



**HAL**  
open science

# Effect of a Perioperative Nutritional Supplementation with Oral Impact® in Patients undergoing Hepatic Surgery for Liver Cancer: A Prospective, Placebo-Controlled, Randomized, Double-Blind Study

Philippe Seguin, Clara Locher, Karim Boudjema, Catherine Hamon,  
Catherine Mouchel, Yannick Mallédant, Eric Bellissant

## ► To cite this version:

Philippe Seguin, Clara Locher, Karim Boudjema, Catherine Hamon, Catherine Mouchel, et al.. Effect of a Perioperative Nutritional Supplementation with Oral Impact® in Patients undergoing Hepatic Surgery for Liver Cancer: A Prospective, Placebo-Controlled, Randomized, Double-Blind Study. *Nutrition and Cancer*, 2016, 68 (3), pp.464-472. 10.1080/01635581.2016.1153670 . hal-01295673

**HAL Id: hal-01295673**

**<https://univ-rennes.hal.science/hal-01295673>**

Submitted on 14 Jun 2016

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

**Effect of a peri-operative nutritional supplementation with Oral Impact® in patients  
undergoing hepatic surgery for liver cancer: a prospective, placebo-controlled, randomized,  
double-blind study**

Philippe SEGUIN, Clara LOCHER, Karim BOUDJEMA, Catherine HAMON, Catherine MOUCHEL, Yannick MALLEDANT, Eric BELLISSANT.

**Philippe SEGUIN.** Department of Surgical Intensive Care. Rennes University Hospital, Rennes 1 University, Rennes, 35000, France. University Hospital, Rennes 1 University, Rennes, 35000, France.

**Clara LOCHER.** Department of Clinical Pharmacology. Inserm 0203, Clinical Investigation Centre. Rennes. University Hospital, Rennes 1 University, Rennes, 35000, France.

**Karim BOUDJEMA.** Department of Liver and Digestive Surgery. Rennes University Hospital, Rennes 1 University, Rennes, 35000, France. University Hospital, Rennes 1 University, Rennes, 35000, France.

**Catherine HAMON.** Department of Pharmacy. Rennes University Hospital, Rennes 1 University, Rennes, 35000, France.

**Catherine MOUCHEL.** Department of Clinical Pharmacology. Inserm 0203, Clinical Investigation Centre. Rennes. University Hospital, Rennes 1 University, Rennes, 35000, France.

**Yannick MALLEDANT.** Department of Surgical Intensive Care. Rennes University Hospital, Rennes 1 University, Rennes, 35000, France. University Hospital, Rennes 1 University, Rennes, 35000, France.

**Eric BELLISSANT.** Department of Clinical Pharmacology. Inserm 0203, Clinical Investigation Centre. Rennes. University Hospital, Rennes 1 University, Rennes, 35000, France.

**Clinicaltrials.gov Identifier:** NCT00151671

**Conflicts of interest:** None

**Word count:** Text word count: 2696

**Abstract (198 words).**

Peri-operative nutrition with supplements containing L-arginine,  $\omega$ 3-polyunsaturated fatty acids, and nucleotides could boost liver function recovery, immune response and resistance to infection after hepatic resection. We conducted a placebo-controlled, randomized, double-blind study to assess the effect of a peri-operative nutritional supplementation with Oral Impact® in patients undergoing hepatic surgery for liver cancer. Treatment was given 3 times daily for 7 days before and 3 days after surgery. Primary outcome was factor V, 3 days after surgery. Thirty-five patients (placebo: 17; Oral Impact®: 18) were included. Five patients (placebo: 3; Oral Impact®: 2) were not operated and 5 (placebo: 2; Oral Impact®: 3) did not undergo hepatic resection. Factor V (mean $\pm$ standard deviation) was 70 $\pm$ 27% and 79 $\pm$ 25% (p=0.409) 3 days after surgery and 90 $\pm$ 30% and 106 $\pm$ 16% (p=0.066) 5 days after surgery, in placebo and Oral Impact® groups, respectively. There were no significant differences between groups on other outcomes assessing liver function recovery (bile production,  $\gamma$ -glutamyl-transferase,  $\alpha$ -foeto-protein), immune response (CD3, CD4, CD8 cells, CD4/CD8 ratio, NK cells, B lymphocytes), number of infections, and tolerance. A 10-day peri-operative nutritional supplementation with Oral Impact® does not improve hepatic function, immune response and resistance to infection in patients undergoing hepatic surgery for liver cancer.

**Key words:** liver cancer, nutrition, Oral Impact®.

## Introduction

In cirrhotic patients, the mortality rate of the surgical resection of the liver is about 10% (1-4). Morbidity, represented by pulmonary complications, ascites, and local or systemic infections, ranges from 30 to 70% (4-6). These complications are mainly due to hepatic insufficiency resulting from reduced parenchyma and to oxidative stress lesions resulting from reperfusion injury (7, 8). It has been shown that a good preoperative nutritional status could reduce the incidence of postoperative complications and consequently the costs of care after surgery (9). Moreover, in patients suffering from malignant and/or significant liver disease, malnutrition is frequent (10-12), optimization of nutritional status may improve hepatic function and pre-operative nutritional status is one of the key points for success of liver resection (7, 13, 14).

These results could be amplified by peri-operative nutrition with supplements containing L-arginine,  $\omega$ 3-polyunsaturated fatty acids, and nucleotides which could boost liver function recovery, immune response, and resistance to infections (15, 16). Indeed, L-arginine, a semi-essential amino acid, increases the synthesis of liver proteins, improves the healing process and preserves immune function. Omega-3 polyunsaturated fatty acids are responsible for the synthesis of the three-series of prostaglandins, the five-series of leucotriens, and of anti-inflammatory mediators. Nucleotides, which are basic components of RNA and DNA, are essential for rapid cell proliferation in case of inflammation or trauma (15, 16). We made the hypothesis that, in patients with liver cancer scheduled to undergo hepatic resection, a peri-operative (during the last 7 pre-operative and the first 3 post-operative days) nutrition enriched with essential amino acids, polyunsaturated fatty acids, and precursors of nucleotides could boost liver function recovery, immune response and resistance to infection after hepatic resection and that all these actions could reduce postoperative morbidity. We assessed the effect of our intervention using the level of factor V at day-3 after surgery. Indeed, postoperative hepatic failure is the most severe complication after liver resection and one of its main characteristic is coagulation disorders (7, 14). In this context, the risk of complications dramatically increases and the prognosis is compromised (3, 17). Thus, after hepatic resection, notably when cirrhosis is present, factor V represents a good biomarker of hepatic function since it has a short half-life and has been shown to vary quickly during the postoperative period (3-5).

