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Review Article

# Immunonutrition and prehabilitation in pancreatic cancer surgery: A new concept in the era of ERAS® and neoadjuvant treatment

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ABSTRACT

Pancreatic cancer (PC) is an aggressive disease, with a growing incidence, and a poor prognosis. Neoadjuvant treatments in PC are highly recommended in borderline resectable and recently in upfront resectable PC. PC is characterized by exocrine insufficiency and nutritional imbalance, leading to malnutrition/sarcopenia. The concept of malnutrition in PC is multifaceted, as the cancer-related alterations create an interplay with adverse effects of anticancer treatments. All these critical factors have a negative impact on the postoperative and oncological outcomes. A series of actions and programs can be implemented to improve resectable and borderline resectable PC in terms of postoperative complications, oncological outcomes and patients' quality of life. A timely nutritional evaluation and the implementation of appropriate evidence-based nutritional interventions in onco-surgical patients should be considered of importance to improve preoperative physical fitness. Unfortunately, nutritional care and its optimization are often neglected in real-world clinical practice. Currently available studies and ERAS® guidelines mostly support the use of pre- or perioperative medical nutrition, including immunonutrition, in order to decrease the rate of postoperative infections and length of hospital stay. Further data also suggest that medical nutrition should be considered proactively in PC patients, to possibly prevent severe malnutrition and its consequences on disease and treatment outcomes. This narrative review summarizes the most recent data related to the role of prehabilitation, ERAS® program, medical nutrition, and the timing of intervention on clinical outcomes of upfront resectable and borderline PC, and their potential implementation within the timeframe of neoadjuvant treatments.



## 1. Introduction

Pancreatic cancer (PC) is an aggressive malignancy with 495,773 new cases and 466,003 deaths worldwide in 2020. It exhibits a 2.6%

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global incidence and causes the 4.7% of all cancer-related deaths [1,2]. From an analysis of data in 48 countries, an increase in incidence and mortality trends for PC emerged especially among women and populations aged 50 years or older, with two-thirds of patients being at least 65 years-old. As a result, PC is expected to become the second most common cause of cancer death after lung cancer by 2030 [3].

Non-metastatic PC is classified as upfront resectable, borderline resectable (BRPC), or locally advanced (LAPC) based on the extent of vascular involvement [4]. For patients with upfront resectable PC, surgery followed by adjuvant chemotherapy remains the treatment of choice. Pancreatoduodenectomy (PD) is recognized as one of the most challenging procedures in the field of GI surgery, with postoperative mortality rate ranging from 3% to 10%, but with a trend towards a decrease in high-volume institutions [5]. Postoperative morbidity after PD ranges from 40% to 60%. Postoperative complications include delayed gastric emptying (DGE), pancreatic fistula (affecting up to 30% of patients after PD), and surgical site infections, which may lead to increased hospital length of stay (LOS), metabolic needs [6] as well as poor long-term survival rates [7–10].

Since upfront surgical resection of PC is feasible in less than 20% of patients at diagnosis, neoadjuvant treatment (NAT) plays a main role in the treatment of PC [11]. NAT, consisting of multi-drug regimen chemotherapy with a minimum duration of 4–6 months for completion, is the current standard of care to downstage non-metastatic BRPC and increase the resectability rate, reducing positive resection margins after surgery, postoperative pancreatic fistula rate and occurrence of local failures [12]. A recent meta-analysis of seven randomized clinical trials (RCT) revealed that NAT improve overall survival (OS) compared with upfront surgery in patients with BRPC [4]. Of interest, consistently with the National Comprehensive Cancer Network (NCCN) guidelines for PC [13], in the last decade an increasing number of cases of upfront resectable PC has been scheduled to NAT as well [4,11]. Among others, a phase III trial including patients with BRPC or resectable PC showed that NAT followed by surgery significantly improved OS *vs.* upfront surgery, with a consistent effect across patients' subgroups [14]. However, a strategy based on NAT administration also to patients with upfront resectable PC implies both potential benefits and disadvantages, as discussed elsewhere [4], and more evidence is required on whether NAT improves OS for these patients [11]. Potential disadvantages of NAT implementation in patients with BRPC or upfront resectable PC include adverse effects leading to reduced food intake with a worsening of malnutrition and sarcopenia [15], but also to potential disease progression, hampering the surgical option.

