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Original research

Preoperative oral immunonutrition versus standard preoperative oral diet in well nourished patients undergoing pancreaticoduodenectomy

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HIGHLIGHTS

- Immunonutrition in surgical patients.
- Preoperative oral immunonutrition and pancreatic surgery.
- Perioperative Nutrition in well nourished patients undergoing pancreatic surgery.
- Postoperative complications after pancreatic surgery.

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ABSTRACT

Background: Pancreaticoduodenectomy is still associated to high morbility, especially due to pancreatic surgery related and infectious complications: many risk factors have already been advocated. Aim of this study is to evaluate the role of preoperative oral immunonutrition in well nourished patients scheduled for pancreaticoduodenectomy.

Methods: From February 2014 to June 2015, 54 well nourished patients undergoing pancreaticoduodenectomy were enrolled for 5 days preoperative oral immunonutrition. A series of consecutive patients submitted to the same intervention in the same department, with preoperative standard oral diet, was matched 1:1. For analysis demographic, pathological and surgical variables were considered. Mortality rate, overall postoperative morbility, pancreatic fistula, post pancreatectomy haemorrhage, delayed gastric emptying, infectious complications and length of hospital stay were described for each groups. Chi squared test, Fisher's Exact test and Student's T test were used for comparison. Differences were considered statistically significant at $p < 0.05$. Statistics was performed using a freeware Microsoft Excel ® based program and SPSS v 10.00.

Results: No statistical differences in term of mortality (2.1% in each groups) and overall morbility rate (41.6% vs 47.9%) occurred between the groups as well as for pancreatic surgery related complications. Conversely, statistical differences were found for infectious complications (22.9% vs 43.7%, $p = 0.034$) and length of hospital stay (18.3 ± 6.8 days vs 21.7 ± 8.3, $p = 0.035$) in immunonutrition group.

Conclusion: Preoperative oral immunonutrition is effective for well nourished patients scheduled for pancreaticoduodenectomy; it helps to reduce the risk of postoperative infectious complications and length of hospital stays.

1. Introduction

Improvements in surgical technique, perioperative management and experience of high volume centers lead to a dramatical reduction of mortality rate after pancreaticoduodenectomy (PD), currently ranging from 3% to 5% [1]. However, the postoperative

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morbidity still elevated remains between 40% and 60% [2–5]. Postoperative complications include pancreatic fistula (POPF), delayed gastric emptying (DGE) and infectious complications (wound infections, Surgical Site Infections – SSI, pneumonia, urinary tract infections) among others [1,6]. POPF and DGE affect from 2% to 30% of patients submitted to PD [7,8]; their occurrence leads to an increase of other postoperative complications, such as infectious complications, with delayed recovery and metabolic alterations.

Reduction of the host response and of the immunity, which are facilitated by low caloric intake and by intestinal bacterial translocation, characterize patients undergoing PD; alteration of postoperative intestinal motility and loss of mucosal barrier function are certainly contributing factors [9,10]. This impaired immunological activity leads to a greater risk of infection and a prolonged hospital stay with increased health care costs.

Preoperative careful evaluation of patients is crucial to set a planned strategy to reduce morbidity [11,12]. Among strategies proposed to reduce complications, artificial enteral diets supplemented with arginine, omega-3 fatty and ribonucleics acids have been suggested to improve immune response, inflammatory pathway and wound healing trough the provision of key nutrients involved in T – lymphocyte activity and other immune functions [13–17]. As a matter of fact Immune-nutrition (IN), and especially arginine, promotes T cell activities, reduces production of IL 1, IL 6 and alpha-TNF and helps tissue regeneration. Furthermore, omega 3 fatty acids are useful to modulate inflammatory status trough reduction of prostacyclin and thromboxane (TX-A2), reduction of prostaglandin G2 and leukotrienes and consequent modulation of cell mediated immunity [18–21]. Finally, RNA supplementation plays a key role for proliferation of cells involved in wound healing [22].

