Enteral versus parenteral nutrition in the conservative treatment of upper gastrointestinal fistula after surgery: a multicenter, randomized, parallel-group, open label, phase III study (NUTRILEAK study)

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Abstract

Background: Postoperative Upper Gastro-Intestinal Fistula (PUGIF) is a devastating complication, leading to a high mortality rate reaching up to 80%, increased length of hospital stay, reduced Health related quality of life (HRQOL) and increased health costs. Nutritional support is a key component of therapy in such cases, related to the high prevalence of malnutrition. In prophylactic setting, enteral nutrition (EN) is associated to shorter hospital stay, lower incidence of severe infectious complications, lower severity of complications and decreased cost compared to total parenteral nutrition (TPN) following major upper gastrointestinal (GI) surgery. In curative setting after fistula occurrence, there are very few evidences available. We hypothesise that EN increases 30-day fistula closure rate in PUGIF, allowing better HRQOL without increasing morbi-mortality. Methods/Design: The NUTRILEAK trial is a multicenter, randomized, parallel-group, open label phase III trial to assess the efficacy of EN (experimental group) compared with TPN (control group) in patients with PUGIF. The primary objective of the study is to compare EN versus TPN in the treatment of PUGIF (after oesophago-gastric resection including bariatric surgery, duodeno-jejunal resection or pancreatic resection with digestive tract violation) in terms of 30-day fistula closure rate. Secondary objectives are to evaluate the 6-month post-randomization fistula closure rate, time of first fistula closure (in days), medical and surgical treatment-related complication rate at 6 months after randomization, fistula related complication rate at 6 months after randomization, type and severity of early (30 days after randomization) and late fistula-related complications (over 30 days after randomization), 30-day and 6-month post-randomization mortality rate, nutritional status at day 30, day 60, day 90 and day 180 post randomization, mean length of hospital stay, patient’s Health related quality of life (HRQOL) (self-assessment questionnaire), oral feeding time and direct costs of treatment. A total of 321 patients will be enrolled.
Discussion: The two nutritional supports are already used in daily practice, but most surgeons are reluctant to use the enteral route in case of PUGIF. This study will be the first randomized trial testing the role of EN versus TPN in PUGIF. Trial registration: ClinicalTrials.gov, NCT03742752. Registered on 14 November 2018.

Background

The incidence of clinically significant postoperative upper gastrointestinal fistula (PUGIF) surgery is approximately 4%-20%, and the associated mortality can be as high as 80% [1]. Clinical presentations may vary from minimally symptomatic to life-threatening situations. Investigations should be undertaken as soon as the diagnosis is suspected because delay greatly worsens the prognosis. Communication and multidisciplinary teamwork are the cornerstones of treatment. When the PUGIF occurs early with acute and important sepsis, the recommendation is surgical treatment. On the contrary, if the fistula occurs later and is non-symptomatic or minimally symptomatic, conservative management with intensive surveillance can be proposed. When the situation is in between these two extremes, endoscopic treatment is often proposed [2,3]. Computerized tomography scans (ct-scan) with oral contrast and low insufflation early endoscopy are the preferred diagnostic tools. Common principles are i) transfer to intensive care unit in case of sepsis, ii) optimization of perfusion, iii) optimization of respiratory function with pulmonary support and intense physiotherapy, iv) large spectrum intravenous antibiotics and antifungal treatment. Any collection located at the anastomosis level should be drained, via radiological, or endoscopic or surgical drain. During this procedure, a fistula-closing attempt may potentially be performed, especially when the PUGIF is diagnosed early with the absence of ischemia [2].

Various promising endoscopic techniques in the treatment of PUGIF have been recently reported (such as over-the-scope (OVESCO)-clip®), but only through very small series or
case reports, and more often in the field of bariatric surgery [4]. The results should therefore be interpreted with caution, offering information more on feasibility than on efficiency. Haemostatic clips associated with fibrin biological glue have been designed for endoscopic management of PUGIF. The limitations are that these clips do not allow treatment of large defects and are not resistant enough to bring together distant anastomotic inflamed edges [2,4,5]. Somatostatin analogues have been demonstrated to reduce fistula output [3,6].

Several prognosis factors of PUGIF have been identified [7]: such as high output, high concentration of toxic bile acids and active digestive enzymes, length of fistula tract larger than 2 cm, elevated postoperative blood glycemia [8] and malnutrition with a serum albumin of <30g/ L [3].