Cancer-related alterations, such as protein catabolism, malabsorption, maldigestion, diarrhea, and vomiting, together with reactions of patients to side effects of anticancer treatments, can frequently cause malnutrition. Cancer-related malnutrition makes patients more vulnerable to surgical injury and is a negative prognostic factor, affecting patients' functional status, tolerance to anticancer therapies, quality of life (QoL) and survival [16,17]. It has been hypothesized that 20–30% of cancer patients may die due to the consequences of malnutrition, rather than of cancer itself [18]. Several studies estimated a prevalence of malnutrition up to 70% in upper GI cancers, and especially in PC [19–21]. Severe malnutrition is also a well-recognized predisposing factor affecting morbidity and mortality of patients undergoing pancreatic resection [12,22]. Pancreatic exocrine insufficiency (PEI) leads to maldigestion, malabsorption, and predisposes to secondary malnutrition. Drugs targeting the PC, including NAT, may contribute to malnutrition as well.

Recently, the concept of sarcopenic obesity has emerged, characterized by the highest ranges of fat mass (body mass index [BMI] >30 kg/m$^2$) and the lowest ranges of muscularity, making the concept of PC malnutrition even more multifaceted and complex [15]. BMI changes and relative weight loss over time are routinely used for preoperative nutritional risk evaluation. However, BMI changes and weight loss are not capable of providing reliable information on several anthropometric features, such as total fat volume and visceral fat volume, known to be affected by pancreatic disease [23]. Preoperative sarcopenia, perioperative interstitial fluid accumulation and sarcopenic obesity have been broadly associated with an increased risk of complications and failure to rescue in patients undergoing pancreatic resections [24–27]. Moreover, malnutrition and sarcopenia in PC patients are associated with an amplification of chemotherapy-induced toxicities, with consequent reduction of adherence to anticancer treatment, prolonged hospital LOS, worsening of QoL and lower survival rates [24–36].

## 2. Aim of the study

Currently available literature and the evidence-based, multidisciplinary, globally implemented Enhanced Recovery After Surgery (ERAS®) protocol mostly support the use of pre- or perioperative medical nutrition protocols, including immunonutrition (IMN), in order to decrease the rate of the postoperative infections and the length of hospital stay. In addition, pre-admission interventions included in prehabilitation programs are increasingly recommended and implemented. This narrative review summarizes the most recent data exploring the impact of prehabilitation, ERAS® program and medical nutrition, including IMN, on clinical outcomes of upfront resectable and BRPC PC, and their potential implementation within the timeframe of NAT.

## 3. Methods

Literature was reviewed by searching PubMed for studies published between January 1st, 1999 and May 27, 2022. The search strategy included combinations of the following terms: pancreatic cancer, nutrition, oral nutritional supplements, malnutrition, cachexia, sarcopenia, survival, nutrients, immunonutrition, prehabilitation, neoadjuvant treatment. Key words were linked using the "OR" or "AND" Boolean functions. Guidelines, clinical trials and observational studies written in English were selected.

## 4. Implementation of neoadjuvant treatments and their effect on body composition and outcomes

NAT implementation in patients with BRPC or upfront resectable PC can cause several adverse effects leading to reduced food intake and to worsening of malnutrition and sarcopenia [15]. This effect can negatively impact the NAT itself, in terms of treatment completion, outcomes and access to subsequent surgery [28]. In this setting, a retrospective analysis of a cohort of 73 patients with PC scheduled for pancreatic resection and including a subset of 24 patients receiving NAT, revealed that the Nutritional Risk Screening (NRS)-2002 was significantly higher in patients who received NAT ($p = 0.026$) *vs.* the upfront resection group. Moreover, loss of appetite ($p = 0.003$) and dyspepsia ($p < 0.0001$) were more frequent in patients receiving NAT. Particularly, a significant difference in nutritional risk was found by chemotherapy regimen, with a higher NRS-2002 detected in the oxaliplatin, irinotecan, fluorouracil and leucovorin (FOLFIRINOX) group *vs.* the gemcitabine/nab-paclitaxel group ($p = 0.035$) [29]. Of note, this study also highlighted the limits of BMI as a tool for nutritional risk detection and prognosis in PC patients, in favor of weight loss.

