ISSN 1948-9366 (online)

World Journal of
Gastrointestinal Surgery

World J Gastrointest Surg 2021 September 27; 13(9): 885-1109

Published by Baishideng Publishing Group Inc

W J G S

World Journal of Gastrointestinal Surgery

Contents

Monthly Volume 13 Number 9 September 27, 2021

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Production Editor: *Jia-Hui Li*; **Production Department Director:** *Xiang Li*; **Editorial Office Director:** *Ya-Juan Ma*.

NAME OF JOURNAL
World Journal of Gastrointestinal Surgery

ISSN
ISSN 1948-9366 (online)

LAUNCH DATE
November 30, 2009

FREQUENCY
Monthly

EDITORS-IN-CHIEF
Shu-You Peng, Varut Lohsiriwat, Jin Gu

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/1948-9366/editorialboard.htm

PUBLICATION DATE
September 27, 2021

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World J Gastrointest Surg 2021 September 27; 13(9): 885-903

DOI: 10.4240/wjgs.v13.i9.885

ISSN 1948-9366 (online)

REVIEW

Neoadjuvant treatment: A window of opportunity for nutritional prehabilitation in patients with pancreatic ductal adenocarcinoma

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Author contributions: Trestini I and Cintoni M were involved in the collection and synthesis of all data and manuscript writing; Rinninella E, Grassi F, Paiella S, Salvia R, Pozzo C, Alfieri S, and Gasbarrini A oversaw the project progress and were involved in the final editing of the manuscript; Bria E, Tortora G, and Milella M were involved in the writing and revision of the manuscript; Mele MC was involved in the idea, writing, and revision of the manuscript; All authors have read and approved the final manuscript.

Conflict-of-interest statement: Trestini I reported speakers' fees from Mylan and Fresenius Kabi. Bria E received speakers' and travels' fee from MSD, Astra-

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Abstract

Patients affected by pancreatic ductal adenocarcinoma (PDAC) frequently present

Zeneca, Celgene, Pfizer, Helsinn, Eli-Lilly, BMS, Novartis and Roche; consultant's fee from Roche, Pfizer; institutional research grants from Astra-Zeneca, Roche. Bria E is currently supported by the Associazione Italiana per la Ricerca sul Cancro (AIRC) under Investigator Grant (IG) No. IG20583. Bria E is currently supported by Institutional funds of Università Cattolica del Sacro Cuore (UCSC-project D1-2018/2019). Tortora G is supported by AIRC, IG18599, AIRC 5x1000 21052. Milella M reported personal fees from Pfizer, EUSA Pharma and Astra Zeneca. Other Authors declare no conflict of interest.

Manuscript source: Invited manuscript

Specialty type: Nutrition and dietetics

Country/Territory of origin: Italy

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

Received: February 12, 2021
Peer-review started: February 12, 2021
First decision: May 13, 2021
Revised: May 28, 2021
Accepted: July 20, 2021
Article in press: July 20, 2021
Published online: September 27,

with advanced disease at the time of diagnosis, limiting an upfront surgical approach. Neoadjuvant treatment (NAT) has become the standard of care to downstage non-metastatic locally advanced PDAC. However, this treatment increases the risk of a nutritional status decline, which in turn, may impact therapeutic tolerance, postoperative outcomes, or even prevent the possibility of surgery. Literature on prehabilitation programs on surgical PDAC patients show a reduction of postoperative complications, length of hospital stay, and readmission rate, while data on prehabilitation in NAT patients are scarce and randomized controlled trials are still missing. Particularly, appropriate nutritional management represents an important therapeutic strategy to promote tissue healing and to enhance patient recovery after surgical trauma. In this regard, NAT may represent a new interesting window of opportunity to implement a nutritional prehabilitation program, aiming to increase the PDAC patient's capacity to complete the planned therapy and potentially improve clinical and survival outcomes. Given these perspectives, this review attempts to provide an in-depth view of the nutritional derangements during NAT and nutritional prehabilitation program as well as their impact on PDAC patient outcomes.

Key Words: Pancreatic cancer; Neoadjuvant treatment; Pancreatic cancer surgery; Nutritional status; Nutritional prehabilitation; Malnutrition

Core Tip: Among pancreatic ductal adenocarcinoma patients with resectable or borderline resectable disease, and those with locally advanced disease with a feasibility of surgical resection of up to 30%, neoadjuvant treatment (NAT) has become the standard of care. NAT may impair functional reserve and lead to nutritional depletion, which may affect therapeutic tolerance, postoperative outcomes or even prevent the possibility of surgery. This review suggests that NAT timeframe may provide a valuable opportunity for nutritional prehabilitation program to minimize the NAT-related nutritional derangements, increase patient's capacity to complete planned therapy, promote tissue healing, and enhance patient's recovery, thus potentially improve outcomes.

Citation: Trestini I, Cintoni M, Rinninella E, Grassi F, Paiella S, Salvia R, Bria E, Pozzo C, Alfieri S, Gasbarrini A, Tortora G, Milella M, Mele MC. Neoadjuvant treatment: A window of opportunity for nutritional prehabilitation in patients with pancreatic ductal adenocarcinoma. *World J Gastrointest Surg* 2021; 13(9): 885-903
URL: https://www.wjgnet.com/1948-9366/full/v13/i9/885.htm
DOI: https://dx.doi.org/10.4240/wjgs.v13.i9.885

INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC), with 458918 new cases in 2018, represents the 14th neoplasia in incidence, and with a 95% overall mortality rate, is the 7th leading cause of cancer-related death[1].

