate. The oral/enteral route of administration is preferred[18].

Preoperatively, oral nutritional supplements (ONS) shall be given to all malnourished cancer and high-risk patients undergoing major abdominal surgery. If patients do not meet their energy needs from normal food, independent of their nutritional status, it is also recommended for them to take ONS preoperatively[18]. Preoperative ONS/EN should be administered before hospital admission to avoid unnecessary hospitalization and nosocomial infections[18]. In malnourished patients requiring nutritional support before surgery, enteral feeding through a nasogastric or nasojejunal tube should be the preferred routes of administration[17]. For patients with malnutrition or severe nutritional risk in which energy requirements cannot be adequately met by ONS/EN, it is recommended preoperative parenteral nutrition (PN), combined with oral nutrition whenever possible. It is also recommended a period of 7 to 14 days of PN before surgery[18]. Nevertheless, it remains unproven that preoperative nutritional support reduces complication rates or enhances recovery[18, 26]. However, the combination of the nutritional intervention with other therapeutic items as in the ERAS prehabilitation program may show significant benefit[27].

Immunonutrition (IM)

Tumor cytokine release leads to high levels of pro-inflammatory cytokines in patients with PC[5]. Through its potential to modulate the perioperative inflammatory response, oral IM containing arginine, glutamine, omega-3 fatty acids and nucleotides has been associated with lower complication rates and LOS after major gastrointestinal cancer surgery, mainly in malnourished patients[17, 18]. The data suggests preferentially a preoperative use, being considered a cost-effective intervention. However, there is currently no clear evidence for the use

of these formulas in comparison to standard ONS in the preoperative period[18]. Heterogeneity among studies that demonstrate benefits is high and the optimal timing for administration is debated[17]. Besides that, specific evidence on IM in pancreatic surgery is scarce[28]. Therefore, IM is not recommended for patients undergoing PD[17].

Preoperative fasting and preoperative treatment with carbohydrates

Patients undergoing surgery who have no specific risk of aspiration shall drink clear fluids until 2 hours (h) before anesthesia. Solids shall be allowed until 6h before anesthesia[17, 18]. There is no evidence that ingesting clear fluids up to 2h before surgery increases the risk of aspiration or regurgitation in comparison to a 12h or longer fast. Exceptions to this are patients with risk factors for aspiration, undergoing emergency surgery and those with DGE or gastroesophageal reflux[18]. Preoperative carbohydrate intake aims to improve metabolic conditioning before surgery, avoiding glycogen-depletion caused by an overnight fast[17]. A carbohydrate-rich oral solution should be taken the evening before (800 ml) and 2h prior to surgery (400 ml)[18]. Carbohydrate loading is safe and does not increase the risk of aspiration[17, 18]. Postoperative insulin resistance is attenuated, as is thirst and anxiety, and there is a reduction of LOS[17, 29]. However, a significant effect on postoperative complications remains to be demonstrated[30].

Early Postoperative Period

Postoperative nutrition

Due to the high morbidity rates after major pancreatic surgery, it is important to identify patients at a high nutritional risk after the procedure, evaluate their nutritional status and, if necessary, implement nutritional support strategies[18]. Relevant parameters include an updated blood work, assessment of their adherence to oral diet and close monitoring.

Early normal diet according to tolerance is safe and should be encouraged, even in the presence of DGE or pancreatic fistula[17, 18]. Oral intake, including clear liquids, shall be initiated as soon as possible after surgery in most patients. Early oral nutrition is associated with a lower rate of complications and LOS, also having benefits concerning postoperative recovery and infection rate[18]. Also, preoperative ONS continued postoperatively may help minimize postoperative weight loss[18].

In patients that it is to be expected a daily intake of less than 50 to 60% of their energy requirements for 7 or more days, postoperative nutritional support strategies should be considered[18, 31]. An individual approach based on patients' nutritional status evaluation, disease presentation and expected postoperative course should guide nutritional support strategy choice. The enteral route should be preferred whenever possible due to its potential to maintain gastrointestinal integrity[17].

Early postoperative EN (within 24h) shall be initiated in patients in whom oral nutrition is not possible or in whom oral intake is expected to be insufficient (<50%) for more than 7 days[18]. Oral intake may be delayed due to swelling, obstruction or impaired gastric emptying, making it difficult to meet nutritional requirements[18]. Early EN has been claimed to reduce infectious complications and has been suggested to reduce the rate of multiple organ failure[18]. In most

patients, a standard whole protein formula is appropriate. In case of small bowel access by a needle catheter jejunostomy (NCJ) no oligopeptide diet is required[18].
It is recommended to start EN with a low flow rate (10 or 20 ml/h) and to increase it considering individual needs due to limited intestinal tolerance. The time to reach the target intake can differ and it may take 5 to 7 days before nutritional requirements are achieved by the enteral route[18]. Tolerance of EN has to be closely monitored in all patients with impaired gastrointestinal function[18].
Partial PN or total PN may be beneficial to avoid a lower energy intake in undernourished patients in whom EN is not tolerated or contraindicated, particularly in patients with postoperative complications impairing gastrointestinal function, who are therefore unable to receive and absorb adequate amounts of oral/enteral feeding for at least 7 days[17, 32].
It is recommended regular reassessments of nutritional status during hospital stay and, if necessary, a continuation of nutritional support therapy after discharge, including dietary counseling for patients who have received nutritional support therapy and still do not fully cover their energy requirements through the oral route[18]. Despite perioperative nutritional therapy, patients with postoperative complications are at risk for further deterioration of nutritional status and also require nutritional follow-up after discharge[18].