Another study included 89 patients with pancreatic ductal

adenocarcinoma (PDAC) treated for 12 weeks with a NAT regimen based on gemcitabine and cisplatin, followed by radiotherapy with concurrent gemcitabine [30]. CT scans analyzed the changes occurring in body composition after the administration of the preoperative therapy *vs.* baseline and their association with relevant oncologic outcomes. The study revealed that underlying sarcopenia was common at baseline (52% of patients) and that NAT routinely induced weight loss, as well as further depletion of skeletal muscle and visceral and subcutaneous adipose tissue. Such changes did not preclude the performance of potentially curative resection, and the degree of skeletal muscle loss correlated with disease-free survival, while the visceral adipose loss was associated with overall and progression-free survival. Underlying sarcopenia was a common finding in PC patients at baseline (63%) also in a study by Cloyd et al. [31], showing that a significant loss in key anthropometric parameters at CT scans occurred over the first year following PD, rather than during the 5/6 month NAT course. Of interest, a skeletal muscle gain between the postoperative period and one-year follow-up was associated with improved OS [31]. Similarly, the CT scans of 78 patients with BRPC detected a 50% rate of sarcopenia at diagnosis, independently from BMI, and a significant decrease of skeletal muscle and adipose tissue occurred during NAT [32].

A cohort study based on the retrospective analysis of CT scans and including 193 patients with BRPC or LAPC undergoing surgical exploration after NAT, revealed a significant loss of adipose tissue during NAT, without muscle wasting. Of interest, patients who underwent resection experienced a 5.9% skeletal muscle area increase during NAT, while the patients who did not undergo resection experienced a 1.7% decrease of skeletal mass area ($p < 0.001$). These results indicate an unexpected positive change in body composition occurring during NAT that could positively affect clinical outcomes [33] and could be among other advantages in favor of an implementation of NAT in upfront resectable PC patients.

## 5. Medical nutrition

Nutritional status of PC patients should be assessed and discussed timely by a multidisciplinary team (MDT), together with the onco-surgical pathway. Nutritionists should be included in the core MDT especially in case of NAT as well as in case of upfront surgery. Indeed, the risk of malnutrition, sarcopenia, cachexia and any weight loss and/or further deterioration should be timely evaluated and prevented. Oral nutritional supplements (ONS) belong to the Foods for special medical purposes category (currently under the Regulation N. 2016/128 of the European Commission). They are commercially available medical nutrition products that provide macronutrients and micronutrients required when normal food is insufficient to maintain or increase energy and nutrient intake [34]. ONS are considered a cornerstone in the treatment plan of malnutrition in cancer patients [35]. An escalation to a medical nutritional therapy by oral, enteral or parenteral route should be considered in cancer patients in case of: a) food intake <50% of the requirements for more than 1–2 weeks; b) the tumor itself impairs oral intake and food progression through the GI tract; c) inadequate food intake anticipated for >10 days due to surgery or anticancer therapy; d) anticipation that patient will not be able to eat and/or absorb the adequate amount of nutrients for a long period time, due to anticancer treatments [36].

Different nutritional interventions for PC patients affected by cachexia are currently available (e.g., ONS, ketogenic diet, L-carnithine supplementation, amino acids, fish oil, etc.) and have been well-reviewed elsewhere [37]. The route of administration of nutritional support depends on each patients' characteristics. If applicable, enteral nutrition should be the first choice, because of greater physiological and economic benefits. In addition, enteral is safer than parenteral nutrition and allows for faster recovery after surgery, as shown by the reduced time to recovery of gastrointestinal function [38]. A protocol based on Early Combined Parenteral and Enteral Nutrition (ECPEN) after PD has been tested as well, with encouraging results in terms of safety and achievement of caloric requirements during the postoperative period [39].