Current PDAC treatment

Surgical resection is the only potentially curative treatment for PDAC[2]. Nevertheless, an upfront surgical approach is often unfeasible, because most patients are diagnosed with an advanced PDAC stage, due to a lack of early symptoms and to the fast tumor progression[2]. In this context, neoadjuvant treatment (NAT) consisting of chemotherapy and/or chemoradiation has become the standard of care to downstage non-metastatic locally advanced PDAC patients[3]. Moreover, NAT is gaining popularity in both borderline and fully resectable patients to allow a more accurate and complete cytoreduction (R0)[4-6]. Resection rates range from 26% to 60% in patients showing a good NAT response, rising to 67.8% in patients with anatomically borderline resectable disease[7], with a high percentage of R0 resections and a more

2021

P-Reviewer: Koustas E
S-Editor: Zhang H
L-Editor: Filipodia
P-Editor: Ma YJ

than doubled median overall survival (OS)[8,9]. Adjuvant treatment after surgery, using a combination of chemotherapy and radiotherapy, is used to increase the local control of disease[3].

Impact of nutritional issues on PDAC

Common presentation hallmarks of PDAC are unintentional weight loss (WL) and malnutrition, defined as "a state resulting from lack of intake or uptake of nutrition that leads to altered body composition and body cell mass leading to diminished physical and mental function and impaired clinical outcome from disease"[10], and sustained by cancer-induced metabolic changes and by a reduced nutrient intake[11]. Moreover, the loss of parenchyma and/or obstruction of the main pancreatic duct may affect both the production of enzymes and their transportation into the duodenum, resulting in nutrients maldigestion and/or malabsorption[12].

Over 80% of PDAC patients present with WL at diagnosis, and more than one-third reports a WL > 10% of their usual body weight[13]; moreover, NAT may worsen nutritional status, impairing postoperative outcomes and even delaying or preventing surgical intervention[14,15]. Malnutrition in PDAC patients may reach high rates (up to 80%) at diagnosis, and it is associated with a worse performance status and a worse OS[16].

Sarcopenia, defined as "a progressive and generalized skeletal muscle (SKM) disorder that is associated with increased likelihood of adverse outcomes"[17], is another frequent condition reported in more than 50% of PDAC patients[18]. It is associated with poorer surgical outcomes and a higher length of hospital stay (LOS) [19], and has been identified as a relevant prognostic factor for OS in patients treated with both gemcitabine (GEM) based and FOLFIRINOX-like (leucovorin, fluorouracil, irinotecan, and oxaliplatin) chemotherapies[20-22].

Improvement of patient nutritional status during NAT and prior to surgery may lead to better surgical outcomes and be an important part of oncological management [23,24]. The best nutritional strategy to manage PDAC patients is still under debate, even if an appropriate nutritional support represents an important therapeutic strategy in the preoperative period[23]. While cancer-related malnutrition is still an underrecognized and undertreated burden in clinical practice[25,26], emerging data show that early closing of the nutritional gap during anticancer treatment can stabilize WL, improve treatment tolerability, reduce the performance status deterioration, and ameliorate survival rate[27,28].

The aim of this review is to explore if the NAT period may represent an exploitable therapeutic window to perform a nutritional prehabilitation program improving clinical and survival outcomes.

METHODOLOGY

This review was conducted on Medline, from inception to January 2021, aiming to identify published studies exploring the role of nutritional status and preoperative nutritional prehabilitation on the outcomes in pancreatic cancer (PC) patients. The inclusion criteria for the studies were as follows: observational, prospective and retrospective studies, case-control studies, cohort studies, narrative reviews, systematic reviews, and meta-analyses; studies including information about nutritional status and/or nutritional prehabilitation on PC patients; exclusive PC studies; and studies written in English. All studies that did not fall into the previous criteria were excluded from the review process.

NUTRITIONAL STATUS CHANGES DURING NEOADJUVANT TREATMENT AND THEIR POTENTIAL RELATIONSHIPS WITH THERAPEUTIC OUTCOMES

Approximately one-third of PDAC patients are diagnosed with locally advanced disease, which prevents an immediate surgical approach[29]. In this setting, NAT has become the standard of care as either exclusive treatment or to achieve resectability[9,30,31], while its use in "borderline" and "resectable" disease is still under debate, even if it has become more popular[32].

This therapeutic implementation represents an additional nutritional concern; in fact, NAT cause several side effects, such as oral ulceration, xerostomia, dysgeusia, indigestion, nausea, vomiting, diarrhea, and alteration of intestinal motility, leading to a reduced food intake, with significant consequences on body composition, and in particular on SKM mass[33]. This in turn, may impact NAT completion, postoperative outcomes or even impede the possibility of surgery[10,34].

A prospective study including patients with upper gastrointestinal cancers found that NAT-treated patients experienced greater losses in the SKM area measured at L3 vertebra by computed tomography (CT) scan, compared with patients receiving palliative chemotherapy (-6.6 cm^2, 95% confidence interval [CI] -10.2 to -3.1; P < 0.001 and -1.2 kg, 95%CI -1.8 to -0.5; P < 0.001, respectively)[35].