In patients undergoing gastrointestinal cancer surgery, positive effects of perioperative IN in terms of reduction of postoperative local (SSI) and general infectious complications as well as length of hospital stays (LOS) have been postulated [15,23,24]. Some authors have recently indicated that preoperative exclusive IN support might be as effective as the perioperative one and might be useful to optimize patient without surgical stress [15,25]. To the best of our knowledge, only few reports of oral preoperative IN in patients scheduled for pancreatic surgery have been proposed [18,25,26] and most of which assess the benefits in malnourished patients [27]. Actually it remains poorly codified the role of immunonutrition in well-nourished patients proposed to undergo major pancreatic surgery [25,28].

The aim of this study was to determine whether preoperative IN alone is efficacious in improving outcomes in patients undergoing pancreatic surgery in well nourished patients. To determine this, we report on overall postoperative and infectious complications after PD as well as on LOS.

2. Material and methods

From February 2014 to June 2015, 54 well nourished patients were scheduled for PD at 4th Division of General Surgery of AOU City of Health and Science, Turin – Italy. Indications to surgery were for pancreatic primary or metastatic malignancy, ampullary or biliary carcinoma and chronic pancreatitis. Patients submitted to neo-adiuvant chemotherapy were excluded from the protocol.

During preoperative period and after the signature of an informed consent, patients were included in a prospective study of preoperative immunonutrients supplemental liquid diet (Oral Impact®, Nestlè Italia) for at least 5 days before pancreatic surgery, in addition to oral standard diet at a dose of 750 ml/day (3 packs). All patients kept a written record of the daily amount of supplemented diet consumed. Nutritional value of this dietary supplement is summarized in Table 1. Exclusion criteria are listed in Table 2. Demographic and surgical data were collected for each patient in a prospective database.

This series of patients submitted to preoperative immunonutrition (IN) was compared with a homogenous cohort of consecutive patients well nourished submitted to PD without preoperative IN and with a standard oral preoperative diet at 4th Division of General Surgery of AOU City of Health and Science, Turin – Italy from October 2012 to January 2014. Data of non IN patients were retrospectively reviewed from a prospectively maintained database. Exclusion criteria were the same as for IN group, listed in Table 2.

Patients were matched 1:1 for age, gender, ASA score, comorbidities, preoperative biliary drainage (endoscopic or percutaneous trans-hepatic drainage), performance status, hemoglobin (g/L), BMI (k/m2), degree of weight loss (with respect to usual body weight in the previous 6 months), mean albumin level (g/dl), plasma levels of total proteins (g/L), pancreatic texture, Wirsung's diameter and type of pancreatic anastomosis.

The following clinical variables were noted for each patients: age, gender, ASA score, comorbidities, preoperative biliary drainage (endoscopic or percutaneous transhepatic drainage), performance status, hemoglobin (g/L), BMI (k/m2), degree of weight loss (with respect to usual body weight in the previous 6 months), mean albumin level (g/dl), plasma levels of total proteins (g/L), pancreatic texture (soft or hard), Wirsung's diameter, histology, type of pancreatic anastomosis, operative time, overall postoperative morbidity, need for a second laparotomy, mortality, pancreatic fistula (POPF), post pancreatectomy haemorrhage (PPH), delayed gastric emptying (DGE), infectious complications and hospital length of stay.

2.1. Surgical technique

All PD considered were performed by the same team of high experienced pancreatic surgeons. All patients underwent standard Whipple procedure with regional lymphadenectomy and subtotal stomach preserving gastrectomy In each case a pancreato-enteric reconstruction was done: pancreato-jejunal anastomosis or pancreato-gastro anastomosis, depending on intraoperative local conditions and features of pancreatic parenchyma. Pancreato-jejunal anastomosis was typically done as an end to side with a double layer of interrupted sutures of polydioxanone 5/0 (PDS II®,

Table 1
IN Composition.