Nutritional support is a key component of PUGIF management, related to high prevalence of malnutrition and nil per mouth required for fistula treatment [9,10]. Therefore, despite fasting, nutritional support is mandatory, and both routes, enteral downstream of the site of leakage (via a feeding jejunostomy or a nasojejunal feeding tube placed radiologically or endoscopically) [11] or parenteral, are possible and currently used. However, the role of enteral nutrition (EN) in maintaining the small intestinal structure and function and in improving postoperative outcomes is well established. Enteral nutrients maintain the structural function compromised by fasting and parenteral nutrition [12,13].

In the prophylactic setting, before the occurrence of any fistula, a literature review based on seven randomized trials showed that EN is associated with shorter hospital stay, lower incidence of severe infectious complications [14], lower severity of complications and decreased costs compared to total parenteral nutrition (TPN) following major upper gastrointestinal (upper GI) surgery [1,15].

In the curative setting, after the fistula occurrence, there are very few evidences
available. Only one randomized clinical trial has suggested the superiority of EN versus TPN after pancreatic surgery with an increase of the 30-day fistula closure rate from 37% in the TPN group to 60% in the EN group [16]. This trial only included pancreatic fistula and did not include all PUGIF that can also occur after oesophago-gastric resection including bariatric surgery, duodeno-jejunal resection or pancreatic resection with digestive tract violation, although the concept of enteral nutritional support is highly relevant in all these situations. Even if EN seems to be promising, the potential risk of increasing the leakage output related to a reflux of nutritional liquid and/or to activate digestive enzymes, consequently reducing the probability of fistula closure rate or increasing the delay of fistula closure, may explain why surgeons are usually reluctant to provide EN [17]. Few small randomized studies suggested the feasibility of EN in 47 patients with upper GI fistula [18], in the treatment of oesophago-jejunal fistula after total gastrectomy in gastric cancer patients [19] and after PUGIF following sleeve gastrectomy [20, 21] but to date no randomized study has been designed to test the superiority of EN versus TPN in PUGIF.

The study aim is consequently to demonstrate the superiority of EN versus TPN in accelerating fistula healing after upper GI surgery.

Methods/design

1. Protocol overview

The NUTRILEAK trial is a multicenter, randomized, parallel-group, open label, phase III study to assess the efficacy of EN compared to TPN in patients with PUGIF. After informed consent, patients will be randomized in a 2:1 ratio to the EN treatment arm and the TPN comparator arm (Figure 1). Patients will be randomized to receive EN through jejunostomy or nasojejunal tube, or to receive TPN through central venous access, picc line, totally implantable venous access or any other approved total parenteral nutrition device.
During the whole study period, other surgical or endoscopic procedures aiming at directly closing the defect will not be allowed (including surgical closure and endoscopic clip, prosthesis or glue). All these measures have anyway not been scientifically demonstrated as efficient in this situation at that time, and can be a confounding factor regarding our primary objective.

On the contrary, surgical, radiological or endoscopic fistula drainage will be allowed during the whole study period. Any interruption of more than 24 hours of the treatment determined by randomization (EN or TPN) will be reported with the cause, duration and solutions given. During hospitalization, patients will be daily evaluated until fistula closure, looking for any fistula or protocol treatment-related complication through physical examination and, if required, through routine laboratory tests and/or imaging according to each center practice.

The present study protocol was written in compliance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 [22]. A completed SPIRIT checklist is available as a supplement (Additional file 1), and the schedule of this study is presented in Fig 1.

2. Objectives

The primary objective is to demonstrate the superiority of EN versus TPN in the treatment of PUGIF after oesophago-gastric resection including bariatric surgery, duodeno-jejunal resection or pancreatic resection with digestive tract violation in terms of 30-day fistula closure rate.

Secondary objectives are the assessment of (i) 6-month post-randomization fistula closure rate, (ii) Time of first fistula closure (in days), (iii) Medical and surgical treatment-related complication rate (EN or TPN) at 6 months after randomization, (iv) Fistula-related complication rate at 6 months after randomization, (v) type and severity of early (30 days
after randomization) and late fistula related complications (over 30 days after randomization), (vi) 30-day and 6-month post-randomization mortality rate, (vii) nutritional status at day 30, day 60, day 90 and day 180 post randomization, (viii) mean length of hospital stay, (ix) patient’s HRQOL (self-assessment questionnaire), (x) time for oral feeding, (xi) direct costs of treatment.