Naumann *et al*[35] analyzed 100 consecutive locally advanced PDAC patients, treated with 4 wk of GEM-based NAT and found that body weight (mean weight from 69.0 kg to 66.4 kg; P < 0.0001), body mass index (BMI) (mean BMI from 24.3 kg/m^2 to 23.4 kg/m^2; P < 0.0001), and CT-derived subcutaneous adipose tissue (SAT) area (mean SAT from 167.1 cm^2 to 139.5 cm^2; P < 0.0001) significantly decreased after NAT. Interestingly, there was no significant correlation between increasing extent of WL and survival (WL < 2.5%: median survival of 10.8 mo (range 3.2–46.8); 2.5% ≤ WL < 5.0%: 10.9 mo (range 5.0–27.6); 5.0% ≤ WL < 7.5%: 10.0 mo (range 3.1–26.5); 7.5% ≤ WL < 10.0%: 8.4 mo (range 3.1–16.3); WL ≥ 10.0%: 7.3 mo (range 6.1–10.2)[36]. A retrospective analysis of 89 patients with potentially resectable PDAC, who received a 12-wk regimen of neoadjuvant GEM/cisplatin followed by short-course radiotherapy with concurrent GEM as part of a phase II study, reported a significant depletion of SKM, (median SKM area/$height^2$ from 47.5 cm^2/m^2 to 46.3 cm^2/m^2; P = 0.01), visceral adipose tissue (VAT) (median VAT area/$height^2$ from 45.1 cm^2/m^2 to 41.2 cm^2/m^2; P = 0.01), and SAT (median SAT area/$height^2$ from 53.0 cm^2/m^2 to 48.7 cm^2/m^2; P = 0.02). Progressive SKM during NAT was related to a shorter disease-free survival (DFS) (hazard ratio [HR] 0.89, 95%CI 0.80-1.00; P = 0.04), while VAT loss was associated with both shorter progression-free survival (HR 0.98, 95%CI 0.96-0.99; P = 0.01) and OS (HR 0.97, 95%CI 0.95-0.99; P = 0.001)[37]. Another retrospective study evaluated 127 PDAC patients who achieved resectability following approximately 5 mo of NAT, using an array of different chemotherapy regimens (mostly GEM- or fluorouracil-based regimens), found minimal changes in SKM (−0.5 ± 7.8%; P > 0.05), VAT (−1.8 ± 62.6%; P < 0.001), and SAT (−4.8 ± 27.7%; P < 0.001)[38]. A more recent retrospective analysis of 147 locally advanced PDAC patients, treated with NAT, showed a mean WL of 3.7 kg (P < 0.0001), a mean SKM area reduction of 4.2 cm^2 (P < 0.0001), while a WL > 5% and a SKM loss were associated with a worse OS (14.5 mo *vs* 20.3 mo; P = 0.04 and 15.1 mo *vs* 22.2 mo; P = 0.007, respectively)[39]. Similarly, Naumann *et al*[39] observed a significant decrease in weight (mean relative WL of 5.3%; P < 0.001), as well as in SAT (from 142.1 cm^2 to 115.2 cm^2; P < 0.0001), VAT (from 114.7 cm^2 to 95.0 cm^2; P < 0.0001) and SKM (from 126.0 cm^2 to 121.5 cm^2; P < 0.0001) during NAT among 141 PDAC patients. Moreover, WL > 5% (HR 2.8, 95%CI 1.28-5.91; P = 0.009) and a reduction in SKM > 5% (HR 5.54, 95%CI 2.56-12.45; P < 0.001) were independently associated with survival[40].

A large multicenter study by Sandini *et al*[40] including 193 PDAC patients who received NAT (64.2% of patients receiving FOLFIRINOX and 44.6% also undergoing chemoradiotherapy) observed a significant loss of adipose tissue during treatment (median total adipose tissue area from 284 cm^2 to 250 cm^2; P < 0.001), with no wasting of lean body mass (median SKM from 122.1 cm^2 to 123 cm^2; P = 0.001). Furthermore, the authors found that an SKM increase was associated with a higher resectability rate (OR 3.7; P = 0.006), suggesting that anabolic potential was preserved in this subset of patients and that the ability to enhance muscle tissue may be related to the treatment response[41]. Conversely, a more recent prospective analysis of 67 PDAC patients reported a deterioration in SKM (median SKM from 128.4 cm^2 to 120 cm^2; P < 0.001), and adipose tissue (intra-muscular adipose tissue, VAT, and SAT) during NAT, using different chemotherapy regimens (FOLFIRINOX: 44% of patients; GEM-based chemotherapy: 47%) (P < 0.0001). In addition, loss of lean tissue (mean fat-free mass loss 2.6 kg, HR 1.1, P = 0.003, mean SKM loss 1.5 kg, HR 1.21; P = 0.001) and loss of fat mass (mean loss 2.8 kg HR 1.09, P = 0.004) during treatment were related to a higher mortality risk. In multivariable analysis, the preservation of muscle during NAT was predictive of better survival (HR 1.21, 95%CI 1.08-1.35; P = 0.025)[42]. An overview of these studies is reported in Table 1.

In PDAC patients treated with NAT, these data highlight that anthropometric, as well as CT-scan derived body composition parameters can be useful to identify high-risk nutritional phenotypes. In the same setting, the inability to maintain body weight and SKM is associated with poor survival outcomes, while the preservation of body

Table 1 Prognostic role of nutritional status changes during neoadjuvant therapy in patients with pancreatic cancer