Oral impact® composition	Amount
Proteins	7.6 g
L-arginine	1.8 g
RNA[b]	0.2 g
Fats (total)	3.9 g
Saturated fatty acids	1.8 g
MCT[a]	1.12 g
Monounsaturated	0.73 g
Polyunsaturated	1.3 g
Linoleic Acid	0.6 g
Ω-3 fatty acids	0.6 g
Carbohydrates	18.9 g
Maltodestrines	7.6 g
Sucrose	10.5 g
Lactose	<0.02 g
Soluber Fibers	1.4 g
Energy	141 g
Water	77 g

[a] MCT, Medium Chain Triglycerides.
[b] RNA, Ribo-Nucleics Acid.

Table 2
Exclusion criteria.

Exclusion criteria
Pregnancy
Kidney failure
Immunosuppression (drugs induced/HIV)
Liver Disease with portal ipertension or Cirrhosis > Child-Pugh A
Inability to feed
Neo-adiuvant chemotherapy
Weight loss ≥10% (with respect to usual body weight) in the past 6 months; BMI < 18 kg/m2
Serum albumin level < 3 g/L;
Karnofsky score < 60

Ethicon) stitches. Pancreato-gastro anastomosis was performed end to side, fashioned in the posterior wall of the stomach with a single layer of interrupted stitches.

Biliary reconstruction and digestive reconstruction were standardized; the first was always carried out by end to side interrupted polydioxanone 5/0 sutures, while gastrojejunostomy was always fashioned as an end to side, single layer with two continuous poliglycolic acid stitches (Vicryl®, Ethicon). Before abdominal wall closure, two open multichannel silicon drains were placed: one behind hepaticojejunostomy (right) and the second close to pancreatic anastomosis (left).

2.2. Perioperative management

From the 1st postoperative day (POD), all patients were treated with total parenteral nutrition (TPN). The caloric and nitrogenous requirements of each patient were calculated as follows: 25–30 kcal/kg/day and 0.2–0.3 g of Nitrogen per Kg/day. The emulsed infusion used were divided into three compartments contain, respectively, glucose (Maximum infusion rate 0.25 g/kg/h), amino acids (Maximum infusion rate 0.1 g/kg/h) and lipid emulsion solution (Maximum infusion rate 0.15 g/kg/h) (19–38 ml/kg body weight/day.). Oral diet was reintroduced progressively from the 5th POD and always in absence of suspected clinical relevant POPF (grade B or C). At first a liquid or creamy diet was given for a day; than it was switched to a solid ones with prevalent protein component (0.8–1 g of protein kg of body weight). TPN was continued as needed in patients with POPF. Finally, artificial nutrition was suspended when patient's oral intake was approximately 800 Kcal/day.

Fluid intake was calculated daily on the basis of input/output. Artificial nutrition and fluids were infused by a central venous line placed during PD.

All patients were treated with short term antibiotic prophylaxis, according to protocol. In case of preoperative cholangitis, intraoperative culture of the bile was done and postoperative antibiotic target treatment was performed accordingly.

Octreotide (Sandostatin®, Novartis Italia), which was started intraoperatively, was given in all patients for 5 days P.O. 100 mcg subcutaneously three times per day [29]; low molecular weight heparin prophylaxis was administered, according to protocol.

Amylase level in drainage fluids was routinely evaluated in the first and the third postoperative days. Drains were removed in the absence of evidence of POPF [30]. If POPF was suspected a CT scan was performed [31]; if radiological imaging confirmed the clinical suspicion of POPF, all necessary treatments (percutaneous drainage, fasting with total parenteral nutrition, antibiotic therapy, reintervention, etc.) were applied.

2.3. Definitions

Well nourished patients were included according to criteria listed in Table 2. Patients who satisfied at least one of the following criteria, weight loss ≥10% (with respect to usual body weight) in the past 6 months; BMI < 18 kg/m2, serum albumin level < 3 g/L and Karnofsky score < 60 were excluded from the protocol.

