

Short- versus long-term complementary nutritional support via needle catheter jejunostomy after pancreaticoduodenectomy: Study protocol of a randomized controlled trial



Philip C. Müller^{a,b,*}, Pascal Probst^b, Felix Moltzahn^a, Daniel C. Steinemann^b, Michael S. Pärli^a, Stefan W. Schmid^a, Sascha A. Müller^a, Kaspar Z'graggen^a

^a Berner Viszeralchirurgie, Clinic Beau-Site, Hirslanden, Schänzlihalde 11, 3013 Bern, Switzerland

^b Department of General-, Visceral- and Transplant Surgery, University Hospital of Heidelberg, Im Neuenheimer Feld 110, 69120 Heidelberg, Germany

ARTICLE INFO

Article history:

Received 17 November 2016

Accepted 20 November 2016

Available online 21 November 2016

Keywords:

Pancreaticoduodenectomy

Nutritional support

Tumor cachexia

Enteral nutrition

Pancreatic resection

Needle catheter jejunostomy

ABSTRACT

Introduction: Pancreatic resection is the only curative treatment for pancreatic cancer. Due to tumor cachexia most patients present with a weight loss at the time of diagnosis. Postoperatively the weight loss is often intensified. Tumor cachexia has an influence on the post-operative morbidity and mortality and on the overall survival. Complementary nutrition has a benefit on the mentioned issues. Needle catheter jejunostomy (NCJ) offers a well-tolerated and safe way for additional nutrition therapy. Until today, the optimal length of postoperative supplementary nutrition has not been evaluated.

Methods and analysis: The study is designed as a randomized controlled trial to compare the effect of complementary nutritional support until discharge and until 8-weeks after discharge for patients after pancreaticoduodenectomy (PD). The primary endpoint is the comprehensive complications index assessed 12 weeks postoperatively. The grading of the complications will be performed by a blinded assessor. The secondary endpoints are: quality of life, a nutritional assessment and the assessment of the effect on adjuvant therapies and 5-year survival. Follow-up visits are planned 1-, 3-, 6-, 12- and 60 month postoperatively. A total sample size of 140 patients was determined for the analysis of the primary endpoint. The confirmatory analysis will be performed based on the intention-to-treat principle.

Ethics and dissemination: The ethics committee of the University of Bern reviewed and approved this study on 22.08.2016 (KEK BE 322/14). The trial was registered in the German Clinical Trial Register (DRKS00010237) on 25.08.2016. The present trial is the first study comparing short- and long-term complementary nutritional support after PD in randomized controlled study. The results will allow a postoperative nutritional therapy after PD based on high quality data. The results will be presented at relevant surgical conferences and written publications of the short-term results and long-term oncologic results are planned within surgical journals.

© 2016 The Authors. Published by Elsevier Ltd on behalf of Surgical Associates Ltd. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

1. Introduction

Pancreatic cancer is the fourth leading cause of cancer-related deaths in Western countries [1,2]. In 90% pancreatic cancer is diagnosed as an advanced disease and thus, the rate of curative resec-

tions is low, which presents the only hope for cure [3–5]. At the time of the diagnosis most patients present with a weight loss, which exceeds more than 10% of body weight. During the course of their disease patients lose up to 25% of the body weight [6]. Tumor cachexia is defined as multifactorial syndrome characterized by an unintentional weight loss of 10% or more of the stable weight over a period of 6 months and is present in more than 80% of patients with pancreatic cancer [6–8]. It's an often-underestimated symptom and associated with muscle atrophy, fatigue, weakness and a significant loss of appetite and characterized by the loss of muscle- and fat mass. Cachexia has an influence on the 30-day morbidity and mortality, survival, quality of life and on the physical performance [9,10]. Postoperatively, delayed gastric emptying occurs in 7–36% after pancreaticoduodenectomy

Abbreviations: NCJ, needle catheter jejunostomy; PD, pancreaticoduodenectomy; CRF, case report form; ITT, intention to treat; SEA, serious adverse event.

* Corresponding author at: Berner Viszeralchirurgie, Clinic Beau-Site, Schänzlihalde 11, 3013 Bern, Switzerland.

E-mail addresses: philip.mueller@hotmail.com (P.C. Müller), pascal.probst@med.uni-heidelberg.de (P. Probst), felix.moltzahn@insel.ch (F. Moltzahn), daniel.steinemann@gmx.ch (D.C. Steinemann), michael.paerli@hirslanden.ch (M.S. Pärli), stefan.schmid@hirslanden.ch (S.W. Schmid), sascha.mueller@hirslanden.ch (S.A. Müller), kaspar.zgraggen@hirslanden.ch (K. Z'graggen).