Ref.	Number of patients enrolled	Neoadjuvant treatment	Body composition changes (*P* value)	Body parameters and clinical outcomes (HR; *P* value)
Naumann *et al*[35], 2013, Retrospective	100	Gemcitabine-based chemoradiation	Weight decrease ($P < 0.0001$), BMI decrease ($P < 0.0001$), SAT decrease ($P < 0.0001$)	WL tended to negatively impact on OS ($P > 0.05$)
Cooper *et al*[36], 2015, Retrospective	89	Gemcitabine and Cisplatin followed by Gemcitabine-based chemoradiation	SKM area/height^2 decrease ($P = 0.01$), VAT area/height^2 decrease ($P = 0.01$), SAT/height^2 decrease ($P = 0.02$)	Loss of SKM was related to a shorter DFS (HR 0.89, $P = 0.04$), loss of VAT was related to shorter PFS (HR 0.97, $P = 0.01$) and OS (HR 0.97, $P = 0.001$)
Cloyd *et al*[37], 2018, Retrospective	127	Gemcitabine, Capecitabine or 5-FU based chemoradiation	SKM stability ($P > 0.05$), VAT decrease ($P < 0.001$), SAT decrease ($P = 0.02$)	Body composition changes during were not associated with OS ($P > 0.05$)
Sandini *et al*[40], 2018, Retrospective	193	FOLFIRINOX-based chemoradiotherapy	TAT area decrease ($P < 0.001$), VAT area decrease ($P < 0.0001$), SKM area increase ($P < 0.0001$)	SKM area/height^2 was higher in patients who underwent resection ($P = 0.004$)
Naumann *et al*[38], 2019, Retrospective	147	Gemcitabine-based chemoradiation	Weight decrease ($P < 0.0001$), SKM area decrease ($P < 0.0001$)	WL > 5% was associated with poor OS (HR 1.56, $P = 0.028$), SKM area loss > 5% was associated with poor OS (HR 1.50, $P = 0.036$)
Griffin *et al*[41], 2019, Retrospective	78	FOLFIRINOX and gemcitabine-based treatments	SKM area decrease ($P < 0.0001$), VAT decrease ($P < 0.0001$), SAT decrease ($P < 0.0001$)	Loss of lean mass was related to poor OS (HR 1.1, $P = 0.003$), loss of SKM was related to poor OS (HR 1.21, $P = 0.001$)
Naumann *et al*[39], 2019, Retrospective	141	Gemcitabine-based chemoradiation	Weight decrease ($P < 0.001$), BMI decrease ($P < 0.0001$), SAT, VAT and SKM areas decrease ($P < 0.0001$)	WL > 5% was associated with worse OS (HR 2.8, $P = 0.009$), SKM area loss > 5% was associated with poor OS (HR 5.54, $P < 0.001$)

BMI: Body mass index; DFS: Disease-free survival; HR: Hazard ratio; IMAT: Intramuscular adipose tissue; OS: Overall survival; PFS: Progression-free survival; SAT: Subcutaneous adipose tissue; SKM: Skeletal muscle; TAT: Total adipose tissue; VAT: Visceral adipose tissue; WL: Weight loss.

composition compartments represents a positive prognostic feature. However, this topic deserves well-designed and adequately sized trials to confirm these preliminary data.

EFFECT OF MALNUTRITION ON SURGICAL AND SURVIVAL OUTCOMES

Postoperative complications

Pancreatic surgery is associated with a relatively high risk of postoperative complications (POCs), due to its technical complexity and to the anatomical location of the pancreas. Most frequent POCs are postoperative pancreatitis (incidence up to 25%-30%)[43,44], delayed gastric emptying (incidence 20%-30%)[45,46], and postoperative pancreatic fistula (10%-15%)[47,48]. Other less common POCs are represented by post pancreatectomy hemorrhage (PPH), intra-abdominal abscesses, anastomotic leakage, venous thrombosis, and biliary stenosis[49,50].

Several studies have highlighted the impact of malnutrition on the incidence of POC. In a retrospective study performed by Kanda *et al*[51] in 2011, a low prognostic nutritional index (PNI), based on serum albumin concentration and total lymphocyte count, was independently associated with the development of POC, particularly postoperative fistula (HR 2.52, 95%CI 1.37-4.63). La Torre *et al*[52] retrospectively correlated nutritional status, assessed by the Malnutrition Universal Screening Tool (MUST), with POC and found that MUST was an independent predictor of overall morbidity (HR 2.66, 95%CI 1.36-8.57; $P = 0.001$) in 143 PDAC patients. In a prospective study published by Darnis *et al*[53] the Nutritional Index Risk resulted an independent factor for the development of PPH ($P = 0.048$). Nanashima *et al*[54] performed a prospective study of 222 PDAC patients to evaluate the relationship between PNI and POC, finding a lower PNI value in patients who developed POC, without statistically significant differences. In a very recent study, Mackay *et al*[55] performed a nationwide analysis of 1306 PDAC patients and found an incidence of 24% of severe POC, which was identified among the independent factors for not receiving adjuvant chemotherapy (OR 0.32), in particular pancreatic fistula (OR 0.51) and PPH (OR 0.36).

Body composition, particularly the presence of sarcopenia, is also associated with POC development[56]. Amini *et al*[57,58] reported that sarcopenia, assessed by total psoas volume, was associated with higher risk of POC (OR 1.79). Nishida *et al*[59] performed a retrospective study finding a higher rate of major POC and particularly of pancreatic fistula development (OR 2.87) in sarcopenic patients (assessed by the SKM index). However, a recent meta-analysis of 42 studies with 7619 patients involved, showed that preoperative sarcopenia was not associated with overall POC development nor with pancreatic fistula[60].

Survival outcomes

Preoperative nutritional status may play a crucial role in survival rate after surgical oncologic resection. A recent meta-analysis by Liu *et al*[61], including 11 studies with 2123 PDAC patients, indicated that a low PNI was a significant independent predictor of a worse OS (HR 1.57, 95%CI 1.40-1.77; P < 0.001). Furthermore, preoperative PNI was found to be an independent risk factor for failure to complete planned adjuvant chemotherapy (OR 6.47; P = 0.033)[62].

Serum albumin may be associated with the nutritional status and is a prognostic factor for several cancers[63-65]. Hendifar *et al*[66], in a cohort of 106 patients with resected PDAC, the authors observed that a decrease in serum albumin was significantly correlated with a worse DFS (HR 2.2; P = 0.024) and preoperative albumin was correlated with a worse OS (HR 0.48; P = 0.008), while preoperative BMI and BMI changes during therapies were not associated with survival outcome, in line with previous analyses[67].