## 6. Immunonutrition: insights from the clinical research

Over the last decade, standard ONS formulas have been modified by the addition of immunonutrients (namely glutamine, arginine, omega-3-fatty acids and ribonucleotides), together with pre- and probiotics, with the aim of inducing the host systemic immune response through the stimulation of the gut-associated lymphoid tissue, improving the control of inflammatory response in cancer patients submitted to major surgery or chemoradiotherapy [40–42]. The mechanisms mediating the effect of IMN on the modulation of inflammatory response have yet to be fully identified. Among others, immunonutrients, and in particular arginine, promote T cell activities, reduce IL-1, IL-6 and TNF-$\alpha$ production and support tissue regeneration and metabolic functions. Furthermore, omega-3 fatty acids are useful to modulate the inflammatory status trough the reduction of thromboxane (TX-A2), prostacyclin, leukotrienes and prostaglandin G2. Finally, RNA supplementation plays a major role in wound healing through increased hydroxyproline synthesis [7,43,44].

Like standard nutritional support, IMN can be administered by mouth, via the enteral and parenteral route [38]. Administration of formulas enriched with immunonutrients in malnourished patients undergoing cancer surgery has been covered by the most recent ESPEN guidelines, reporting a grade of recommendation B/0 for their perioperative or at least postoperative administration in the setting of major cancer surgery [45]. The timing of IMN supplementation plays a key role in PC patients scheduled for PD, as it aims to not only administer calories to patients, but also to improve cellular and humoral immunity, modulate inflammation, and provide metabolic support, with potentially relevant effects on clinical outcomes. Concerning the preoperative administration of IMN to patients undergoing PD, in a small randomized trial, oral supplementation with arginine, omega-3 fatty acids, and RNA for five days before the surgical procedure in addition to a 50% amount reduction of regular food, led to a lower rate and severity of infectious complications *vs.* control patients [44]. In addition, IMN led to decreased levels of plasma prostaglandin E2 (PGE2), increased serum eicosapentaenoic acid and eicosapentaenoic acid/arachidonic acid ratios and increased T-cell differentiation, with an overall protective effect against postoperative complications. These positive outcomes were confirmed by a study enrolling 54 well-nourished patients undergoing PD [7].

The results described above were confirmed by a first systematic review and meta-analysis of four RCT where IMN was administered with different timings before and/or after PD and compared to standard enteral nutrition [38]. Preoperative enteral IMN was superior to enteral nutrition in reduction of postoperative infectious complications rate (RR 0.58, 95% CI 0.37–0.92; $p = 0.02$). These results were partially consistent with findings from another more recent systematic review including nine selected RCTs comparing specific nutrition therapies in patients submitted to PD [5]. Among the different protocols assessed by authors, preoperative IMN plus postoperative IMN provided the best clinical benefits in terms of decreased infectious complications and postoperative pancreatic fistula. Similar results were obtained by Furukawa et al. in patients submitted to PD for PC with either high or low skeletal muscle mass

index [46]. A systematic review and meta-analysis of RCT enrolling patients with resectable PC undergoing PD and irreversible electroporation, assessed the effect of IMN on immune system, postoperative complications and hospital LOS. The trials included in the meta-analysis compared the pre-, peri- or postoperative oral supplementation of IMN with a standard diet [47]. Despite the lack of significant differences in $CD4^+$ and $CD8^+$ levels at postoperative days 3 and 7 between the groups, IMN significantly decreased the rate of infectious complications and the hospital LOS by modulating the immune system, especially in the preoperative group.

The studies summarized above mostly support the positive role of preoperative IMN in patients submitted to PD. The rationale for a preoperative administration of IMN relies on clinical data suggesting that the benefit of an immune-enhancing diet may take up to 7 days to manifest [48]. Moreover, the administration of preoperative IMN could provide effective concentrations of immunonutrients before the surgical stress, with adequate tissue and plasma concentrations during the operation and early after the operation, in order to counterbalance properly the immunosuppression at its peak [49]. Consistently with this rationale, no significant additional effect of perioperative *vs*. preoperative IMN on postoperative immunity and infectious complications in patients undergoing PD was found in a prospective RCT [50]. Of note, the administration of single immunonutrients to PC patients (e.g. glutamine or eicosapentaenoic acid) showed no significant beneficial effect in PC patients [51,52], suggesting a synergic/complementary effect of multiple immunonutrients in preoperative or perioperative setting of PC.