## Data and Methods

### Study design

This was a prospective, monocentric, placebo-controlled, randomized (allocation ratio: 1:1), double-blinded, two-parallel-group study conducted in the French University hospital of Rennes. The study protocol was approved by the Consultative Committee for the Protection of People in Biomedical Research of Rennes, on September 11<sup>th</sup> 2002 (Protocol n°02/45-421). Written informed consent was obtained from all patients prior to inclusion.

### Patients

Adults above 18 years undergoing hepatectomy of at least 2 segments for primary (or secondary after amendment of August 30<sup>th</sup> 2004) liver cancer with cirrhosis defined by a Child Pugh score < 8 (or liver fibrosis [score of 3] after amendment of August 30<sup>th</sup> 2004) were eligible for the study. Exclusion criteria included pregnancy, recent weight loss of more than 10% of body weight, immunological deficiency (constitutional or secondary to HIV-infection, corticosteroid treatment > 0.3 mg/kg daily, splenectomy), portal vein or hepatic artery thrombosis, and biliary duct dilatation. Inclusion and exclusion criteria were checked during the pre-anesthetic visit.

### Randomization

Randomization was centrally performed, concealed, and equilibrated by blocks of 10 according to a computer-generated list under the responsibility of the biostatistician. The randomization list was kept sealed by the pharmacist of the center. One week before scheduled surgery, eligible patients were randomly assigned to receive either the placebo (Novartis Nutrition, Bern, Switzerland) or the nutritional oral diet (Oral Impact®; Novartis Nutrition, Bern, Switzerland) according to the randomization list. Sequentially numbered boxes, containing patients' treatments, were delivered to the investigators by the pharmacist following the order of the randomization list. All patients, medical and nursing staffs, and pharmacists remained blinded throughout the study period.

## Treatments

Treatments were given to patients as sachets of 74 g of powder ready to be dissolved in 250 ml of water (final volume after dilution: 300 ml). Oral Impact® was enriched with L-Arginine 3.8 g,  $\omega$ 3-polyunsaturated fatty acids 1.0 g, and RNA 0.4 g (table 1). Both the placebo and Oral Impact® had the same coffee taste and appearance. The treatment (300 ml of placebo or of Oral Impact®) was taken 3 times daily for 10 days. In the 7 preoperative days, it was taken in addition to regular food. In the 3 postoperative days, it was the only feeding and was administered via a nasogastric tube.

Treatment compliance was rigorously assessed i) in the 7 preoperative days by checking the diary card (given by the pharmacist to the patient before the start of treatment) in which the patient had to report the number of sachets taken daily and by counting the sachets brought back by the patient to the pharmacist the day before surgery, and ii) in the 3 postoperative days by checking nursing files.

## Data collection and evaluation

At inclusion, age, sex, height, usual weight, body mass index, current weight, weight loss during the last 6 months, Child-Pugh score,  $\gamma$ -glutamyl-transferase ( $\gamma$ -GT),  $\alpha$ -foeto-protein ( $\alpha$ -FP), albumin, pre-albumin, prothrombin ratio, and factor V were recorded.

The day of operation defined the day-0 of the protocol. The nature (continuous or intermittent) and duration of hepatic vascular occlusion as well as the number of hepatic segments resected were recorded. Transfusion requirements (red blood cells and/or fresh frozen plasma) were also recorded. After operation, patients were monitored daily until day-10 and then at day-30.

## Outcome measures

The primary outcome was factor V at day-3. Secondary outcomes included liver volume measured by liver contrast-enhanced (CT) scanner at day-10 and 30, bile production at day-1, 3, 5 and 7, factor V at day-1, 5, 7, 10 and 30, prothrombin ratio,  $\gamma$ -GT and  $\alpha$ -FP at day-1, 3, 5, 7, 10 and 30, numbers of CD3, CD4, CD8, NK and B lymphocytes, CD4/CD8 ratio, and phagocytic capacity of monocytes and granulocytes at day-5 and 30 using the Phagotest kit (Orpegen, Heidelberg, Germany), the number,

type (local or systemic) and delay of occurrence of postoperative infections, and the number and type of other adverse events (either related or not to treatment).

#### Sample size and statistical analysis

In a retrospective analysis of the patients hospitalized in our surgical intensive care unit after liver resection for primary or secondary liver cancer with cirrhosis, we estimated that factor V at day-3 post surgery was  $35 \pm 15\%$  (mean  $\pm$  standard deviation). We computed that 50 patients were required to detect an increase of 15% of this mean value with 95% power in a bilateral test performed with a 5% type I error.

All statistical analyses were performed using SAS v 9.1.3 software (SAS Institute, Cary, NC, USA). Data are expressed as means  $\pm$  standard deviations [95% confidence intervals, CI] or number of patients (percentages). Continuous variables were compared between groups using Student t test or Wilcoxon *T* test, as appropriate. Categorical variables were compared between groups using chi square test or Fisher exact test, as appropriate. The delays of occurrence of the first postoperative infection (censored variable) were compared between groups using the log-rank test. For all analyses, a p-value  $< 0.05$  was considered statistically significant.

#### Results

All inclusions were performed between April 9, 2003 and February 27, 2008. On July 22, 2008, the sponsor, the principal investigator and the methodologist met and decided to stop the study because the inclusion rate had dramatically slowed down during the 7 first months of 2008 with only one inclusion.

#### *Study flow chart*

A total of 35 patients (placebo: 17; Oral Impact®: 18) were included in the study (figure 1). Five patients (placebo: 3; Oral Impact®: 2) were not operated and 5 patients (placebo: 2; Oral Impact®: 3)

were operated but did not undergo hepatic resection. Thus 25 patients (placebo: 12; Oral Impact®: 13) were evaluated for efficacy.