A recent systematic review of PDAC patients showed that sarcopenia was independently associated with a shorter OS in five of eight studies, many of which used measurements of total psoas area or total psoas index for comparison, without identifying an optimal cut-off, that indeed varied widely[56]. Another systematic review and meta-analysis by Bundred *et al*[60] reported that preoperative sarcopenia was related to lower OS in both resectable (HR 1.95; P < 0.001) and in actually resected patients (HR 1.78; P < 0.001), even if the conclusions were limited by the high heterogeneity (I^2: 92%) between studies, due to the different methods of body composition assessment.

Regarding DFS, a retrospective analysis by Okumura *et al*[68] determined that a low preoperative SKM was a negative independent prognostic factor both for OS (HR 2.0; P < 0.001) and DFS (HR 1.6; P = 0.007), the completion rate of adjuvant chemotherapy in patients with low psoas muscle mass index was significantly lower (65.6% *vs* 80.1%; P < 0.001) but upon multivariate analysis, only a low PNI remained an independent prognostic factor for worse OS and DFS. In line with these findings, Sugimoto *et al* retrospectively showed that the measure of height-adjusted and sex-standardized amount of the SKM area was related to both OS (HR 1.36; P = 0.035) and DFS (HR 0.84; P = 0.007) in patients undergoing upfront surgical resection for PDAC[69].

Sarcopenic obesity (defined as the presence of sarcopenia in an obese patient)[70] was significantly associated with a worse OS (12.9 mo *vs* 20.7 mo; P = 0.04) in the study by Cooper *et al*[36] in patients with potentially resectable PDAC treated within a phase II trial of NAT. A meta-analysis by Mintziras *et al*[18] including 11 studies comprising 2297 PDAC patients, found that sarcopenia was significantly associated with a poor OS (HR 1.49; P < 0.001) and the mortality risk was even higher in sarcopenic obese patients (HR 2.01; P < 0.001). Recently, a retrospective analysis of PDAC patients that underwent pancreatic resection, confirmed that sarcopenic obese patients had a worse OS (14 *vs* 23 mo; P = 0.007)[19].

EVIDENCE FOR POTENTIAL CLINICAL BENEFIT WITH PREOPERATIVE NUTRITIONAL PREHABILITATION

In the Enhanced Recovery After Surgery (ERAS) era, the “prehabilitation,” an intervention aimed at enhancing a patient’s functional capacity to enable him/her to better cope with a stressful event, has become an evolving area of interest[71]. In this context, preoperative nutritional therapy is increasingly recognized as a crucial component to optimize nutrient stores in preparation for the metabolic demands of surgical trauma, conditioning patients to become stronger for an earlier recovery[23]. Major surgery involves several metabolic and nutritional changes, through the activation of an inflammatory cascade and the release of stress hormones and cytokines, whose intensity is correlated with the degree of tissue injury[72]. Therefore, an adequate preoperative physiological reserve is required to meet the functional demands of the surgical stress and to support the stress-induced mobilization of nutritional substrates[73]. Of note, patients with low preoperative reserves, including malnourished, frail and sarcopenic ones, may exhaust their nutritional reserves rapidly and, therefore, they cannot respond to the increased requirements following surgery[23].

Pancreatic surgery is identified as one of the most challenging surgical areas, due to the magnitude of the dissection and resection, the anatomical location, the resultant global stress, and the relatively high rate of morbidity[34,74]. Several studies have reported improved postoperative outcomes and shorter LOS in patients treated according to ERAS principles, as compared to those receiving conventional care[61,75,76]. As many patients scheduled for PDAC surgery are nutritionally depleted, particular attention should be paid to the preoperative nutritional optimization in this clinical scenario[77], as recommended by evidence-based guidelines for preoperative care for pancreaticoduodenectomy by the ERAS Society, the European Society for Clinical Nutrition and Metabolism (ESPEN), and the International Association for Surgical Metabolism and Nutrition, published in 2013[78]. Preoperative care should include careful nutritional assessment, detection of body composition parameters, and thus a personalized preoperative nutritional optimization[79]. Oral feeding remains the best approach[80], while the role of oral nutritional supplements (ONSs) in malnourished patients is well established, and the ONS role in well-nourished ones is still debated.

According to ERAS Society guidelines, routine use of preoperative enteral nutrition is not recommended, but there is a low-level evidence suggesting that a preoperative nutritional support may be indicated in patients with malnutrition[78]. A recent systematic review of studies conducted on ERAS protocols for patients scheduled for pancreaticoduodenectomy since 2013 emphasized the role of preoperative oral immuno-nutrition in the prevention of incisional wound infections, as well as in the reduction of surgical stress, and suggested that preoperative enteral nutrition should be applied for 10 to 14 d before surgery in patients with severe malnutrition[81].

The recently published International Study Group on Pancreatic Surgery consensus statement regarding nutritional support for pancreatic surgery established that nutritional counselling and ONSs are recommended in patients with moderate malnutrition with no evidence of gastric obstruction, or in those who have a moderate risk of nutritional worsening in the early postoperative period. An aggressive preoperative nutritional support by enteral or parenteral feeding should be considered if at least one of the following criteria, reflecting severe malnutrition, is met[34]: WL > 15% within 6 mo; BMI < 18.5 kg/m^2; subjective global assessment grade "C" or nutritional risk score ≥ 5; and serum albumin < 30 g/dL (with no evidence of hepatic or renal dysfunction).