<http://dx.doi.org/10.1016/j.isjp.2016.11.001>

2468-3574/© 2016 The Authors. Published by Elsevier Ltd on behalf of Surgical Associates Ltd.

This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

(PD) [11–13]. Patients who suffer from this complication can be expected to suffer a considerable nutritional deficit over months of convalescence [14]. Taken together, these issues represent an indication for complementary nutritional support. Complementary enteral feeding is possible over a naso-jejunal tube or a needle catheter jejunostomy (NCJ). Although studies did not show a difference regarding the nutritional supply, jejunal feeding tubes have a higher complication rate. But the German Society for Nutritional Medicine recommendation confirms our clinical experience, that if performed in a standardized technique and in experienced hands complication rates are low [15]. Furthermore the NCJ guarantees a better long-term nutrition therapy that is well tolerated by the patients [16]. The convalescence is as well the preparatory phase for a possible adjuvant therapy; complications during that time can be a reason to delay or to cancel a planned adjuvant treatment. A routine oral supplementation for the out patient setting is not recommended, but still revealed a benefit for the recovery of the nutritional status, a reduction of the complication rate and an improvement of the quality of life in patients who could not cover their energy demand after abdominal surgery in the domestic setting [17–20]. The aim of this study is to compare the effect of long-term postoperative complementary nutritional support with short-term support over a NCJ in patients after PD with pancreatic cancer.

2. Methods and analysis

The study is a randomized controlled trial intended to compare the effect of short- versus long-term nutritional support over a NCJ after PD. The trial design allows objective assessment of the potential benefits and risks of a short-term nutritional support compared to a long-term nutritional support.

The following hypothesis will be tested:

H0. The Comprehensive Complication Index for long-term and short-term nutritional support is the same.

H1. The Comprehensive Complication Index (CCI) for long-term and short-term nutritional support is different.

2.1. Trial design

The study is designed as a single center randomized controlled trial to compare the effect of short term (until discharge) and long-term (until eight weeks after discharge) complementary nutritional support over a NCJ after PD for pancreatic carcinoma. The trial scheme is illustrated in Fig. 1.

2.2. Study population and eligibility criteria

All patients aged over 18 years and referred to PD for suspected pancreatic carcinoma will be screened for inclusion (Table 1). Patients screening includes an investigation of the previous medical history, a physical examination, a standard preoperative evaluation on the extent of the pancreatic disease and a standardized nutritional assessment.

2.3. Trial location

The trial will be conducted at the Department of Visceral Surgery, Clinic Beau-Site, Bern, Switzerland. The Beau-Site Clinic is a center with extensive experience in pancreatic surgery. 70 pancreatic resections are performed a year by a single senior surgeon.

2.4. Trial organization

The principal investigator (K.Z.) is responsible for the preparation of the study protocol and the case report form (CRF). The principal investigator is as well responsible for screening, recruitment, data collection and completion of the CRFs. All PD at the trial institution are performed by the principal investigator with an experience of >300 performed PDs. The perioperative management was standardized prior to the creation of the study protocol.

2.5. Sample size

The sample size was determined for the primary endpoint: CCI assessed at 90-day after surgery. The following assumptions were made according to the data of our own department, showing a 10-point reduction (mean outcome in short-term nutritional support 30, mean outcome in long-term nutritional support 20, standard deviation 20) of the CCI in patients with long-term nutritional support after PD compared to short-term nutritional support. With a type I error (α) of 0.05 and power ($1-\beta$) of 0.80 63 patients in each group are needed in a superiority analysis. With a drop-out rate of 10%, the total number needed per arm is 70, resulting in a total patient number of 140 patients.

2.6. Trial timeline

Annually, a total of 70–90 patients with pancreatic carcinoma are expected to be referred to the trial institution for elective PD. We expect a recruitment rate of 70–80%. The recruitment of 140 patients is planned to be finished within 26 months. The time interval from first patient to last patient out will be 86 months.

2.7. Randomization, allocation and blinding

Randomization will be done by a study nurse the day before the planned discharge from the hospital. The patients will be randomized using an online randomization tool (<http://randomizer.at>). Randomization will be stratified by the NRS-Score in blocks of varying size with a 1:1 ratio to the first experimental and the second experimental group. The surgical residents will perform the study visits. Due to the nature of the intervention blinding of the surgeon or the patient is not possible, the investigators (PCM, PP) of the primary endpoint will be blinded when calculating (http://www.assessurgery.com/calculator_single) the primary outcome (CCI) from a surgical report.