Two patients (Oral Impact® group) did not receive randomized treatment at all, one because of a supply problem and the other because of the detection, just before treatment delivery, of a weight loss of more than 10% during the 6 months preceding inclusion. Thus 33 patients (placebo: 17; Oral Impact®: 16) could be evaluated for treatment tolerance. Among the 33 patients who received study treatment, 8 patients (placebo: 5; Oral Impact®: 3) received their treatment during the 7 pre-operative days only because they did not undergo hepatic resection.

#### *Baseline characteristics, treatment before surgery, hepatic surgery characteristics, and compliance*

There was no significant difference between groups for baseline characteristics (table 2). Seven patients in each group had chemoembolization ( $p=0.890$ ) and 8 patients in each group had portal vein embolization ( $p=0.877$ ) prior to surgery. There was no significant difference between groups for hepatic surgery characteristics (table 3).

Among the 33 patients who received study treatment, a high preoperative compliance, as defined by  $>80\%$  of sachets taken during the 7 preoperative days, was observed in 27 patients (placebo: 13, Oral Impact®: 14). Two patients had a medium compliance, and for the 4 last patients, data were missing.

Among the 25 patients who underwent hepatectomy, the post-operative compliance was also high: full compliance was recorded in 17 patients, and only one sachet was missed for 4 patients. Overall, no significant difference between the two groups was observed.

#### *Primary outcome*

Two patients (Oral Impact® group) were not evaluated on day-3 post surgery for the main endpoint. Mean  $\pm$  standard deviation [95% CI] factor V on day-3 post surgery was  $70\pm 27\%$  [53% ; 87%] and  $79\pm 25\%$  [62% ; 96%] ( $p=0.409$ ) in placebo and Oral Impact® groups, respectively. Estimated effect size [95% CI] was 9% [-13% ; +32%]. Normalized ( $> 80\%$ ) factor V on day-3 post surgery was observed in 3/12 (25%, [0% ; 50%]) and 6/11 (55%, [25% ; 84%]) in placebo and Oral Impact® groups, respectively ( $p=0.214$ ). Estimated effect size [95% CI] was 30% [-9% ; +68%].

### *Liver function recovery*

There was no statistically significant difference between the two groups on liver volume at day-10 ( $p=0.229$ ) and day-30 ( $p=0.655$ ) and on bile production at day-1, 3, and 5 (figure 2).

There was no statistically significant difference between the two groups on the evolutions with time until day-30 of factor V and prothrombin ratio levels (figure 3). There was no statistically significant difference between the two groups on the percentage of patients with normalized factor V at day-1 ( $p=0.322$ ), day-5 ( $p=0.090$ ), day-7 ( $p=0.155$ ), day-10 ( $p=1.000$ ) and day-30 ( $p=1.000$ ).

There was no statistically significant difference between the two groups on the other secondary outcomes assessing liver function recovery except for  $\gamma$ -GT and  $\alpha$ -FP at day 7:  $\gamma$ -GT levels were  $146\pm 95$  and  $247\pm 147$  IU/L ( $p=0.043$ ) in placebo and Oral Impact® groups, respectively, and  $\alpha$ -FP levels were  $18\pm 34$  and  $33\pm 49$   $\mu\text{g/L}$  ( $p=0.030$ ) in placebo and Oral Impact® groups, respectively (figure 3).

### *Immune response*

There was no statistically significant difference between the two groups on the immunological biomarkers at day 5 (table 4), except for the phagocytic capacity of monocytes ( $p=0.018$ ) and of granulocytes ( $p=0.003$ ) which were reduced in the Oral Impact® group as compared to the placebo group (-8.3% and -9.4%, respectively).

There was no statistically significant difference between the two groups in the response of lymphocytes to Pokweed mitogen, phyto-hemagglutinin, and concanavalin A, both at day 5 ( $p=0.603$ ,  $p=1.000$ , and  $p=0.211$ , respectively) and at day 30 ( $p=0.161$ ,  $p=0.307$ , and  $p=0.362$ , respectively).

### *Post-operative infections*

Four patients in the placebo group and 1 patient in the Oral Impact® group had at least one infection. There was no statistically significant difference between the two groups in the percentages of patients with at least one infection ( $p=0.157$ ). For the 4 patients of the placebo group, 7 infections were declared with 3 surgical site infections (1 abdominal wall abscess, 1 intra-abdominal abscess, and 1

ascites infection), 2 urinary tract infections, 1 staphylococcal bacteremia and 1 Clostridium difficile-associated diarrhea. For the patient of the Oral Impact® group, 2 surgical site infections were declared (2 postoperative peritonitis). There was no statistically significant difference between the two groups in the percentages of patients with at least one surgical site infection ( $p=0.316$ ) and in the percentages of patients with at least one systemic infection ( $p=0.586$ ). There was no statistically significant difference between the two groups on the delays of occurrence of the first postoperative infection ( $p=0.262$ ).

#### *Adverse events related to treatment (tolerance)*

Among the 33 patients who received study treatment, no adverse event related to treatment was reported.

#### *Adverse events not related to treatment*

Among the 35 patients randomized, 22 patients underwent 31 adverse events: 12 patients had 18 adverse events in the placebo group and 10 patients had 13 adverse events in the Oral Impact® group. Among the 31 adverse events, 20 serious adverse events were recorded: 9 in the placebo group and 11 in the Oral Impact® group.

Ten adverse events led to hepatectomy cancellation (6 tumor progressions, 2 ascites and edema, 1 hepatic atrophy, 1 psoriatic arthropathy aggravation). The other 21 adverse events occurred the day of surgery or during the post-operative period. Among them, 5 were directly linked to hepatic surgery (3 hepatic bleeding, 1 biliary fistula, and 1 abdominal pain).

## **Discussion**

In liver cirrhosis and cancer patients, malnutrition is a common feature which increases the risk of postoperative complications, mainly infectious (18-26). Moreover, liver cirrhosis enhances the risk of post-resection liver failure (7). The properties of L-arginine and  $\omega$ 3-polyunsaturated fatty acids led us

to evaluate the impact of a perioperative immunonutrition in patients who had a high degree of liver fibrosis or cirrhosis, liver cancer and who needed partial hepatectomy.