The benefit of preoperative nutritional intervention combined with physical exercise is still a subject of debate. In this regard, a recent Asian analysis among 108 patients undergoing hepato-pancreato-biliary surgeries for malignancy showed that the implementation of prehabilitation, integrating preoperative exercise and nutritional therapy, has the potential to improve outcome, preventing serum albumin deterioration (median, 0.10 *vs* -0.30; P = 0.001), increasing total muscle/fat ratio (median, 1.83 *vs* 1.75; P < 0.001), shortening postoperative LOS (median, 23 d *vs* 30 d; P = 0.045), leading to a potential positive economic impact[82].

Focusing on prehabilitation in 40 patients (45% PDAC) undergoing pancreaticoduodenectomy, a recent randomized controlled trial by Ausania *et al*[83] estimated the effect of preoperative nutritional support, control of diabetes and exocrine pancreatic insufficiency and physical, as well as respiratory training. Although prehabilitation was not associated with a lower POC incidence, a lower rate of delayed gastric emptying (5.6% *vs* 40.9%; P = 0.01) and a lower clinically relevant pancreatic fistula rate (11.1% *vs* 27.3%; P = n.s.) were found in the prehabilitation group. However, this study had several limitations in terms of methodology and was potentially flawed by the short prehabilitation time (patients receiving only 7 d of prehabilitation were included).

In this context, Okumura *et al*[68] suggested that although the ideal period of preoperative nutritional and exercise therapeutic protocols is not established, at least 1 mo before surgery is required to improve nutritional status. Unfortunately, routine nutritional assessment within the ERAS programs is only partially implemented, probably due to insufficient awareness about nutritional issues among health professionals, lack of structured collaboration between surgeons and clinical nutrition specialists, and the absence of dedicated resources[79].

Studies evaluating nutritional optimization before surgery for PDAC are producing encouraging early results, but definitive clinical evidence is very limited. Further studies on this topic are eagerly warranted.

NUTRITIONAL MANAGEMENT

Nutritional management should be started preoperatively to optimize nutritional status in preparation for the increased metabolic requirements of surgical injury. An overview of the suggested nutritional interventions during NAT for PDAC is shown in Figure 1 and in Table 2. An accurate identification of patients at high nutritional risk or already malnourished is crucial to choose the optimal type and timing of nutritional intervention[84]. There are many nutritional risk tools that can be used in clinical practice. Of note, none of the available clinic-biological scores for nutritional assessment meets the diagnostic performance criteria to predict POC after pancreatic surgery, and the proportion of patients at high risk for deranged nutritional status varies using different scores[85].

The inconsistency in predicting poor outcomes with different nutritional screening tools may lead to either insufficient or excessive nutritional treatments, with potentially harmful effects. In this regard, the new Global Leadership Initiative on Malnutrition (GLIM) criteria for the diagnosis and grading of malnutrition have been introduced and recently validated in a large population of patients undergoing abdominal surgery, including pancreatic resections[86]. According to GLIM criteria, a patient can be defined malnourished if, after a positive risk screening test for malnutrition, presents at least one phenotypic criterion (non-intentional WL, low BMI, or reduced muscle mass) and one etiologic criterion (reduced food intake/assimilation, or inflammation/disease burden)[87].

Numerous studies have shown the prognostic impact of body composition assessment by CT-scan in oncological patients and in those undergoing cancer treatments[88-91]. Especially, in patients undergoing NAT, CT scans are usually performed several times during treatment. Therefore, CT scan-based body composition analysis could be easily implemented in routine clinical practice.

Energy intake

Energy balance in catabolic condition, as in PDAC patients, is deeply influenced by changes in dietary intake[92], therapy-linked factors[93], and decreased levels of physical activity[94].

Okusaka *et al*[95] found that a longer survival time was associated with a high energy intake in patients affected by advanced PDAC (P = 0.02). Moreover, Bye *et al* [96] in their work, found a correlation between PDAC-specific symptoms (*e.g.*, pain, fatigue, nausea), WL, and poor energy intake. The caloric requirement of PDAC patients should be assessed in a personalized way and when energy expenditure is not measured individually, ESPEN guidelines suggest an intake of 25-30 kcal/kg/day[97].

In conclusion, assessment of energy intake should be guaranteed in PDAC patients with the aim to elaborate a personalized nutritional strategy in order to decrease the risk of WL and consequently malnutrition.

Protein intake

Recent literature data on nutritional support in oncological patients attribute high relevance to correct protein intake (PI), with the aim to promote muscle anabolism [98]. Sarcopenic patients, similar to oncological ones, have poor protein stores and this could contribute to increased POC, LOS and mortality[23]. The most recent and interesting theories affirm that the best way to prepare the patient to the surgical trauma should be a multimodal approach, which includes nutritional changes, psychological support, and physical training[99,100]. ESPEN guidelines on nutrition in cancer patients set the PI target to 1.2-1.5 g/kg per day. However, it is not clarified if there are specific amino acid mixtures that can improve clinical outcomes in this setting[97].

Several studies have highlighted the role of branched-chain amino acids (BCAAs) to decrease muscle catabolism[101]. Between the first studies conducted on this field of research, Tayek *et al*[102] found a higher response in terms of protein accretion and albumin synthesis using BCAA-enriched parenteral nutrition (PN) formulas with respect to standard PN. More recently, Deutz *et al*[103] conducted a randomized, controlled, double-blind study on 25 cancer patients, with the interventional group receiving a functional food enriched with 40 g of protein and leucine. In this group, the rate of muscle protein synthesis was higher than the control group (P = 0.02). β-

Table 2 Nutritional recommendation during neoadjuvant therapy in patients with pancreatic cancer

Nutritional recommendation during neoadjuvant therapy in patients with pancreatic cancer	
Energy intake	Total energy expenditure should be measured; otherwise, 25 to 30 kcal/kg/d should be guaranteed
Protein intake	1.2-1.5 g/kg/d should be prescribed
Fish oil	Fish oil supplementation may improve the metabolic derangements
PERT	Tumor in the head: start PERT immediately
	Tumor in the body/tail: Perform PEI test before prescribing PERT
Immunonutrition	Immunonutrition-based supplements may improve clinical outcomes

PERT: Pancreatic enzymes replacement therapy; PEI: Pancreatic exocrine insufficiency.