2.8. Interventions

After performing a PD and before abdominal closure a NCJ (Freka®, Fresenius Kabi, Germany) is placed in the proximal jejunum. Total parenteral nutrition (TPN) is delivered continuously via central venous catheter from post-operative day (POD) 1 to POD 7 [21]. The artificial nutrition is designed to target 30 kcal/kg/day. Oral food intake was allowed after the surgery and increased according to tolerance. The NCJ is daily rinsed with water. On POD 8 complementary nutrition over the NCJ is started with Survimed® (Fresenius Kabi, Schweiz). Survimed® is a low-molecular, balanced supplementary enteral nutrition especially for patients with maldigestion or malabsorption (Table 2).

2.9. Intervention group: Long-term complementary nutritional support

To the intervention arm complementary nutritional support is given over a NCJ from POD 8 for 8 weeks after discharge from the hospital. 50% of the caloric requirement calculated from the

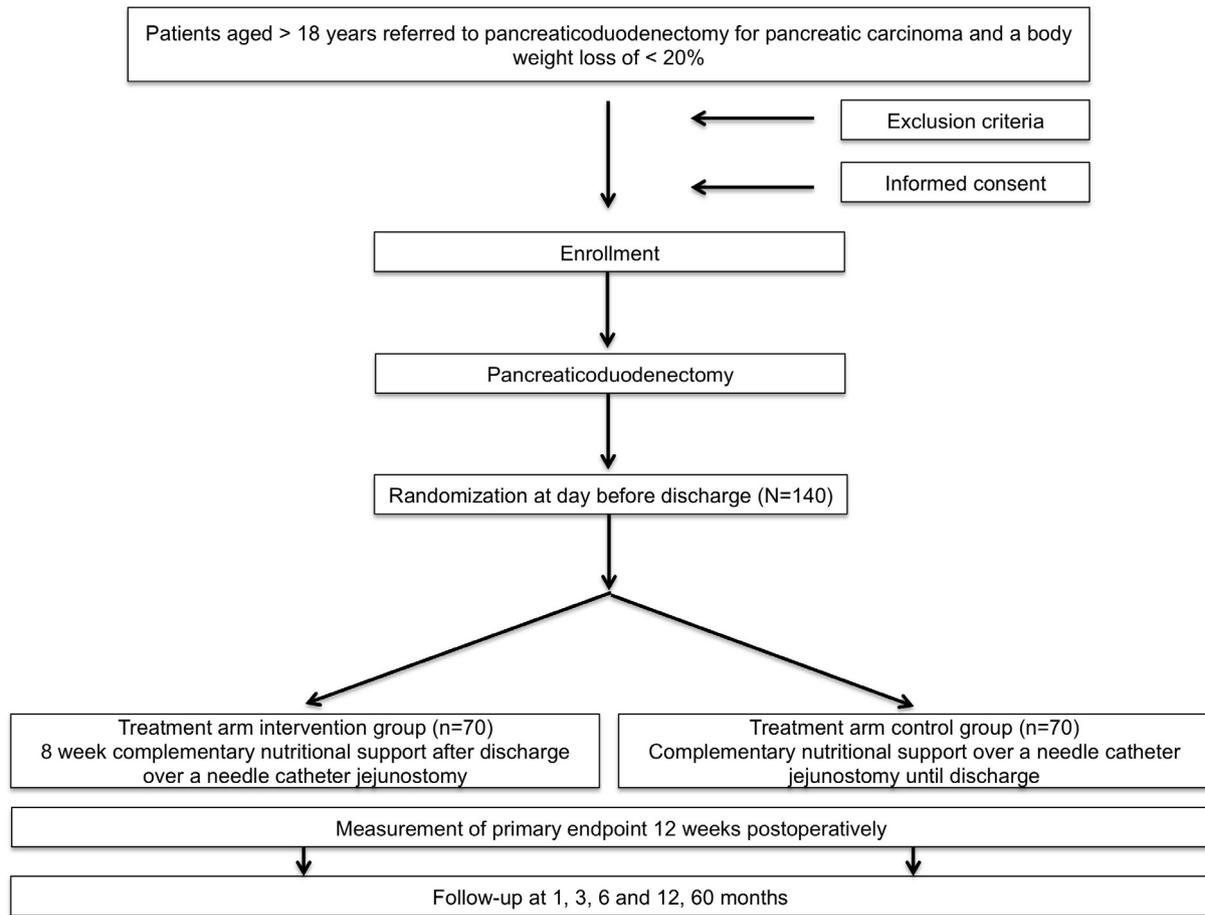


Fig. 1. Trial scheme.