Postoperative routes of administration for nutritional support therapy

When EN is necessary, a proper route of administration must be decided. Nowadays, it is established that nasogastric intubation after surgery does not improve outcomes and their routine use must be avoided[17]. Routine nasogastric

intubation is associated with an increased LOS, with delays in both liquid and solid diet initiation and independently correlated with DGE[33]. Placement of a nasojejunal tube (inserted via the nose with its tip passed distally at the time of operation) or NCJ (inserted distal to the anastomosis) should be considered for all candidates for EN undergoing pancreatic surgery, mainly for malnourished patients[18]. For patients at nutritional risk, NCJ may be superior to nasojejunal or nasoduodenal tubes since these are associated with a significant rate of accidental dislodgement[18, 34]. In these patients, it may even be considered leaving NCJ to continue nutritional support therapy after discharge[18].

Postoperative glycemic control

Early postoperative hyperglycemia (blood glucose > 140 mg/dL) and high glucose variability are associated with adverse clinical outcomes after PD in patients with or without diabetes[17]. Preoperative hemoglobin A1c levels may help to identify patients at a higher risk of worse postoperative glycemic control after major abdominal surgery[17]. The optimal glycemic target during the perioperative period remains to be determined[35] but it is recommended that glucose levels are maintained as close to normal as possible without compromising patient safety[17].

Late Postoperative Period

After discharge from the hospital, improvement in nutritional status and quality of life are the main evaluation criteria[18].

It is not certain that routine early or late postoperative administration of ONS improves outcomes but there are beneficial effects in terms of nutritional status, rate of minor complications, well-being and quality of life in patients who cannot

meet their nutritional requirements at home[18]. This applies mainly to patients after major gastrointestinal surgery[36].

In some patients, after pancreatic surgery, the oral caloric intake will be inadequate for a longer period with a risk for postoperative malnutrition[18]. If long-term EN is necessary, placement of a percutaneous endoscopic gastrostomy (PEG) is recommended[18]. The guidelines for PEG placement recommend the intervention for EN of at least two to three weeks[37]. However, for patients who are expected to be administered EN after surgery, a NCJ may be implemented during the procedure. This may be advantageous because it does not need to be removed at the time of discharge from the hospital, unlike nasojejunal tubes. So, if it is necessary supplementary EN it can be continued via NCJ at home with 500 or 1000 kcal/d overnight[18]. Appropriate training will enable most patients to administer EN through NCJ themselves[38].

Critical Analysis

In PA, there is a great chance that patients develop malnutrition, which consequently affects their quality of life, morbidity and mortality. Before these patients undergo PD, it is important that they have the best nutritional status possible to avoid even more nutritional depletion because of the magnitude of this surgery. In PD, nutritional monitoring is necessary throughout every stage of the procedure. Therefore, there are guidelines such as the ESPEN and ERAS ones that serve as a guide to aid nutritionists to adapt their patient's diets preoperatively and postoperatively.

The use of a well-established and standardized ERAS protocol is useful to have a common language, to conduct multicenter studies and for the evidence-based management of patients. There is an ERAS guideline specifically related to PD which involves several aspects related to patient care before, during and after surgery. In this guideline, some aspects related to the nutritional monitoring of patients undergoing PD are considered. However, ERAS is not an exclusively nutrition-related guideline. Nevertheless, the use of ERAS pathways in pancreatic surgery reduces complications, hospital LOS and costs. ESPEN has a specific guideline for clinical nutrition in surgery, being uniquely based in the aspects involved in the nutritional management of these patients. However, in this guideline many aspects refer to general gastrointestinal surgery. So, not every recommendation is specific for pancreatic surgery.

The clinical expertise of the nutrition practitioner that accompanies these patients is determinant to decide the applicability of all the recommendations of the guidelines. It's key that nutrition professionals do not follow just one guideline. The different guidelines should be analyzed, being also necessary to consider hospital context so that a better assistance can be provided to PA patients undergoing PD.

Conclusions

Surgical resection is the only method that may have cure potential when it comes to PA, being PD the most executed procedure. As this is a challenging surgery in patients that may be weakened, therapeutic options related to improving their nutritional status are useful and must be implemented, ideally since the preoperative period and extended even after discharge. ESPEN and ERAS

guidelines are an important starting point to aid professionals to make the best decisions and individualize their assistance.

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