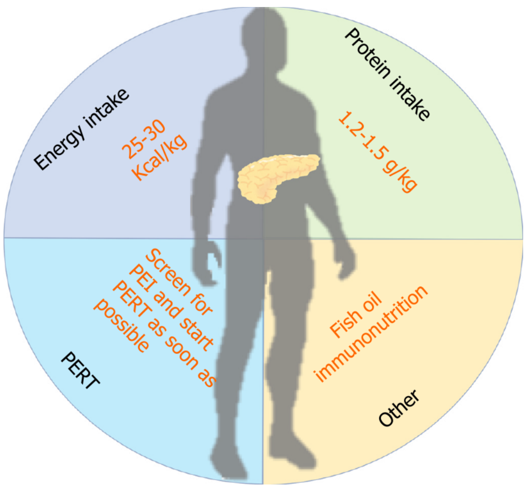

Figure 1 Suggested nutritional interventions during neoadjuvant treatment for pancreatic ductal adenocarcinoma. PEI: Pancreatic exocrine insufficiency; PERT: Pancreatic enzyme replacement therapy.

hydroxy-β-methylbutyrate (HMB) is a metabolite of the essential amino acid leucine, which induces an anabolic effect in cancer patients, promoting regenerative events, suppressing protein degradation, and activating anabolic signaling pathways[104]. In many murine preclinical studies HMB showed the potential to reduce WL, tumor weight, and to attenuate protein degradation[105,106]. In the study by May *et al*[107], which also included advanced PDAC patients, the authors found an increase of fat-free mass (FFM) in patients treated with a mixture of HMB (3 g/d), L-arginine (14 g/d), and L-glutamine (14 g/d) *vs* the control group. On the other hand, a randomized, double-blind, placebo-controlled trial performed by Berk *et al*[108], showed no statistical differences in FFM among patients treated with the same mixture. Despite the lack of a strong evidence from the literature, it is advisable to refer to ESPEN guidelines and recommend a PI of 1.2-1.5 g/kg per day in PDAC patients.

Fish oil

Fish oil (FO) is an anti-inflammatory nutraceutical, which is often used to improve the imbalance between omega-3 (w-3 FA) and omega-6 fatty acids (w-6 FA) in oncologic patients among others[109]. Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are the w-3 FA acids found in FO that are able to induce an anti-inflammatory response[110]. Moreover, many epidemiological studies have suggested that a high consumption of FO and therefore of w-3 FA reduces the risk of pancreatic cancer[111]. These molecules are also involved in the synthesis of cell membranes[112], hormones, receptors, prostaglandins, and leukotrienes[113]. Moreover, EPA and DHA show anabolic effects when used on sarcopenic patients like oncological ones[114]. Barber [115] analyzed the impact of FO on patients with cancer cachexia, concluding that FO had the potential to normalize the metabolic derangements of oncological patients.

For all of these reasons, FO can be useful both in surgical and medical patients affected by PDAC, through oral, enteral, or parenteral administration. Werner *et al* [116] performed a randomized, double-blind, and controlled trial, comparing the administration of 500 mg FO (60% of FO and 40% of medium-chain triglycerides, 6.9 g/100 g of EPA and 13.6 g/100 g DHA) *vs* 500 mg marine phospholipids (8.5 g/100 g EPA and 12.3 g/100 g DHA) three times per day for 6 consecutive weeks. The authors found a stabilization of body weight after 6 wk in both groups (P = 0.001 and P = 0.003, respectively). Moreover, they found a significant increase in the amount of anti-inflammatory EPA and DHA, a decrease of the pro-inflammatory arachidonic acid and an increase in high-density lipoprotein in the patient's plasma of FO group. Arshad *et al* [117] described a reduction in the concentration of pro-inflammatory cytokines and growth factors using intravenous omega-3 enriched lipid emulsion with improvement in survival outcomes, in patients affected by locally advanced or metastatic PDAC eligible for GEM treatment.

Pancreatic enzyme replacement

Pancreatic exocrine insufficiency (PEI) is a frequent condition that can profoundly affect the nutritional status of PDAC patients. PEI is defined as the clinical condition in which the quantity of enzymes secreted by the pancreas are not sufficient to guarantee the physiological digestive processes and can be caused by lack of production by the pancreas and/or by the obstruction of ducts by external causes, such as tumors[118]. Symptoms of PEI may vary from micronutrient deficiency to abdominal pain, flatulence, WL, and steatorrhea, defined as the presence of more than 7 g fat in the feces per day[119,120]. PEI in PDAC patients ranges from 30% to 100%, according to the method used to diagnose the condition[121].

Pancreatic enzyme replacement therapy (PERT) can improve the malabsorption-related symptoms through the amelioration of protein and fat digestion processes[122, 123].