Table 1
Eligibility criteria.

Inclusion criteria	Exclusion criteria
<ul style="list-style-type: none"> • Pancreaticoduodenectomy for pancreatic carcinoma • <20% body weight loss • Age ≥ 18 	<ul style="list-style-type: none"> • Metastatic pancreatic carcinoma, other than lymphatic metastases • Cardiac or renal diseases that prohibit enteral nutrition • Parenteral nutrition • Secondary tumor • Active chronic gastrointestinal diseases • Stop of complementary nutrition therapy for over three days
<ul style="list-style-type: none"> • Informed consent 	

Table 2
Contents of Survimed®.

Substance	per 100 ml
Proteins (g)	4.5
Fat (g)	2.8
Carbohydrates (g)	14.3
Fibres (g)	0.08
Water (ml)	85
Energy (kcal)	100

IBW is supplemented over the NCJ from discharge until postoperative week 5. From week 5 to week 8 after discharge 30% of the caloric requirement calculated from the IBW are supplemented over the NCJ. The NCJ is removed 8 weeks after discharge.

2.10. Control group: Short-term complementary nutritional support

To the control arm complementary nutritional support is given over a NCJ from POD 8 until the day of discharge from the hospital. 50% of the caloric requirement calculated from the ideal body weight (IBW) is supplemented over the NCJ until the day of discharge. The feeding tube is left in place for a possible cross over if the general condition or the nutritional status worsens significantly during the 8 weeks after discharge. The NCJ is removed 8 weeks after discharge.

2.11. Perioperative management, discharge, and follow up

Perioperative thrombosis prophylaxis will be performed according to current guidelines [22]. Single-shot antibiotics (Cefuroxime and Metronidazole) will be given 30 min before surgery. Perioperative care was given according to the guidelines for enhanced recovery after surgery with the difference of the above mentioned nutrition management [23]. All patients will be followed up at an ambulatory checkup scheduled 1, 3 and 6 months postoperatively. The ambulatory checkup will comprise taking the medical history, a clinical examination, and an assessment of the primary and secondary endpoints. The follow-up at 12 and 60 months after the surgery will be completed by a phone interview (see Table 3).

2.12. Primary and secondary endpoints

2.12.1. Primary endpoint

The primary endpoint will be the CCI 90 days after the operation. The morbidity will be graded according to the

Clavien-Dindo classification [24]. The morbidity of the patient is assessed at study visit two (at the day of discharge), three (1 month postoperative) and four (3 months postoperative). The type of complication is noted in detail in the CRF and on an additional surgical report by the primary investigator without grading the complication. Afterwards the surgical report is sent to two independent investigators (PCM, PP) not working at the trial conducting hospital. The assessors of the primary endpoint are blinded to the study arm of the participants, grade the complications and calculate the CCI.

2.12.2. Secondary endpoints

2.12.2.1. Quality of life. The quality of life is measured with the Quality of Life Questionnaires (QLQ) from the European Organization for Research and Treatment of Cancer (EORTC). The QLQ C30 records the quality of life of cancer patients and the QLQ PAN26 the quality of life of patients with pancreatic cancer.

2.12.2.2. Nutritional assessment. The following parameters will be assessed: the body mass index, the nutritional-risk-screening score (NRS-2002). Furthermore, a bioelectrical impedance analysis and the hand dynamometry are measured.

2.12.2.3. Oncological outcome. The delay or the abortion of planned adjuvant therapies and the reason for it will be assessed. Furthermore, the 5-year survival will be evaluated by telephone interviews with the patients or by contacting their general practitioner.

2.13. Data management

Data will be entered in a CRF by the principal investigator or a designated surgical resident. Participant names and collected data are subject to medical confidentiality. In the case of resignation, collected data may be pseudonymized unless the participant explicitly requests that all data should be erased. A designated study nurse will enter the data from the CRF into a database. At the end of the trial, the original CRFs and final database will be archived by the principal investigator for 10 years.

2.14. Safety and reporting of serious adverse events

Serious adverse events (SEAs), defined according to the guidelines for good clinical practice by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, will be reported from the day of first

enrollment until the regular end of the trial. All SAEs will be documented in a separate SEA-form and the CRF, and will be reported to the principal investigator within 24 h of being noted. If the principal investigator considers a SAE as unexpected and related to the study intervention, he will submit a report to the ethics committee within three days. The morbidity and the SAEs will be evaluated twice: after randomization of one-third of the patients and after randomization of two-thirds of the patients. In case of relevant differences between the morbidity and the SAEs between the groups, a report will be submitted to the local ethics committee. The trial may be terminated based on the decision of the principal investigator according to the assessment of the ethics committee.