We did not find any favorable effect of a 10-day perioperative nutritional supplementation with Oral Impact® in patients undergoing hepatic surgery for liver cancer. Since the sample size was lower than calculated, this result could reflect insufficient power. However, there was no tendency for a difference between groups, both on the main and secondary endpoints, and this hypothesis is not the most likely. Finally, we just found significant differences between the two groups on the phagocytic capacity of monocytes and granulocytes and these differences were not in favor of Oral Impact®.

Our results contrast with those of studies performed in gastrointestinal surgery for cancer in which two recent meta-analyses showed that immunonutrition significantly reduced overall complications, whatever the time of administration (preoperative, both pre and postoperative, postoperative) (20, 21). Moreover, in patients who had gastrointestinal surgery, a perioperative immunonutrition was shown to lower the rate of postoperative infections, the duration of antibiotic use and the length of hospital stay, whatever the preoperative nutritional status of the patients (27-29). Finally, a perioperative immunonutrition was also shown to improve postoperative immunity, to prevent the early postoperative impairment of phagocytosis and to decrease the inflammatory response (IL-6 and TNF- $\alpha$ ) observed after major surgery (30-34). However, liver regeneration after partial hepatectomy is a complex and non univocal process where cytokines, mainly TNF- $\alpha$  and IL-6, play a central initiating role (35). In such a specific context, limiting the postoperative inflammatory response, as probably done by perioperative immunonutrition, may explain why we did not find any improvement in hepatic function. Concerning the phagocytic capacity of monocytes and granulocytes, a daily measure of these variables between day-0 and day-5 would have been useful to help in the interpretation of the Oral Impact® induced-decrease. On the other hand,  $\gamma$ -GT and  $\alpha$ -FP, two biomarkers of hepatocellular regeneration (36), were both increased in the oral Impact® group suggesting that the recovery of a functional liver mass was enhanced but without a strong impact on the hepatic function, as assessed by factor V and liver volume at day-10 and day-30. Moreover, the mean value of factor V at day-3 was 70% whereas 35% was expected. Such a difference probably resulted from the improvements of

the management of liver cancer which occurred during the period of the study and were not initially anticipated, notably embolization of the portal vein, chemo-embolization and intermittent clamping. It is noteworthy that concomitantly to the application of these new strategies, the mortality rate of liver resection considerably decreased, from > 10% to < 5% during the last decades (37, 38).

In conclusion, although well-tolerated, a 10-day administration of a nutritional supplementation with Oral Impact® did not show any tendency to improve hepatic function in patients undergoing hepatic surgery for liver cancer.

**This work was done at the university hospital from Rennes (France)**

**Corresponding author:** Pr. Seguin Philippe. Service de Réanimation Chirurgicale. Hôpital de Pontchaillou, 2 Rue Henri Le Guilloux, 35033 Rennes cedex, France. Tel: (33)299289371. Fax: (33)299282421. E-mail: [philippe.seguin@chu-rennes.fr](mailto:philippe.seguin@chu-rennes.fr)

**Funding source:** The study was selected and supported by the 2005 Regional Clinical Research Hospital Program (R0903).

**Acknowledgments:** none

Accepted manuscript

**References**

1. Belghiti J, Hiramatsu K, Benoist S, Massault P, Sauvanet A, et al. Seven hundred forty-seven hepatectomies in the 1990s: an update to evaluate the actual risk of liver resection. *J Am Coll Surg* **191**, 38-46, 2000.
2. Grazi GL, Cescon M, Ravaioli M, Ercolani G, Gardini A, et al. Liver resection for hepatocellular carcinoma in cirrhotics and noncirrhotics. Evaluation of clinicopathologic features and comparison of risk factors for long-term survival and tumour recurrence in a single centre. *Aliment Pharmacol Ther* **17** (2 suppl), 119S-129S, 2003.
3. Balzan S, Belghiti J, Farges O, Ogata S, Sauvanet A et al. The "50-50 criteria" on postoperative day. An accurate predictor of liver failure and death after hepatectomy. *Ann Surg* **242**, 824-829, 2005.
4. Capussotti L, Muratore A, Amisano M, Polastri R, Bouzari H, et al. Liver resection for hepatocellular carcinoma on cirrhosis: analysis of mortality, morbidity and survival--a European single center experience. *Eur J Surg Oncol* **31**, 986-993, 2005.
5. Midorikawa Y, Kubota K, Takayama T, Toyoda H, Ijichi M, et al. A comparative study of postoperative complications after hepatectomy in patients with and without chronic liver disease. *Surgery* **126**, 484-491, 1999.
6. Poon RT, Fan ST, Lo CM, Liu CL, Lam CM, et al. Extended hepatic resection for hepatocellular carcinoma in patients with cirrhosis: is it justified? *Ann Surg* **236**, 602-611, 2002.
7. Hammond JS, Guha IN, Beckingham IJ, Lobo DN. Prediction, prevention and management of postresection liver failure *Br J Surg* **98**, 1188-1200, 2011.
8. Selzner N, Rudiger H, Graf R, Clavien PA. Protective strategies against ischemic injury of the liver. *Gastroenterology* **125**, 917-936, 2003
9. McClave SA, Snider HL, Spain DA. Preoperative issues in clinical nutrition. *Chest* **115** (5 suppl), 64S-70S, 1999.
10. Merli M, Nicolini G, Angeloni S, Riggio O. Malnutrition is a risk factor in cirrhotic patients undergoing surgery. *Nutrition* **18**: 978-986, 2002.