In the paper by Roberts *et al*[124], the use of PERT was associated with an increase of survival among PDAC patients (survival time ratio: 2.62, 95%CI 2.27-3.02). Landers *et al*[125] performed a pilot study to determine the efficacy of PERT in metastatic PDAC patients, using 50.000 IU of pancrealipase for each meal and 25.000 IU for each snack, showing an improvement of symptoms and quality of life (QoL) assessed at 1 and 3 wk after the start of treatment. A retrospective analysis by Domínguez-Muñoz *et al*[126] was conducted among 160 patients with unresectable PDAC. The authors divided into two groups the study population: the first group followed the standard of care, while the second one was screened for PEI and started PERT if necessary. Survival in the second group was longer than in the first one (HR 2.117, 95%CI 1.493-3.002; P < 0.001). Moreover, also in patients with significant WL at diagnosis, PERT was associated with longer survival (HR 2.52, 95%CI 1.55-4.11; P < 0.001). PERT is, therefore, useful to treat malnutrition in PDAC patients affected by PEI, and is associated with an improvement in QoL and survival[127]. Nevertheless, the optimal dose and optimal timing of PERT administration in PDAC patients is not well defined [128]. A very recent position paper by Pezzilli *et al*[12] aimed to give recommendations on PERT in the PDAC setting, concluding that patients with head PDAC should be given enzymes, while a diagnostic evaluation should be performed using fecal elastase in patients affected by body or tail neoplasm prior to giving them PERT. Moreover, in the next few months, a Cochrane Systematic Review on this issue is planning to be published[129].

In conclusion, due to the underrecognition of this condition and its metabolic consequences, PEI should be investigated in all patients affected by PDAC, and PERT should be started as soon as possible, when necessary.

Immunonutrition

Immunonutrition (IN) can be defined as modulation of the activity of the immune system by specific food or nutrients, called immunonutrients; the most important are w-3 FA, glutamine, arginine, and nucleotides[130].

The role of the IN has been studied only in a few series in the surgical setting. In 2011 Klek *et al*[131] performed a prospective, randomized, double-blind clinical trial evaluating the impact of IN on surgical patients affected by PDAC or gastric cancer, finding differences in postoperative LOS (P = 0.006), infectious POC (P = 0.04), overall morbidity (P = 0.01), and mortality (P = 0.03). The group of Shirakawa *et al*[132] also found a lower rate of incisional wound infection in the IN group *vs* standard therapy (P = 0.012). Gade *et al*[133] performed a randomized controlled trial enrolling 35 surgical patients, with the aim to define the effect of 7 d of oral IN supplementation in PDAC patients. However, the author found no statistically significant improvements in the IN group. Silvestri *et al*[134] studied the impact of oral IN in non-malnourished PDAC patients undergoing pancreaticoduodenectomy and found a significative impact on LOS (P = 0.035) and infectious POC (P = 0.034). On the contrary, no differences in terms of mortality and overall morbidity rate were found. While IN in surgical PDAC patients reduces POC, LOS, and improves survival rate, no data were found in the recent literature on IN use during NAT.

NAT AS A WINDOW OF OPPORTUNITY FOR NUTRITIONAL PREHABILITATION

Patients undergoing multimodal oncological care are at increased risk of progressive nutritional worsening, with deleterious effects on surgical and oncological outcomes [135,136]. In this setting, current standard of care creates a minimum timeframe of four to 6 mo for NAT completion. This time period could thus represent a valuable opportunity for prehabilitation, to minimize the nutritional/metabolic impact of NAT, but published literature is scarce on this topic[34,137]. Indeed, most studies investigating ERAS programs/prehabilitation for PDAC excluded patients who had received preoperative NAT[82,84].

Recently, a prospective randomized control study by Akita *et al*[138] aimed at exploring whether a nutritional intervention consisting in 560 kcal/day of EPA-enriched nutritional supplements might impact on nutritional status in PDAC patients who received GEM-based neoadjuvant chemoradiotherapy. The authors reported that the psoas major muscle area ratio was significantly higher in the nutritional intervention group (median, 0.96 *vs* 0.89; P = 0.001), and that patients who consumed ≥ 50% of the EPA-enriched supplement presented significantly higher SKM ratios (P = 0.042). With regards to patients following NAT for locally advanced PDAC, a recent prospective analysis evaluated the impact of the preoperative IN supplementation on surgical outcomes in subjects undergoing irreversible electroporation surgery. Patients receiving IN presented a lower decrease in nutritional risk index (-12.6 *vs* -16.2; P = 0.03), serum albumin levels (-1.1 *vs* -1.5; P < 0.01), and experienced a statistically significant decrease in POC (P = 0.05) and LOS (10.7 *vs* 17.4; P = 0.01)[139].

Only a preliminary prospective study has reported the feasibility of a preoperative prehabilitation program, including nutritional counselling by a dietitian, of IN for 5 d before surgery and an exercise program, in patients with borderline resectable PDAC who received NAT[82].

In other areas of surgery, multimodal prehabilitation in patients receiving NAT has recently generated growing interest and seems to have a potential clinical benefit. Recently, a retrospective study of 22 patients, planning to undergo NAT for esophageal cancer, found a trend to a lower WL (3.0% *vs* 4.4%; P = 0.05) and a lower percentage of patients requiring postsurgical readmission rates at 30-d and 90-d (0.0% *vs* 18.2%; P = 0.14 and 18.2% *vs* 27.3%; P = 0.6, respectively) in those submitted to a structured prehabiliation program, which included tailored nutritional counselling, psychological support and supervised physical exercise[140].

CONCLUSION

Despite the lack of high-quality clinical evidence, many PDAC patients with resectable, borderline resectable, and locally advanced disease, nowadays undergo NAT as part of an integrated, multimodal, treatment program. Since NAT may provide an interesting window of opportunity to implement nutritional prehabilitation in PDAC patients and the limited available data on this issue suggest a reduction in POC, LOS and readmission rates, well-designed, controlled, randomized clinical trials are needed to establish new recommendations in this NAT setting.

ACKNOWLEDGEMENTS

The authors gratefully want to thank Mr. Philip Egger for his kindly revision of the English language and style.

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