## 7. Supportive pancreatic enzyme replacement therapy

As mentioned above, patients with PC may commonly experience pancreatic exocrine insufficiency (PEI) either before diagnosis, during non-surgical treatment and following surgery. PEI can lead to maldigestion, malabsorption, and secondary malnutrition. Together with nutritional support, pancreatic enzyme replacement therapy (PERT) for PEI is essential to ensure optimal nutritional status in PC patients who will receive surgery, NAT, adjuvant or palliative treatment [53,54]. Surprisingly, only very few RCTs have been carried out so far for PERT in the setting of resectable PC or BRPC, sometimes with inconsistent outcomes [55–57]. Some countries issued specific guidelines for PERT in PC, while others took a pragmatic approach [53,54,58].

The awareness about PEI rates in PC patients and the importance of its treatment with PERT should be increased, with the aid of novel RCTs aimed at providing clinical data to support the use of this therapy. According to an expert opinion recently published by Roeyen et al. [54], most patients undergoing PD will need PERT, and also in BRPC patients, PERT should be initiated based on clinical symptoms in order to have patients as fit as possible to receive NAT and surgery.

## 8. The perioperative management – the ERAS® protocol

Efforts to preserve physical fitness (muscle and adipose tissue) in PC patients might represent a critical strategy in the preoperative period. Such efforts might include dietary and physical prehabilitation programs, and the concurrent administration of ONS and drugs targeting inflammation and cachexia [30].

ERAS® is an evidence-based, multidisciplinary, globally implemented protocol aimed at reducing the surgical stress and improving the patients' recovery and QoL after major surgery. Interventions offered in the ERAS® protocol act synergistically and include patient information and education, preoperative carbohydrate loading until 2 h before surgery, minimally invasive surgery, optimal pain treatment, early feeding, and postoperative mobilization [59,60]. The ERAS® protocol has been validated in different surgical settings, including PD, whose first guidelines and recommendations were published in 2012 [61]. A meta-analysis supported the positive impact of ERAS® pathway on postoperative recovery after PD, revealing significantly lower rates of DGE, abdominal infections, postoperative complications, and shorter hospital LOS in the ERAS® group of patients *vs.* the control group managed with the traditional perioperative protocol [62]. A more recent meta-analysis, including a total of 20 studies with 3613 patients submitted to PD, partially confirmed previous results: the overall postoperative complication rate (OR = 0.62, 95% CI: 0.53–0.74, P < 0.00001), minor complication rate (Clavien-Dindo I-II) (OR = 0.70, 95% CI: 0.58–0.86, P = 0.0005), the incidence of DGE (OR = 0.51, 95% CI: 0.42–0.63, P < 0.00001) and hospital LOS (weighted mean difference = −4.27, 95% CI: 4.81~-3.73, P < 0.00001) were significantly lower in the ERAS® group *vs.* the control group [63].

With specific reference to the nutritional aspects of ERAS® protocol for PD, the 2012 guidelines did not warrant the routine use of preoperative artificial nutrition but recommended the optimization of malnourished patients with oral supplements or enteral nutrition preoperatively (Evidence level: very low; Recommendation grade: weak) [61]. Updated ERAS® recommendations for PD based on the best available evidence and on expert consensus have been published recently [64] and reported the highest level of evidence for five items, including preoperative nutritional interventions for patients with severe weight loss (>15% or BMI <18.5 $kg/m^2$ secondary to their disease). A recent position paper of the International Study Group of Pancreatic Surgery (ISGPS) highlighted the need for considering preoperative nutritional support in order to decrease postoperative complications in patients meeting one out of the four following criteria: weight loss >15% within 6 months, BMI <18.5 $kg/m^2$, subjective global assessment grade C or nutritional risk score >5, and serum albumin level <30 g/L (without any evidence of renal or hepatic dysfunction) [22]. Finally, according to ERAS® recommendations, patients should be allowed a normal diet after PD, without restrictions according to tolerance, while artificial nutrition, preferably through the enteral route, should be considered as an individual approach according to the nutritional status assessment [64]. DGE, one of the most common complications after PD, delays oral food intake, with a consequent reduction of patient's QoL and prolongation of hospitalization. Further efforts and strategies should be developed to increase the early tolerance to oral nutrition and improve the gastrointestinal function in patients with PC submitted to PD [23,65].