11. Read JA, Choy ST, Beale PJ, Clarke SJ. Evaluation of nutritional and inflammatory status of advanced colorectal cancer patients and its correlation with survival. *Nutr Cancer* **55**: 78-85, 2006.
12. Huhmann MB, August DA. Perioperative nutrition support in cancer patients. *Nutr Clin Pract* **27**, 586-592, 2012.
13. Kearns PJ, Young H, Garcia G, Blaschke T, O'Hanlon G, Rinki M, Sucher K, Gregory P. Accelerated improvement of alcoholic liver disease with enteral nutrition. *Gastroenterology* **102**, 200-205, 1992.
14. Schreckenbach T, Liese J, Bechstein WO, Moench C. Posthepatectomy liver failure. *Dig Surg* **29**, 79-85, 2012.
15. Schloerb PR. Immune-enhancing diets: products, components, and their rationales. *JPEN J Parenter Enteral Nutr* **25** (2 suppl), 3S-7S, 2001.
16. Todd SR, Gonzalez EA, Turner K, Kozar RA. Update on postinjury nutrition. *Curr Opin Crit Care* **14**, 690-695, 2008.
17. Yokoyama Y, Ebata T, Igami T, Sugawara G, Ando M, Nagino M. Predictive power of prothrombin time and serum total bilirubin for postoperative mortality after major hepatectomy with extrahepatic bile duct resection. *Surgery* **155**, 504-511, 2014.
18. Snyderman CH, Kachman K, Molseed L, Wagner R, D'Amico F, et al. Reduced postoperative infections with immune-enhancing nutritional supplement. *Laryngoscope* **109**, 915-921, 1999.
19. Felekis D, Eleftheriadou A, Papadakos G, Bosinakou I, Ferekidou E, et al. Effect of perioperative immuno-enhanced enteral nutrition on inflammatory response, nutritional status, and outcomes in head and neck cancer patients undergoing major surgery. *Nutr Cancer* **62**, 1105-1112, 2010.
20. Marik PE, Zaloga GP. Immunonutrition in high-risk surgical patients: a systematic review and analysis of the literature. *JPEN J Parenter Enteral Nutr* **34**, 378-386, 2010.
21. Cerantola Y, Hübner M, Grass F, Demartines N, Schäfer M, et al. Immunonutrition in gastrointestinal surgery. *Br J Surg* **98**, 37-48, 2011.
22. Tepaske R, Velthuis H, Oudemans-van Straaten HM, Heisterkamp SH, van Deventer SJ, et al. Effect of preoperative oral immune-enhancing nutritional supplement on patients at high risk of infection after cardiac surgery: a randomised placebo-controlled trial. *Lancet* **358**, 696-701, 2001.

23. DiCecco SR, Francisco-Ziller N. Nutrition in alcoholic liver disease. *Nutr Clin Pract* **21**, 245-254, 2006.
24. Alberino F, Gatta A, Amodio P, Merkel C, Di Pascoli L, et al. Nutrition and survival in patients with liver cirrhosis. *Nutrition* **17**, 445-450, 2001.
25. Navasa M. Bacterial infections in patients with cirrhosis: reasons, comments and suggestions. *Dig Liver Dis* **33**, 9-12, 2001.
26. Argilés JM. Cancer-associated malnutrition. *Eur J Oncol Nurs* **9(2 Suppl)**, 39S-50S, 2005.
27. Braga M, Gianotti L, Radaelli G, Vignali A, Mari G, et al. Perioperative immunonutrition in patients undergoing cancer surgery: results of a randomized double-blind phase 3 trial. *Arch Surg* **134**, 428-433, 1999.
28. Senkal M, Zumtobel V, Bauer KH, Marpe B, Wolfram G et al. Outcome and cost-effectiveness of perioperative enteral immunonutrition in patients undergoing elective upper gastrointestinal tract surgery. *Arch Surg* **134**, 1309-1316, 1999.
29. Okamoto Y, Okano K, Izuishi K, Usuki H, Wakabayashi H et al (2009) Attenuation of the systemic inflammatory response and infectious complications after gastrectomy with preoperative oral arginine and omega-3 fatty acids supplemented immunonutrition. *World J Surg* **33**, 1815-821, 2009.
30. Braga M, Gianotti L, Vignali A, Carlo VD. Preoperative oral arginine and n-3 fatty acid supplementation improves the immunometabolic host response and outcome after colorectal resection for cancer. *Surgery* **132**, 805-814, 2002.
31. Daly JM, Lieberman MD, Goldfine J, Shou J, Weintraub F et al. Enteral nutrition with supplemental arginine, RNA, and omega-3 fatty acids in patients after operation: immunologic, metabolic, and clinical outcome. *Surgery* **112**, 56-67, 1992.
32. Gianotti L, Braga M, Vignali A, Balzano G, Zerbi A et al. Effect of route of delivery and formulation of postoperative nutritional support in patients undergoing major operations for malignant neoplasms. *Arch Surg* **132**, 1222-1229, 1997.

33. Gianotti L, Braga M, Fortis C, Soldini L, Vignali A et al. A prospective, randomized clinical trial on perioperative feeding with an arginine-, omega-3 fatty acid-, and RNA-enriched enteral diet: effect on host response and nutritional status. *JPEN J Parenter Enteral Nutr* **23**, 314-320, 1999.
34. Giger U, Büchler M, Farhadi J, Berger D, Hüsler J et al. Preoperative immunonutrition suppresses perioperative inflammatory response in patients with major abdominal surgery-a randomized controlled pilot study. *Ann Surg Oncol* **14**, 2798-2806, 2007.
35. Michalopoulos GK. Liver regeneration after partial hepatectomy: critical analysis of mechanistic dilemmas. *Am J Pathol* **176**, 2-13, 2010.
36. Horn KD, Wax P, Schneider SM, Martin TG, Nine JS et al. Biomarkers of liver regeneration allow early prediction of hepatic recovery after acute necrosis. *Am J Clin Pathol* **112**, 351-357, 1999.
37. Thompson HH, Tompkins RK, Longmire WP. Major hepatic resection. A 25-year experience. *Ann Surg* **197**, 375-388, 1983.
38. Virani S, Michaelson JS, Hutter MM, Lancaster RT, Warshaw AL et al. Morbidity and mortality after liver resection: results of the patient safety in surgery study. *J Am Coll Surg* **204**, 1284-1292, 2007.