Postoperative mortality was defined as deaths occurring before hospital discharge or POD 90. Postoperative morbidity rate included all complications following surgery until hospital discharge and/or readmission.

Postoperative pancreatic fistula (POPF), post pancreatectomy haemorrhage (PPH) and delayed gastric emptying (DGE) were defined according to the International Study Group Pancreatic Surgery (ISGPS) [32–34].

Infectious complications were defined as presence of clinical symptoms associated with a bacteriologically positive culture. Pneumonia was defined by the presence of fever with a suggestive thoracic X-ray image improving under antibiotics [35]. Urinary tract infection was defined as suggestive symptoms associated with a positive urine culture. Wound infection was defined based on the evidence of pus in the wound with isolation of pathogenic agents in culture requiring wound opening [36]. Intra-abdominal abscess was defined as a collection treated by percutaneous drainage with positive culture [36]. In case of Surgical Site Infection, Center Disease Control (CDC) [37] criteria for diagnosis and definitions were used. Sepsis was defined as presence of typical clinical signs associated to positive culture.

2.4. Statistical analysis

Data are expressed as number (%) for categorical variables and median ± standard deviation for continuous variables.

Comparison between qualitative variables were evaluated by chi squared test or Fisher's Exact test as requested; Student's T test was used to compare quantitative ones. All test were two sided. Differences were considered statistically significant at $P < 0.05$. Statistical analysis was performed using a freeware Microsoft Excel ® based program and SPSS v 10.00.

3. Results

Among the 54 patients enrolled, 6 (11%) did not complete preoperative oral protocol and were excluded from analysis, according to previous studies published by Giger et al. which demonstrated a decrease in inflammatory responses, but failed to demonstrate a significant clinical benefit for short IN supplementation [26]. Complete data on compliance to treatment will be described further.

Characteristics of patients are detailed in Table 2. IN group patients were matched 1:1 with a group of well nourished patients previously submitted to DP in the same department by the same experienced pancreatic surgical team: there were no significant differences in terms of gender, age, comorbidities, ASA score, mean albumin level (g/dl), BMI, presence of biliary drainage and performance status between the two groups.

The majority of patients (88.5%) were submitted to PD for ampullary and periampullary primary or metastatic malignancy. As described in Table 3, no differences regarding surgical indications between the groups were found: as a matter of fact 43/48 patients (89.6%) underwent PD for primary or secondary malignancy in IN group as well as 42/48 (87.5%) in patients who didn't underwent immunonutrition.

All patients underwent an open PD. As mentioned before, all patients were submitted standard Whipple procedure with regional lymphadenectomy and subtotal stomach preserving gastrectomy. Type of pancreatic anastomosis and pancreatic remnant features are summarized with other surgical data in Table 4. No

Table 3
Descriptive data.

Variables	Oral impact®	No impact®	p value
Patients	48	48	
Gender			0.220
Men	26	20	
Women	22	28	
Medium age (years)	62.27 ± 11.45	63.90 ± 11.80	0.493
ASA[a] score 1 + 2	33	34	0.962
ASA 1	7	7	
ASA 2	26	27	
ASA 3	15	13	
ASA 4	0	1	
Patients with 1 comorbidity	31	30	0.999
Patients with 2 comorbidity	19	18	0.999
Hemoglobin (g/L)	13.3 ± 1.2	12.9 ± 0.9	0.660
Plasma levels of total proteins (g/L)	6.5 ± 0.4	6.2 ± 0.1	0.453
Serum albumin level (g/dl)	3.7 ± 0.5	3.8 ± 0.1	0.177
Mean BMI[b]	24.5 ± 3.5	24.7 ± 3.3	0.773
Degree of weight loss (%)[c]	4.2 ± 0.5	4.5 ± 0.7	0.267
Biliary drainage	17	16	0.999
PTBD[e]	5	5	
EBD[d]	12	11	
Karnofsky performance status scale			0.862
100	9	11	
90	35	34	
80	4	3	

[a] ASA, American Society of Anesthesiologist.
[b] BMI, Body Mass Index.
[c] Degree of weight loss (with respect to usual body weight in the previous 6 months).
[d] EBD, Endoscopic Biliary Drainage.
[e] PTBD, Percutaneous Bilary Drainage.