With particular reference to IMN in ERAS® protocol, the 2012 guidelines suggested to consider IMN for 5–7 days perioperatively in the absence of complications (Evidence level: moderate; Recommendation grade: weak) [61]. Perioperative IMN has also been suggested until restoration of an oral diet providing at least 60% of nutritional requirements [60]. However, the perioperative use of IMN in PC patients has not been recommended by the updated ERAS® guidelines for PD, due to scarcity and heterogeneity of available studies [64] suggesting the necessity of additional trials.

The compliance to the ERAS® protocol in PC is still low [66,67]. Different strategies and solutions have been proposed to increase the global compliance to ERAS® program, including a higher level of engagement of MDTs, systematic training programs and the implementation of prehabilitation programs (described below). The implementation of ERAS® program in the setting of PD should be able, at least in principle, to increase the overall fitness of PC patients, thus improving their surgical candidacy through the greater ability to withstand the postoperative stress response [67].

## 9. Implementation of prehabilitation

ERAS® protocols have largely focused on optimization of the surgical and recovery pathways in the hospital setting, with little focus on preoperative optimal management of patients, particularly in a NAT setting. The pre-surgical as well as the NAT period could actually represent a window of opportunity to boost and optimize patient's health, improve compliance to anticancer treatments and the nutritional status, providing a compensatory "buffer" for the postoperative reduction of physiological reserve [68]. The term "prehabilitation" defines a program that includes a series of pre-admission interventions to be initiated 3–6 weeks before surgery, aiming at improving body composition and physical performance, reducing the surgery-related morbidity and facilitating patient's recovery [64]. Cancer prehabilitation has been also defined as "a process of care that occurs between the diagnosis and the beginning of acute treatment, providing targeted interventions that improve a patient's health to reduce the incidence and the severity of current and future impairments" [69]. The prehabilitation program is frequently multimodal, including nutritional supplementation, physical exercise, and anxiety reduction strategies that should be considered in case of proven functional and nutritional deficits.

The concept of prehabilitation is now evolving as an integral part of the ERAS® protocol described above and is strongly recommended by the most recent ERAS® guidelines for perioperative care for PD, with a moderate level of evidence [64]. Some concerns preventing a global recommendation of prehabilitation prior to PC surgery are: 1) weak evidence of a direct association between prehabilitation and improved perioperative outcomes [70] and 2) the risk of a potential delay of surgery [67].

A prehabilitation program tested in a small, randomized trial involving 40 pancreatic surgical patients (n = 18 treated with prehabilitation and n = 22 treated with the standard care), was unable to show a reduction of postoperative complications following PD, with the exception of a significantly lower DGE [71]. However, according to a recent systematic review including six studies and 193 PC patients submitted to NAT or to upfront resection, prehabilitation was associated not only to a lower DGE, but also to a shorter hospital LOS, in addition to an improvement in muscle mass or function [72]. The introduction of prehabilitation prevented nutritional deterioration, improved physical fitness before surgery, and shortened the postoperative hospital stay (median, 23 *vs*. 30 days; p = 0.045) for 76 patients undergoing hepato-pancreato-biliary surgeries for malignancy *vs*. a control no-prehabilitation group [73]. Currently, there are no specific evidence-based recommendations for nutritional therapy in a prehabilitation program; however, growing evidence is supporting the positive effect of nutritional intervention in the setting of a prehabilitation program on reduction of weight loss and on increase of patients' "fit for ERAS®" [40].

## 10. Is it time to consider changes in management of preoperative nutritional intervention?

Prevention of malnutrition or its adequate management through a timely nutritional therapy is increasingly considered an essential key point of cancer therapeutic pathways. Patients with PC represent an oncologic population with high nutritional risk and a higher prevalence of malnutrition. They manifest early debilitating symptoms with nutritional impact, which in turn lead to deterioration of the functional status [74]. This requires a prompt intervention and a proactive rather than reactive management of malnutrition. However, despite the increased awareness among clinicians (particularly among surgeons), recent studies investigating the real-life situation regarding malnutrition and dietetic consultation confirmed a high prevalence of cachexia in PC patients [75–77]. Of note, Trestini et al. revealed that nutritional status and the OS of PC patients improved upon an early nutritional counselling, analyzing the data from 109 patients affected by PDAC and undergoing chemotherapy [78]. Of interest, the analysis of data from 454 consecutive patients with BRPC or LAPC (enrolled before decision of surgery) showed that continuous weight loss during the third-month induction treatment (chemotherapy or chemo-radiation), more than weight loss at diagnosis, significantly precluded tumor resection and was an independent factor of shorter OS in unresected patients [79]. These data suggest that a prompt and appropriate nutritional support is mandatory since the early phases of the disease, as more PC patients could benefit from their induction treatment and be selected for surgery at re-staging.