**Legend for figures**

**Figure 1:** Flow chart

**Figure 2:** Evolution with time of liver volume (A) and bile production (B)

**Figure 3:** Evolution with time of factor V (A), prothrombin ratio (B),  $\gamma$ -GT (C), and  $\alpha$ -FP (D)

Accepted manuscript

**Table 1:** Formulations of Placebo and Oral Impact®

|                                     | <b>Placebo</b>         | <b>Oral Impact®</b>    |
|-------------------------------------|------------------------|------------------------|
| <b>Appearance</b>                   | Sachet of powder, 74 g | Sachet of powder, 74 g |
| <b>Energy, kcal</b>                 | 307                    | 309                    |
| <b>Energy source</b>                |                        |                        |
| <b>Protein</b>                      | 28%                    | 22%                    |
| <b>Carbohydrate</b>                 | 47%                    | 53%                    |
| <b>Fat</b>                          | 25%                    | 25%                    |
| <b>Protein, g</b>                   | 21.3                   | 16.8                   |
| <b>L-arginine, g</b>                | 0                      | 3.8                    |
| <b>Carbohydrate, g</b>              | 36.6                   | 40.2                   |
| <b>Maltodextrin, g</b>              | 0                      | 18.2                   |
| <b>Fat, g</b>                       | 8.4                    | 8.3                    |
| <b>Omega-3 fatty acid, g</b>        | 0                      | 1.0                    |
| <b>Medium-chain triglyceride, g</b> | 2.88                   | 2.2                    |
| <b>Ribonucleic acid, g</b>          | 0                      | 0.4                    |
| <b>Fiber, g</b>                     | 0                      | 3.0                    |
| <b>Sodium, mg</b>                   | 321                    | 321                    |
| <b>Potassium, mg</b>                | 402                    | 402                    |
| <b>Phosphore, mg</b>                | 216                    | 216                    |
| <b>Taste</b>                        | coffee                 | coffee                 |

**Table 2:** Baseline characteristics (patients randomized)

|   | <b>Placebo</b><br>(n = 17) | <b>Oral Impact®</b><br>(n = 18) | <b>p-value</b> |
|---|----------------------------|---------------------------------|----------------|
| <b>Age, years</b>                                 | 68±6                       | 65±8                            | 0.239          |
| <b>Sex, male (%)</b>                              | 14 (82.4)                  | 17 (94.4)                       | 0.338          |
| <b>Height, cm</b>                                 | 169±6 #                    | 169±5                           | 0.974          |
| <b>Usual weight, kg</b>                           | 80±16                      | 77±13                           | 0.449          |
| <b>Body Mass Index</b>                            | 28.0±4.6 #                 | 26.9±4.5                        | 0.462          |
| <b>Current weight, kg</b>                         | 79±15                      | 75±13                           | 0.417          |
| <b>Weight loss during the last 6 months, %</b>    | 1.6±2.4                    | 1.9±3.9                         | 0.559          |
| <b>Child-Pugh score</b>                           |                            |                                 |                |
| <b>A5 (%)</b>                                     | 11 (64.7)                  | 14 (77.8)                       | 0.196          |
| <b>A6 (%)</b>                                     | 6 (35.3)                   | 2 (11.1)                        |                |
| <b>B7 (%)</b>                                     | 0 (0.0)                    | 1 (5.6)                         |                |
| <b>B8 (%)</b>                                     | 0 (0.0)                    | 1 (5.6)                         |                |
| <b>γ-glutamyl transferase, (RR: &lt; 55 IU/L)</b> | 211±214                    | 154±87                          | 1.000          |
| <b>α-foeto protein, (RR: &lt; 10 µg/L)</b>        | 263±591 \$                 | 757±2794 #                      | 0.940          |
| <b>Albumin, (RR: 35 – 50 g/l)</b>                 | 38.0±5.3                   | 38.7±4.8                        | 0.702          |
| <b>Pre-albumin, (RR: 0.2 – 0.4 g/l)</b>           | 0.18±0.08 #                | 0.18±0.08 \$                    | 0.912          |
| <b>Prothrombin ratio, (RR: 70 – 120 %)</b>        | 81±9                       | 82±19                           | 0.240          |
| <b>Factor V, (RR: 70 – 120 %)</b>                 | 106±20 #                   | 108±21 #                        | 0.719          |

Continuous variables are means ± standard deviations. Categorical variables are numbers of patients (percentages). For continuous variables, the p-values are those of the Student t test except for weight loss, γ-glutamyl transferase, α-foeto protein and prothrombin ratio for

which they are those of the Wilcoxon  $T$  test. For categorical variables, the p-values are those of the Fisher exact test. RR: reference range. #: 1 missing value. \$: 2 missing values.

Accepted manuscript

**Table 3:** Hepatic surgery characteristics (patients operated)

|  | <b>Placebo<br/>(n = 14)</b> | <b>Oral Impact®<br/>(n = 16)</b> | <b>p-value</b> |
|--|-----------------------------|----------------------------------|----------------|
| <b>Hepatic vascular occlusion, yes</b>     | 9 (64.3)                    | 11 (68.8)                        | 1.000          |
| <b>Nature of vascular occlusion</b>        |                             | #                                | 1.000          |
| <b>Continuous</b>                          | 1 (11.1)                    | 2 (20.0)                         |                |
| <b>Intermittent</b>                        | 8 (88.9)                    | 8 (80.0)                         |                |
| <b>Duration of vascular occlusion, min</b> | 26.9 ± 8.4                  | 30.8 ± 8.9 #                     | 0.339          |
| <b>Number of segments resected</b>         |                             |                                  | 0.895          |
| <b>None</b>                                | 2 (14.3)                    | 3 (18.8)                         |                |
| <b>1</b>                                   | 0 (0.0)                     | 1 (6.2)                          |                |
| <b>2</b>                                   | 1 (7.1)                     | 2 (12.5)                         |                |
| <b>3</b>                                   | 3 (21.4)                    | 1 (6.2)                          |                |
| <b>4</b>                                   | 4 (28.6)                    | 4 (25.0)                         |                |
| <b>5</b>                                   | 4 (28.6)                    | 5 (31.3)                         |                |
| <b>Transfusion, yes</b>                    | 4 (28.6)                    | 1 (6.3)                          | 0.157          |

Duration of vascular occlusion is mean ± standard deviation. Other variables are numbers of patients (percentages). For duration of vascular occlusion, the p-value is that of the Student t test. For other variables, the p-values are those of the Fisher exact test. #: 1 missing value.