2.15. Methods for minimising bias

2.15.1. Minimising selection bias

Consecutively screened and eligible patients will be included in the present study. Patients will be allocated concealed by postoperative randomization at the day before the planned discharge using a centralized web based tool (<http://randomizer.at>). Block randomization of variable sizes (6 and 12) stratified by the NRS-Score will be performed. A sufficient number of individuals will be recruited according to the sample size calculation in order to prevent random error and to achieve sufficient power.

2.15.2. Minimising performance bias

All PD will be performed by the same surgeon. A standardized postoperative management was implemented prior to the beginning of the study.

2.15.3. Minimising detection bias

Blinding of the surgeon or the patient to the intervention is not feasible. The primary endpoint (CCI) is graded and calculated by blinded assessors based on medical records taken at study visit 2 (at the day of discharge), 3 (1 month postoperative), 4 (3 months postoperative).

2.15.4. Minimising attrition bias

The trial will be reported according to the CONSORT statement [www.consort-statement.org; accessed 14.04.2016]. The trial will be registered with the Swiss National Clinical Trials Portal [www.kofam.ch] and a WHO primary trial registry. The trial protocol with full information about endpoints and profound explanation of planned statistical analysis will be published according to the

Table 3
Flow of the trial – course of examinations.

Visit	1 Screening visit	2 Day of discharge	3 1month post- operative	4 3months post- operative	5 6 months post- operative	6 12 months post- operative	7 60 months post- operative
Past and current medical history	X						
Physical examination and personal data	X	X	X	X	X	X	
Informed consent	X						
Randomization		X					
Blood tests	X	X	X	X			
Quality of life	X	X	X	X	X	X	X
Nutritional Assessment	X	X	X	X	X	X	X
Karnofsky index	X	X	X	X	X	X	X
Bioelectrical impedance analysis	X	X	X	X			
Hand dynamometry	X	X	X	X			
Complications		X	X	X	X	X	X
Oncologic Outcome		X	X	X	X	X	X

SPIRIT statement (additional file 1) [www.spirit-statement.org; accessed 14.04.2016] to avoid risk of selective reporting [25].

2.15.5. Other bias

Financial relationships with providers of medical devices or any conflict of interest that could inappropriately influence the work within this project will be stated explicitly.

2.16. Statistical analysis

Statistical analysis will be performed with GraphPad® Prism version 5.00 (GraphPad Software, San Diego California USA). A two-sided P value < 0.05 will be considered significant. For baseline characteristics, descriptive statistics will be used. For analysis of the primary outcome, a Mann-Whitney U tests will be applied. For categorical secondary endpoints, chi-square statistics will be used. To compare continuous secondary endpoints, Mann-Whitney U tests will be applied. No interim analysis is planned for this study.

Missing values will be replaced with the last available value (the last observation carried forward approach). Data from patients who withdraw from the study will be disregarded unless exclusion is based on postoperative patient wishes and the patient agrees to the use of the already obtained data.

The confirmatory analysis will be performed based on intention-to-treat (ITT) patients and with respect to ITT principles. A standard sensitivity analysis will be performed on the per-protocol population.

2.17. Good Clinical practice

The trial was conceived and will be conducted according to all relevant national and international rules and regulations, such as the guidelines for good clinical practice by the ICH-GCP [26] and Declaration of Helsinki (2013) [27].

2.18. Registration

The trial was registered in the German Clinical Trial Register (http://drks-neu.uniklinikfreiburg.de/drks_web/) under the registration number DRKS00010237 on 25.08.2016.

2.19. Protocol version

This manuscript refers to the third version of the full study protocol issued on 22.06.2016. Protocol modifications will be reported to all investigators, the local ethics committee, the Clinical Trials Register, all trial participants, and the journal.

3. Discussion

Malnutrition after PD for pancreatic carcinoma is associated with a higher rate of complications, a shorter survival and a longer postoperative stay. Previous studies showed the positive effect of supplementary nutrition on the above mentioned issues [17–19,28]. After PD patients often experience a delayed tolerance of liquid and solid food. The optimal length of a postoperative enteral nutritional support has not been evaluated. The European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines support a regular reassessment of the nutritional status during the hospital stay and if necessary support an additional nutritional therapy after discharge (Grade of recommendation C (weak)) [29]. For a long-term nutritional support a NCJ is superior to the nasogastric tube since the nutritional supply is equal but the NCJ is better tolerated by the patient and is associated with little complica-

tions in experienced hands [16,30]. The study investigates the hypothesis that long-term postoperative nutrition after discharge is able to reduce 90-day morbidity and could have a potential positive effect on the practicability of adjuvant therapies. A recent review on the perioperative nutritional support after pancreatic surgery defined the effect of supplementary nutrition on adjuvant therapies as an issue that warrants special attention [31].