Table 4
Indication to Surgery.

Indication to surgery	Oral impact®	No impact®
Pancreatic carcinoma	28	27
Ampullary carcinoma	6	5
Biliary carcinoma	8	8
p NET[a]	3	4
Cystic lesions	1	1
Pancreatitis	1	1
Metastatic lesions	1	2

[a] p NET, pancreatic Neuro-Endocrine Tumor.

Table 5
Surgical Data.

Surgical data	Oral impact®	No impact®	p value
Classical Whipple/PPPD[a]	48/0	47/1	
Type of Pancreatic anastomosis	48	48	0.089
Pancreato-gastro anastomosis	41	33	
Pancreato-jejunal anastomosis	7	15	
Mean operative time (min)	315.0 ± 49.2	298.3 ± 38.5	0.063
Vascular resection (SMV/PV)[b]	1	1	
Soft pancreas			0.999
Yes	19	18	
No	29	30	
Wirsung diameter			0.414
< 3 mm (or not visible)	26	22	
> 3 mm	22	22	

[a] PPPD, Pylorus Preserving Pancreaticoduodenectomy.
[b] SMV/PV, Superior Mesenteric Vein/Portal Vein.

differences were identified between the two groups for each variable.

As previously mentioned, 6 patients failed to complete the treatment proposed and were excluded from analysis. Considering only patients which completed the protocol, 18.7% (9/48) reported adverse symptoms during assumption of Oral Impact: moreover, the protocol wasn't interrupted for more than 2 somministrations. In 3 cases abdominal distension was described, in 2 cases diarrhea and in 2 cases nausea; 1 patient had one episode of vomiting and 1 patient presented abdominal cramps. All these patients had a better tolerance when a more staggered administration was spread out during the day.

Postoperative mortality was 2.1% (1/48) for each groups. Overall postoperative complications rate in IN group was 41.6% (20/48) while in untreated patients was 47.9% (23/48); POPF, PPH and DGE rate according to ISGPS severity are described in Table 5 as well as postoperative mortality and overall complications rate. No differences were observed between the two groups in terms of pancreatic specific complications. The incidence of infectious complications in the group of patients that received IN was 22.9%, significantly lower than untreated patients (43.7%, P = 0.034). Length of stay was also significantly decreased with the use of IN at 18.3 ± 6.8 days vs 21.7 ± 8.3 days in control group (P = 0.035) Table 6.

4. Discussion

The prevalence of malnutrition in oncological surgery patients is high: it was found in 17–46% of patients in general surgery and in 50%–80% of gastrointestinal cancer patients [38,39]. The value of perioperative artificial nutrition in terms of reduction postoperative morbidity has already been demonstrated [15,24,40,41]. In this article we demonstrate that preoperative nutrition using IN significantly benefits well nourished patients undergoing open surgery for pancreatic cancer.

During the years artificial nutrition has progressively been modified by adding specific substrates (arginine, omega 3 fatty acids, RNA) in order to modulate immunometabolic response [42]. The mechanisms of benefit of these active ingredients are only partially understood but may include the restoration of arginine availability necessary to maintain metabolic functions. These include the production of endothelial nitric oxide, maintaining adequate vasodilation and tissue oxygenation, particularly at the level of wounds and anastomosis. Furthermore arginine is a necessary substrate for normal T lymphocyte function; consequently, adaptive T cell dysfunction due to lack of arginine,

Table 6
Outcomes.