**Table 4:** Immunological results at day-5 post-surgery (patients operated and resected)

|  | <b>Placebo</b><br><b>(n = 12)</b> | <b>Oral Impact®</b><br><b>(n = 13)</b> | <b>p-value</b> |
|--|-----------------------------------|--|----------------|
| <b>Lymphocytes, (RR: 1000 – 4000 /mm<sup>3</sup>)</b>                      | 1488 ± 1014                       | 1708 ± 1068                            | 0.371          |
| <b>CD3, (RR: 1000 – 2200 /mm<sup>3</sup>)</b>                              | 1007 ± 648                        | 1057 ± 469 #                           | 0.831          |
| <b>CD4, (RR: 530 – 1300 /mm<sup>3</sup>)</b>                               | 735 ± 481                         | 692 ± 256 #                            | 0.778          |
| <b>CD8, (RR: 330 – 920 /mm<sup>3</sup>)</b>                                | 253 ± 202                         | 355 ± 303 #                            | 0.299          |
| <b>CD4/CD8 ratio (RR: 1.1 – 2.9)</b>                                       | 4.5 ± 4.5                         | 2.8 ± 1.9 #                            | 0.285          |
| <b>NK, (RR: 70 – 480 /mm<sup>3</sup>)</b>                                  | 197 ± 200                         | 217 ± 116 #                            | 0.285          |
| <b>B, (RR: 110 – 570 /mm<sup>3</sup>)</b>                                  | 263 ± 236                         | 405 ± 636 #                            | 0.707          |
| <b>CD3+DR+, %</b>  | 12 ± 10                           | 9 ± 6 #                                | 0.602          |
| <b>CD3+CD25+, %</b>  | 25 ± 15                           | 23 ± 12 #                              | 0.687          |
| <b>CD25+DR+, %</b>   | 4 ± 2                             | 6 ± 7 \$                               | 0.901          |
| <b>CD25+, %</b>  | 30 ± 17                           | 30 ± 15 \$                             | 0.908          |
| <b>CD14+, %</b>  | 0.5 ± 0.5                         | 0.9 ± 2.0 #                            | 0.869          |
| <b>Phago-test, monocytes, arbitrary unit based on mean fluorescence</b>    | 683 ± 49                          | 626 ± 40 #                             | <b>0.018</b>   |
| <b>Phago-test, granulocytes, arbitrary unit based on mean fluorescence</b> | 733 ± 59                          | 664 ± 39 #                             | <b>0.003</b>   |

Variables are means ± standard deviations. The p-values are those of the Student t test except for lymphocytes, CD8, CD4/CD8 ratio, NK, B lymphocytes, CD3+DR+, CD25+DR+, CD14+, phago-test monocytes for which they are those of the Wilcoxon *T* test. RR: reference range. #: 1 missing value. \$: 2 missing values.

Figure 1.