90-day postoperative morbidity has been chosen as the primary endpoint because it presents a surrogate marker for the benefits of an improved nutritional status. Secondly, the endpoint includes the possible downside of the additional nutrition namely complications of the NCJ, which are lost catheters in a third of the cases [30]. Grading complications according to Clavien-Dindo and calculating the CCI summarizes all postoperative complications and is said to be more sensitive than existing morbidity endpoints [32].

Several measures were taken to minimize bias. Selection bias is prevented using a web based randomization. Performance bias is minimized with a standardized perioperative treatment scheme and all interventions are performed by the same surgeon. Grading of the primary endpoint is performed by two blinded assessors, which should minimize the detection bias.

For the planning, conduct and analysis of this trial no external funding was received, also in order to prevent a possible industry bias [33].

The present study is the first randomized controlled trial that compares the possible benefits of long-term complementary perioperative nutritional support to short-term nutritional support for patients after PD. The results of the study would have a wide impact on the postoperative management of patients with pancreatic cancer after PD.

4. Ethics and dissemination

The ethics committee of the University of Bern reviewed and approved this study on 22.08.2016 (KEK BE 322/14).

The results of the study are intended to be presented at national and international medical congresses on corresponding fields of interest (hepatobiliary surgery, abdominal surgery, nutrition). Written publications of the short-term results (until 1 year after the surgery) and long-term oncologic results are planned within surgical journals. The authorship for written publications has to be confirmed by all lead investigators and will only be granted in the case of substantive contributions to the design, conduct, data analysis, and interpretation. After completion of the full study report, anonymized participant-level datasets and the statistical code for generating results will be available by contacting the principal investigator.

Authors' contributions

PCM, FM, PP and KZ conceived the design of the study and wrote the manuscript. PCM, DCS and PP carried out the sample size calculation. MSP, SWS and SAM performed a critical revision of the manuscript. All authors read and approved the final manuscript.

Competing interests

The authors have no competing interests to declare.

Funding

This research received no specific grant from any funding agency in the public, commercial or non-for profit sectors.