3. Inclusion criteria

All patients diagnosed with a postoperative digestive fistula in the recruiting centers will be screened for eligibility to participate in the study. Inclusion criteria are patients: (i) older than 18 year-old, (ii) who signed the written informed consent form (additional file 2), (iii) who underwent upper GI surgery for benign or malignant disease i.e. oesophago-gastric resection including bariatric surgery, duodeno-jejunal resection or pancreatic resection with digestive tract violation, (iv) who have had the diagnosis of an active postoperative digestive fistula untreated or persisting after failure of a dedicated surgical or endoscopic procedure to close the fistula. The fistula should have been diagnosed since less than 72h before randomization and confirmed on at least two criteria among the followings: (a) clinical symptoms, (b) ct-scan/ultrason imaging/endoscopic diagnosis, (c) biologic/bacteriology diagnosis on fluid output, (d) intraoperative diagnosis at time of reoperation, (v) have the indication of nil per mouth or just clear liquids for comfort, (vi) require an artificial nutritional support, (vii) have an American society of anaesthesiology (ASA) score 1, 2 or 3, (viii) have a life expectancy longer than 6 months, (ix) have no history of allergy or product intolerance to the nutritional product used in the study, (x) have an ongoing healthcare insurance, (xi) are able to understand the Information letter.

4. Exclusion criteria

Patients with any of the following criteria will not be included for participation in the study: (i) scheduled surgical or endoscopic treatment with the aim to close the fistula
(suture, prosthesis, clip or glue). In case of such treatment failure, patients are eligible to participate to the study. Endoscopic or surgical drainage are not exclusion criteria (meaning that drainage is authorized only before randomization), (ii) Patient diagnosed with an isolated pancreatic fistula (without digestive content) after a pancreatic resection without digestive tract violation, (iii) history of current severe uncontrolled cardiovascular, pulmonary, renal or liver failure, (iv) presence of a severe and evolutive life threatening pathology, (v) uncontrolled sepsis/situation related to the fistula (including but not limited to: abscess, bleeding, fistula with the trachea or the aorta), (vi) requirement of a nutritional support combining both the enteral AND parenteral routes together, (vii) peritoneal carcinomatosis or distant metastasis, (viii) pregnant and/or lactating women, (ix) freedom privacy, (x) patient currently participating or having participated in another interventional clinical trial related to nutritional support or fistula management during 30 days prior to the beginning of the study (Note: participation in a prior clinical trial not related to nutritional support or fistula management does not exclude the patient from participation).

5. Endpoints

The primary endpoint is the fistula closure rate at 30 days after randomization. Fistula closure will be defined as no output fluid during 48 hours in wound or drainage and absence of any fluid collection on imaging (ct-scan with contrast injection). The secondary endpoints are (i) 6-month fistula closure rate, (ii) time of first fistula closure, defined as time in days from randomization to first fistula closure within 6 months after randomization (iii) medical and surgical treatment related complication rate at 6 months, including complications related to the nutritional support such as tube related complications (dislodgment, infection, occlusion), venous catheter related complications (thrombosis, infection), or any other nutritional route related complications, (iv) fistula
related complication rate at 6 months, (v) type and severity of early (before 30 days after randomization) and late complications (over 30 days after randomization) according to the Dindo-Clavien classification [23], (vi) mortality rate within 30 days and within 6 months after randomization, (vii) nutritional status will be evaluated at day 30, day 60, day 90 and day 180 post randomization based on weight, serum albumin and pre-albumin concentration, C-reactive protein (CRP) and grip test (muscular strength) (viii) length of hospital stay in healthcare structure (including home hospitalization) based on the cumulative number of days of hospitalization during the whole study period (from randomization until the end of the study), (ix) patient’s HRQOL score based on Short Form 36 (SF36) and EuroQoL5D (EQ5D) questionnaires at inclusion, D30, D60, D90 and D180, (x) time to oral diet covering at least 60% of their daily requirement from randomization date, (xi) direct economic costs of therapy from a societal perspective, including the following costs: hospitalization (inpatient and home settings), nutritional products, early and late complications occurring during follow-up.

6. Randomization

Patient will be randomized at inclusion during hospitalisation after verification of suitability for inclusion. Patients will be randomized using the Clinsight system (ENNOV).

Randomizing 2 cases for one control has been chosen based on the positive results of the Klek et al. publication exhibiting a higher 30-day fistula closure rate in the EN group for patients with pancreatic fistula, which is a similar context [16]. In addition, European Guidelines are in favour of EN for patients needing artificial nutrition with a grade A level of evidence (without the context of PUGIF where nothing has been demonstrated to date).

A dynamic randomization procedure by minimization will be done to achieve a balance of the following prognostic factors: the type of fistula (high versus low -output, high output
fistula defined as effluent greater than 200 ml/24 h), malignant/non-malignant disease and somatostatin analogue use. The variable center will also be considered in the minimization procedure. Taking into account the fistula outflow, stratification on the surgical procedure/organ will not be included in the minimization procedure since the 2 are strongly linked.