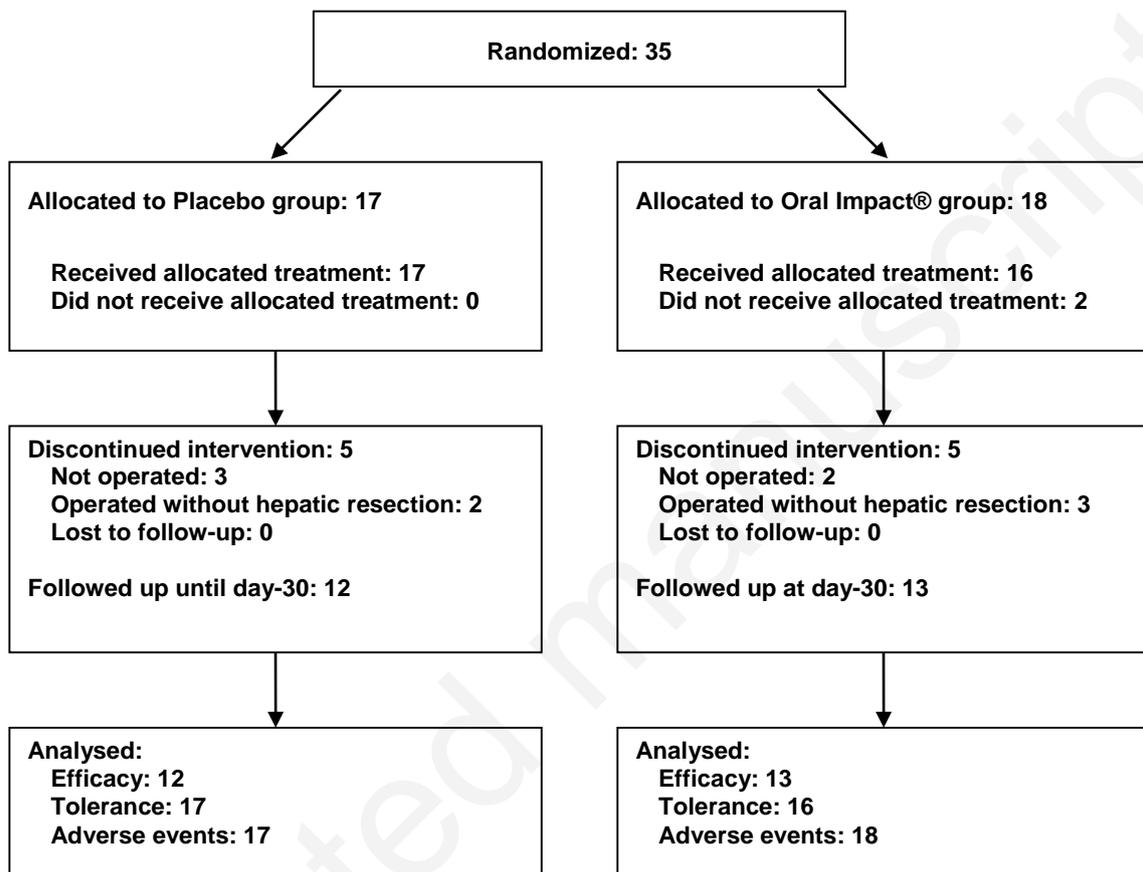
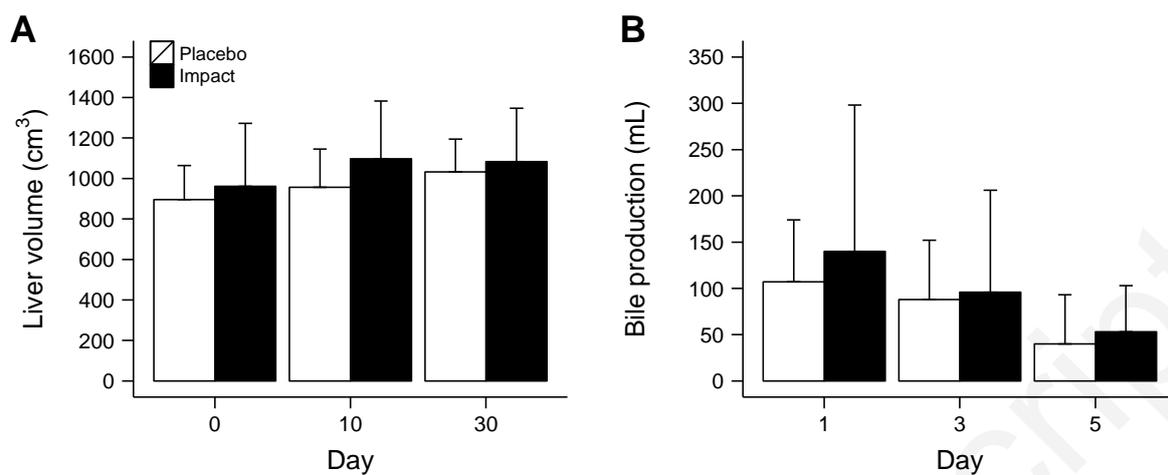
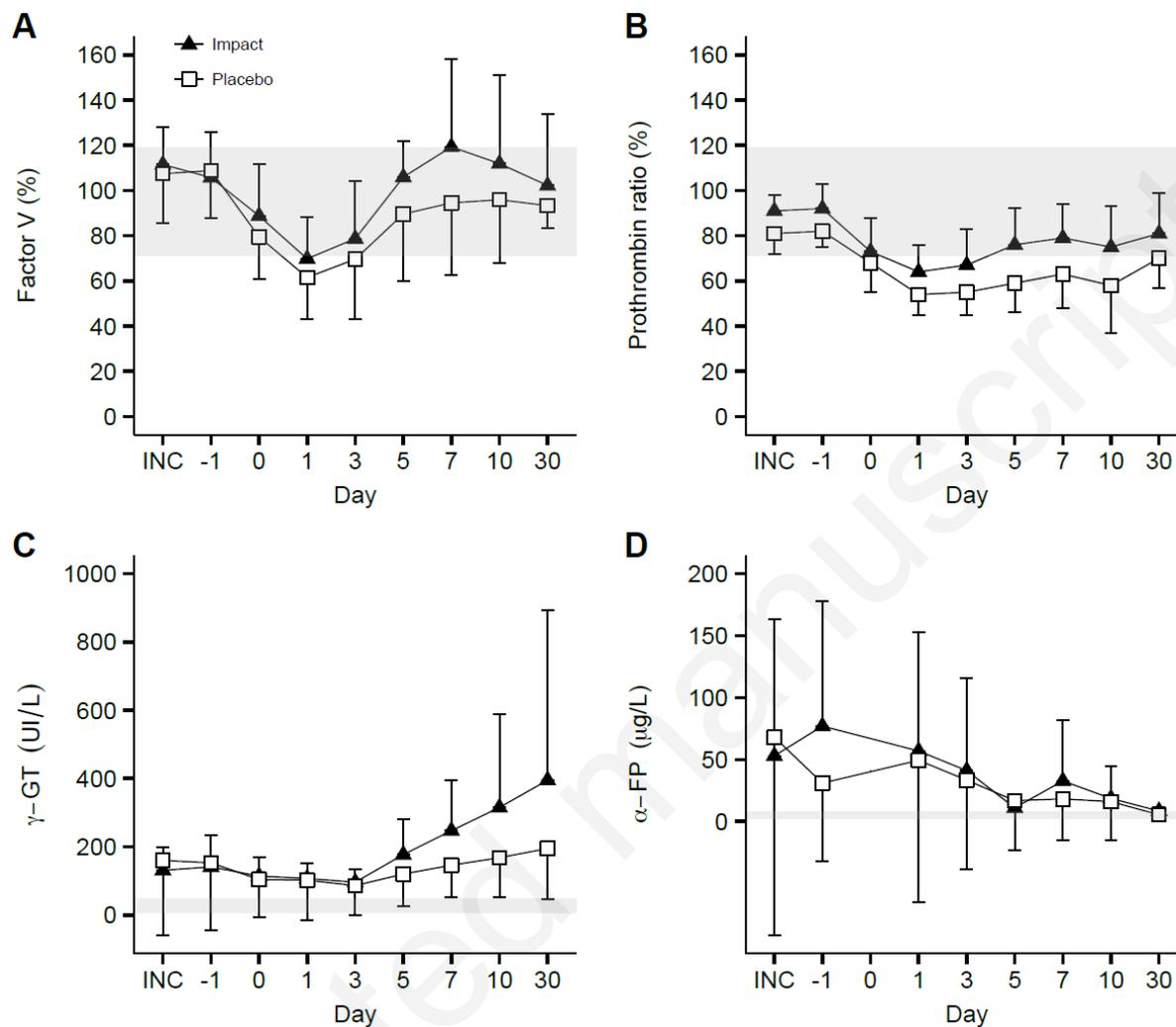


Figure 2:



Due to catheter obstruction, bile production could not be measured at day 1 and 3 in 9 patients (placebo: 4, Oral Impact®: 5), and at day 5 in 16 patients (placebo: 9, Oral Impact®: 7).

Figure 3.



Gray-shaded areas represent reference range in adults. INC: inclusion.