References

- [1] M. Carpelan-Holmström, S. Nordling, E. Pukkala, R. Sankila, J. Lüttges, G. Klöppel, C. Haglund, Does anyone survive pancreatic ductal adenocarcinoma? A nationwide study re-evaluating the data of the Finnish Cancer Registry, *Gut* 54 (2005) 385–387, <http://dx.doi.org/10.1136/gut.2004.047191>.
- [2] H. Friess, R. Isenmann, P. Berberat, J. Kleeff, M.W. Büchler, Prognosis in pancreatic carcinoma, *Ther. Umsch. Rev. Thérapeutique* 53 (1996) 401–407.
- [3] K.C. Conlon, D.S. Klimstra, M.F. Brennan, Long-term survival after curative resection for pancreatic ductal adenocarcinoma. Clinicopathologic analysis of 5-year survivors, *Ann. Surg.* 223 (1996) 273–279.
- [4] J. Kleeff, C. Michalski, H. Friess, M.W. Büchler, Pancreatic cancer: from bench to 5-year survival, *Pancreas* 33 (2006) 111–118, <http://dx.doi.org/10.1097/01.mpa.0000229010.62538.f2>.
- [5] M. Wagner, C. Redaelli, M. Lietz, C.A. Seiler, H. Friess, M.W. Büchler, Curative resection is the single most important factor determining outcome in patients with pancreatic adenocarcinoma, *Br. J. Surg.* 91 (2004) 586–594, <http://dx.doi.org/10.1002/bjs.4484>.
- [6] J. Bachmann, K. Ketterer, C. Marsch, K. Fechtner, H. Krakowski-Roosen, M.W. Büchler, H. Friess, M.E. Martignoni, Pancreatic cancer related cachexia: influence on metabolism and correlation to weight loss and pulmonary function, *BMC Cancer* 9 (2009) 255, <http://dx.doi.org/10.1186/1471-2407-9-255>.
- [7] A. Laviano, M.M. Meguid, A. Inui, M. Muscaritoli, F. Rossi-Fanelli, Therapy insight: cancer anorexia-cachexia syndrome—when all you can eat is yourself, *Nat. Clin. Pract. Oncol.* 2 (2005) 158–165, <http://dx.doi.org/10.1038/nponc0112>.
- [8] T. Okusaka, S. Okada, H. Ishii, M. Ikeda, H. Kosakamoto, M. Yoshimori, Prognosis of advanced pancreatic cancer patients with reference to calorie intake, *Nutr. Cancer* 32 (1998) 55–58, <http://dx.doi.org/10.1080/01635589809514717>.
- [9] K.C. Fearon, M.D. Barber, J.S. Falconer, D.C. McMillan, J.A. Ross, T. Preston, Pancreatic cancer as a model: inflammatory mediators, acute-phase response, and cancer cachexia, *World J. Surg.* 23 (1999) 584–588.
- [10] K.A. Nelson, D. Walsh, F.A. Sheehan, The cancer anorexia-cachexia syndrome, *J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol.* 12 (1994) 213–225.
- [11] M.I. van Berge Henegouwen, T.M. van Gulik, L.T. DeWit, J.H. Allema, E.A. Rauws, H. Obertop, D.J. Gouma, Delayed gastric emptying after standard pancreaticoduodenectomy versus pylorus-preserving pancreaticoduodenectomy: an analysis of 200 consecutive patients, *J. Am. Coll. Surg.* 185 (1997) 373–379.
- [12] J.H. Balcom, D.W. Rattner, A.L. Warshaw, Y. Chang, C. Fernandez-del Castillo, Ten-year experience with 733 pancreatic resections: changing indications, older patients, and decreasing length of hospitalization, *Arch. Surg.* 136 (2001) 391–398.
- [13] B.W. Miedema, M.G. Sarr, J.A. van Heerden, D.M. Nagorney, D.C. McIlrath, D. Ilstrup, Complications following pancreaticoduodenectomy, current management, *Arch. Surg.* 127 (1992) 945–949, discussion 949–950.
- [14] L.A. Mack, I.G. Kaklamanos, A.S. Livingstone, J.U. Levi, C. Robinson, D. Sleeman, D. Franceschi, O.F. Bathe, Gastric decompression and enteral feeding through a double-lumen gastrojejunostomy tube improves outcomes after pancreaticoduodenectomy, *Ann. Surg.* 240 (2004) 845–851.
- [15] A. Weimann, S. Breitenstein, J.P. Breuer, S.E. Gabor, S. Holland-Cunz, M. Kemen, F. Längle, N. Rayes, B. Reith, P. Rittler, W. Schwenk, M. Senkal, DGEM Steering Committee, [Clinical nutrition in surgery. Guidelines of the German Society for Nutritional Medicine], in: *Chir. Z. Für Alle Geb. Oper. Medizin* 85 (2014) 320–326, <http://dx.doi.org/10.1007/s00104-014-2737-7>.
- [16] J.B. Osborne, L.A. Collin, E.C. Posluns, E.J. Stokes, K.A. Vandenbussche, The experience of head and neck cancer patients with a percutaneous endoscopic gastrostomy tube at a Canadian cancer center, *Nutr. Clin. Pract. Off. Publ. Am. Soc. Parenter. Enter. Nutr.* 27 (2012) 661–668, <http://dx.doi.org/10.1177/0884533612457181>.
- [17] A.M. Keele, M.J. Bray, P.W. Emery, H.D. Duncan, D.B. Silk, Two phase randomised controlled clinical trial of postoperative oral dietary supplements in surgical patients, *Gut* 40 (1997) 393–399.