Surgical outcomes	Oral impact®	No impact®	p value
POPF[c]	5 (10.4%)	8 (16.6%)	0.550
Grade A	2	4	
Grade B	2	2	
Grade C	1	2	
PPH[d]	3 (6.2%)	2 (4.2%)	0.999
DGE[a]	9 (18.7%)	10 (20.8%)	0.999
Grade A	7	8	
Grade B	2	2	
Overall Morbility (n.patients)	20 (41.6%)	23 (47.9%)	0.410
Infectious complications	11 (22.9%)	21 (43.7%)	0.034
SSI (Incisional area)	3	2	
SSI (Organ spaced)	4	9	
Pulmonary infection	2	6	
Urinary infection	2	3	
Sepsis	0	1	
Reintervention	5 (10.4%)	6 (12.5%)	0.999
Mortality	1 (2.1%)	1 (2.1%)	
LOS (days)[b]	18.3 ± 6.8	21.7 ± 8.3	0.035

[a] DGE, Delayed Gastric Emptying.
[b] LOS, Length Hospital Stay.
[c] POPF, Post Operative Pancreatic Fistula.
[d] PPH, Post Pancreatectomy Haemorrhage.

commonly seen in certain cancers and after surgical trauma can be prevented. Furthermore, interactions between arginine, omega 3 fatty acids and other nutrients may help modulate inflammatory responses.

It has already been shown that IN improves the outcomes in critically ill patients [43–45]. Particularly strong evidence of benefit is observed with its use peri-operatively leading to reduction of postoperative complications contributing to an enhanced recovery and decrease in hospital length of stay [13,46]. Enteral post-operative IN has already been proven to be efficacious, even if theoretically limited by difficulties in delivering adequate amounts of key nutrients in the immediate postoperative period, when surgery-induced immunosuppression is higher [47].

Preoperative IN supplementation has already been demonstrated to be safe and effective in gastrointestinal cancer surgery, providing reduction in postoperative complications (especially infections) and LOS [15,18,23,48]; several clinical trials provided positive results with an IN administered for at least 5 days before surgery [15,41]. However, there are few specific reports [18,25] of preoperative IN for patients undergoing pancreatic surgery, especially in well nourished patients, in whom the usefulness of this nutritional support had to be proven. This article demonstrates that indeed preoperative use of IN is beneficial for well nourished patients undergoing pancreatic surgery.

Despite the study limitations due to absence of randomization and number of patients, we planned to avoid selection bias. Only open PD consecutively performed by an experienced team of HPB surgeons were selected. To avoid bias and strengthen the quality of the study, the IN groups was compared with a cohort of consecutive patients submitted to the same intervention with the same technique by the same experienced surgeons. Distribution between the two groups was totally homogeneous in terms of demographic and preoperative clinical characteristics (age, gender, comorbidity, median age, ASA score, performance status, presence of biliary drainage, histology). Furthermore, there were no differences detected in preoperative nutritional status and of surgical variables (type of pancreatic anastomosis, mean operative time, vascular resection, pancreatic texture, Wirsung diameter). Thus we are confident to say that the design of the study allows for human unbiased determination of benefit coming from the use of IN Ref. [49].

Despite a high compliance to preoperative treatment (89% of patients completed the whole protocol), the present study failed to show reduction of pancreatic specific complications (POPF, PPH, DGE) in patients treated with preoperative IN; even though a positive trend was demonstrated, no significant statistical difference was reached for reduction of overall pancreatic related complications in patients receiving IN (41.6% vs 47.9%, P = NS).