In this setting, Rovesti et al. [15] suggested the introduction of a multidisciplinary Nutritional Oncology Board in routine daily clinical practice, aimed at assessing an early systematic screening of PC patients and at implementing nutritional support from the time of disease diagnosis onward. A prompt and appropriate nutritional support and/or monitoring of all patients with PDAC through a board of professionals with specific skills and training in clinical nutrition within the oncological setting has been proposed also elsewhere [80], with the application of highly validated tools for nutritional screening [81], the analysis of a wide range of parameters not limited to weight loss and BMI and the implementation of PERT to counteract PEI.

Another potential strategy to reduce the nutritional derangements in PC patients is to consider the time window used for NAT as an opportunity to perform a longer patients' prehabilitation, in order to limit the impact of NAT on nutritional status/metabolism and improve the surgical outcomes [28,40,68]. Data about this potential strategy in PC patients are still scarce, but a recent pilot prehabilitation program that included intervention in several clinical domains (the STRENGTH program), demonstrated the feasibility and the effectiveness of a structured program for patients receiving NAT for esophageal adenocarcinoma [82].

## 11. Conclusions

Malnutrition and derangement of body composition before NAT and surgery have a detrimental impact on outcomes and survival of PC patients scheduled to an onco-surgical approach. Unfortunately, nutritional care and its optimization appear still neglected in this setting. Medical nutrition protocols should be considered not only in the pre- and peri-operative period, and in reaction to malnutrition, but proactively at time of diagnosis, in order to prevent severe malnutrition and its consequences on disease and treatment outcomes. Surgeons and clinicians, working in the setting of a MDT, should change their perspective from a rehabilitation-to a prehabilitation-based approach. Currently available studies mostly support the use of preoperative oral IMN in order to decrease the risk of postoperative infectious complication and the hospital LOS. However, there is an urgent need of additional RCTs to establish the roles and indications for the administration of IMN in PC patients undergoing PD. Moreover, well-sized and well-designed prospective studies should be performed to better assess the effectiveness of prehabilitation programs starting at PC diagnosis and not when NAT, as well as surgery, has already been scheduled.

## CRediT authorship contribution statement

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Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Visualization, Writing – original draft, Writing – review & editing. **Paolo Pedrazzoli:** Investigation, Methodology, Project administration, Resources, Supervision, Validation, Writing – original draft, Writing – review & editing. **Oronzo Brunetti:** Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Visualization, Writing – original draft, Writing – review & editing. **Alessandro Rizzo:** Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Validation, Visualization, Writing – review & editing. **Marta Sandini:** Data curation, Formal analysis, Investigation, Methodology, Resources, Software, Visualization, Writing – original draft, Writing – review & editing. **Salvatore Paiella:** Data curation, Formal analysis, Investigation, Methodology, Validation, Writing – original draft, Writing – review & editing. **Nicolò Pecorelli:** Data curation, Formal analysis, Methodology, Project administration, Resources, Software, Visualization, Writing – original draft, Writing – review & editing. **Luigi Pugliese:** Formal analysis, Investigation, Resources, Validation, Visualization, Writing – review & editing. **Andrea Pietrabissa:** Investigation, Project administration, Supervision, Validation, Visualization, Writing – review & editing. **Alessandro Zerbi:** Investigation, Project administration, Supervision, Validation, Visualization, Writing – review & editing. **Roberto Salvia:** Investigation, Methodology, Project administration, Supervision, Validation, Visualization, Writing – review & editing. **Ugo Boggi:** Investigation, Project administration, Supervision, Validation, Visualization, Writing – review & editing. **Amanda Casirati:** Formal analysis, Investigation, Methodology, Resources, Visualization, Writing – original draft, Writing – review & editing. **Massimo Falconi:** Investigation, Project administration, Supervision, Validation, Visualization, Writing – review & editing. **Riccardo Caccialanza:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Supervision, Visualization, Writing – original draft, Writing – review & editing.

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