- [18] A.H. Beattie, A.T. Prach, J.P. Baxter, C.R. Pennington, A randomised controlled trial evaluating the use of enteral nutritional supplements postoperatively in malnourished surgical patients, *Gut* 46 (2000) 813–818.
- [19] J. MacFie, N.P. Woodcock, M.D. Palmer, A. Walker, S. Townsend, C.J. Mitchell, Oral dietary supplements in pre- and postoperative surgical patients: a prospective and randomized clinical trial, *Nutrition* 16 (2000) 723–728, Burbank Los Angel. Calif.
- [20] J. Kondrup, H.H. Rasmussen, O. Hamberg, Z. Stanga, Ad Hoc ESPEN Working Group, Nutritional risk screening (NRS 2002): a new method based on an analysis of controlled clinical trials, *Clin. Nutr. Edinb. Scotl.* 22 (2003) 321–336.
- [21] J. Perinel, C. Mariette, B. Dousset, I. Sielezneff, A. Gainant, J.-Y. Mabrut, S. Bin-Dorel, M.E. Bechwaty, D. Delaunay, L. Bernard, A. Sauvanet, M. Pocard, E. Buc, M. Adham, Early enteral versus total parenteral nutrition in patients undergoing pancreaticoduodenectomy: a randomized multicenter controlled trial (Nutri-DPC), *Ann. Surg.* (2016), <http://dx.doi.org/10.1097/SLA.0000000000001896>.
- [22] A. Encke, S. Haas, S. Sauerland, S3-Leitlinie Prophylaxe der venösen Thrombembolie (VTW). VASA 2009; S/76, n.d.
- [23] K. Lassen, M.M.E. Coolsen, K. Slim, F. Carli, J.E. de Aguilar-Nascimento, M. Schäfer, R.W. Parks, K.C.H. Fearon, D.N. Lobo, N. Demartines, M. Braga, O. Ljungqvist, C.H.C. Dejong, ERAS[®] Society, European Society for Clinical Nutrition and Metabolism, International Association for Surgical Metabolism and Nutrition, Guidelines for perioperative care for pancreaticoduodenectomy: Enhanced Recovery After Surgery (ERAS[®]) Society recommendations, *Clin. Nutr. Edinb. Scotl.* 31 (2012) 817–830, <http://dx.doi.org/10.1016/j.clnu.2012.08.011>.
- [24] D. Dindo, N. Demartines, P.-A. Clavien, Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey, *Ann. Surg.* 240 (2004) 205–213.
- [25] A.-W. Chan, J.M. Tetzlaff, D.G. Altman, A. Laupacis, P.C. Gøtzsche, K. Krleža-Jerić, A. Hróbjartsson, H. Mann, K. Dickersin, J.A. Berlin, C.J. Doré, W.R. Parulekar, W.S.M. Summerskill, T. Groves, K.F. Schulz, H.C. Sox, F.W. Rockhold, D. Rennie, D. Moher, SPIRIT, Statement: defining standard protocol items for clinical trials, *Ann. Intern. Med.* 158 (2013) 200–207, <http://dx.doi.org/10.7326/0003-4819-158-3-201302050-00583>.
- [26] J.R. Dixon, The international conference on harmonization good clinical practice guideline, in: *Qual. Assur.* 6 (1998) 65–74, San Diego Calif.
- [27] World Medical Association, World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects, *JAMA* 310 (2013) 2191–2194, <http://dx.doi.org/10.1001/jama.2013.281053>.
- [28] V. Di Carlo, L. Gianotti, G. Balzano, A. Zerbi, M. Braga, Complications of pancreatic surgery and the role of perioperative nutrition, *Dig. Surg.* 16 (1999) 320–326, doi:18742.
- [29] A. Weimann, M. Braga, L. Harsanyi, A. Laviano, O. Ljungqvist, P. Soeters, DGEM (German Society for Nutritional Medicine), K.W. Jauch, M. Kemen, J.M. Hiesmayr, T. Horbach, E.R. Kuse, K.H. Vestweber, ESPEN (European Society for Parenteral and Enteral Nutrition), in: *Clin. Nutr. Edinb. Scotl.* 25 (2006) 224–244, <http://dx.doi.org/10.1016/j.clnu.2006.01.015>.
- [30] J.G. Myers, C.P. Page, R.M. Stewart, W.H. Schwesinger, K.R. Sirinek, J.B. Aust, Complications of needle catheter jejunostomy in 2022 consecutive applications, *Am. J. Surg.* 170 (1995) 547–550.
- [31] F. Bozzetti, L. Mariani, Perioperative nutritional support of patients undergoing pancreatic surgery in the age of ERAS, *Nutrition* 30 (2014) 1267–1271, <http://dx.doi.org/10.1016/j.nut.2014.03.002>, Burbank Los Angel. Calif.
- [32] K. Slankamenac, R. Graf, J. Barkun, M.A. Puhon, P.-A. Clavien, The comprehensive complication index: a novel continuous scale to measure surgical morbidity, *Ann. Surg.* 258 (2013) 1–7, <http://dx.doi.org/10.1097/SLA.0b013e318296c732>.
- [33] P. Probst, P. Knebel, K. Grummich, S. Tenckhoff, A. Ulrich, M.W. Büchler, M.K. Diener, Industry bias in randomized controlled trials in general and abdominal surgery: an empirical study, *Ann. Surg.* 264 (2016) 87–92, <http://dx.doi.org/10.1097/SLA.0000000000001372>.