Conversely, the IN group had a statistical significant reduction of postoperative infectious complications (22.9% vs 43.7%, $P = 0.034$) and reduction of LOS (18.3 ± 6.8 vs 21.7 ± 8.3 days, $P = 0.035$). These results are similar to those described by other authors [18,25,50,51]; Cerantola et al. published a meta-analysis of 21 clinical trial and more than 2700 patients analysed in which perioperative IN was demonstrated to be effective to reduce overall and infectious complication rate when used preoperatively [50]. Importantly, in this study, length of stay was only reduced if IN was administered both before and after surgery [50,51]. Similar results were presented by Marik et al. and by Bozzetti et al. in patients submitted to major abdominal surgery for cancer; in a multivariate model, they found that perioperative IN was a protective independent factor to decrease infectious complications [46,52].

Similar to previous studies [16,18,25], our results suggest the utility of preoperative IN. The rationale is to provide effective concentrations of immunonutrients before surgical stress. We delivered 5 days of preoperative IN as this has found to be efficacious in other studies. In fact, the use of IN for only 3 days as published by Giger et al., demonstrated a decrease in inflammatory responses, but failed to demonstrate a significant clinical benefit [26,53].

Timing of IN supplementation thus becomes essential. The role of IN in well nourished patients is not to provide calories but to modulate inflammation, improve cellular and humoral immunity, and to provide metabolic support necessary to maintain intestinal perfusion and tissue oxygenation. All of these physiologic benefits combined may be important in reducing incidence of postoperative infectious complications and LOS [52].

Only a few papers concerning IN for pancreatic surgery has been published [25,26,55,56], and only one regarded the 5 days preoperative oral IN in well nourished patients scheduled for PD [25]. Our results are similar to those reported by Shirakawa et al. not only in terms of reductions of post-operative infectious rate and reduction of LOS and also in terms of compliance to treatment. As a matter of fact, only 6 patients (11%) did not complete the protocol; they were excluded from intention to treat analysis according to results of previous trials which reported a clinical inefficacy of short IN supplementation [26,53]. Among IN group patients, 81.7% had completed the proposed treatment without the occurrence of adverse events.

All patients enrolled in our study were defined as “resectable” patients at preoperative assessment [54]; no patient was submitted to preoperative chemo-radiation therapy and only one underwent portal vein resection during PD for unexpected vein infiltration; more and more neo-adjuvant protocol are ongoing and it is possible to assume that in the near future even more patients can be subjected to preoperative oncological treatment for borderline resectable or locally advanced pancreatic carcinoma. Neoadjuvant chemoradiotherapy or chemotherapy alone contributes to further worsening the nutritional status and immunity of candidates to surgery, with deleterious effects on postoperative course; in patients scheduled for PD after neoadjuvant therapy these risks of postoperative complications are higher; multidisciplinary approach and timing of nutritional intervention become even more essential.

5. Conclusions

The present data showed that preoperative oral IN is safe, well tolerated and effective for non-malnourished patients undergoing PD. Thanks to its good tolerability, it represents an important tool for the perioperative management of patients scheduled for PD for resectable disease and also for borderline resectable or locally advanced cancers considered for neoadjuvant treatment.

Ethical approval

Ethical approval is not necessary because there are already validated studies on the subject.

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Author contribution

All authors contributed equally to this work:

S. Silvestri, A. Franchello and G. Fronda proposed the protocol and operated on all the patients. A. Franchello, D. Cassine and S. Silvestri designed the study. All authors searched papers in literature, revised them and discussed critically the results. G. Deiro, D. Bonfanti, L. De Carli and F. Fop collected clinical data, updated the

database and did the statistics with S. Silvestri. All data and implications were discussed from all authors. S. Silvestri, A. Franchello, D. Campra, G. Deiro, R. Galletti and D. Cassine wrote the manuscript; A. Franchello and G. Fronda supervised the paper and made definitive changes on final version. All Authors approved the final version of the manuscript.

Contributors:

Enzo C. Farina MD (4th Division of Surgery, AOU City of Health and Science, Turin) and M. Santarelli MD (4th Division of Surgery, AOU City of Health and Science, Turin) for methodological and statistical supervision as well as for Surgical Site Infections survey and treatment opinions.

Conflict of interest

No conflict of interest to disclose.

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