7. Treatment methods

Each nutritional support will be planned to provide a similar amount of calories and proteins. According to the French guidelines on perioperative nutrition [24], the amount of calories will be 30-35 kcal/kg/d including proteins. The protein or amino acid intake will represent 18 to 20% of caloric intake; it will be 1.35 to 1.5 g/kg/d (ie nitrogen: 0.21 to 0.24 g/kg/d).

EN or TPN will start in the first 72h following randomization, leading to the need of tube or catheter placement (if not already placed and according to randomization arm) in the meantime.

EN can be delivered through a jejunostomy or a nasojejunal tube. A polymeric hypercaloric hyperprotidic product without immunonutrients will be chosen. The nutritional product will be the one usually used in each center. EN will be started slowly (20mL/H) with a progressive increase in the infusion rate every day according to the tolerance of the patient. The expected infusion rate to cover nutritional needs should be obtained in a week. If the tolerance of EN does not allow to meet the energy and protein requirements at the end of the first week, it will be necessary to start a complementary parenteral nutrition to cover up the nutritional requirements. EN will be infused at a continuous rate via an enteral pump. In case of obstruction or fall of enteral tube, feeding tube should be replaced immediately with the agreement of the surgeon. If it is impossible to replace an enteral tube, a parenteral nutrition should be started on the day.
TPN will be delivered through a central venous access, a picc-line or a totally implantable venous access port or any other approved total parenteral nutrition device. The parenteral nutritional product will be chosen according to the patient nutritional requirements as defined in the study and to the habits of each center (industrial or compounding bag). However, it is recommended to avoid a parenteral formulation containing a long chain triglyceride lipid emulsion and to add intravenous glutamine (Dipeptiven®) in TPN [25]. If Dipeptiven® is added to parenteral nutrition (recommended dose: 0.3 to 0.5 g/Kg/j of dipeptide), the amount of amino acids (or nitrogen) will be included in the calculated amount of protein intake. Parenteral nutrition will include electrolytes, vitamins and trace elements every day. Phosphate serum level should be assessed every 72h. TPN should be infused on 24 hours with a pump. In case of catheter obstruction or bacteraemia related to catheter, central venous catheter will be replaced and complications will be treated according to guidelines [26, 27].

Patients need appropriate care, according to local procedures, to avoid complications on feeding tube or enteral venous catheter.

For all patients, as usual, glycemia will be checked regularly. In case of hyperglycaemia (> 10 mmol/L or 1.8 g/L), glycemia should be maintained between 7.8 and 10 mmol/L (1.4 to 1.8 g/L) with the use of insulin.

Nil per mouth (except a maximum of 500 ml/day of clear liquids for comfort per mouth) will be required during fistula treatment and until at least 5 days after fistula closure. Then, oral alimentation will be progressively introduced under nutritionist supervision with a previously known energetic value and the proportion of oral alimentation ingested will be monitored daily.

8. Data collection and follow-up
The patients will be followed-up at 30, 60, 90, 180 days after randomization. The follow-up
protocol includes a clinical examination (weight, temperature, arterial blood pressure), assessment of status fistula closure, paraclinic examination (ct-scan with injection and ingestion of contrast product) for patients who do not show any output of fluid during 48 hours in wound or drainage, assessment of time to first fistula closure through the “Auto-evaluation of fistula associated symptoms” Questionnaire, laboratory tests (cell blood count (CBC), haemoglobin, white blood count (WBC) with neutrophils, lymphocytes, monocytes, eosinophils, basophils, platelets, haematocrit, red blood cell count, Aspartate Transaminase (ASAT), Alanine Amino-Transaminase (ALAT), Alkaline Phosphatase (ALP), Gamma Glutamyltransferase (GGT), total bilirubin, creatinine, CRP, serum albumin and pre-albumin concentration, total protein, sodium, potassium, chloride, urea, glucose), nutritional assessment: weight, total protein, serum albumin and pre-albumin concentration, grip test for muscular strength measurement, assessment of World Health organization (WHO) Performance Status, quality of life questionnaires SF 36 and EQ 5D.

The study is planned to last 42 months, with a 36-month inclusion period and a 6-month follow-up period. The results of the primary endpoint will be available 30 days after the end of the inclusion period (3 years).

9. Participating centers

To prevent institutional bias, the centers participating in this trial are experienced in upper GI surgery. In this study 27 french centers will participate: Lille university hospital (2 departments), Bordeaux university hospital (2 departments), Lyon university hospital (2 centers), Amiens university hospital, Brest university hospital, Caen university hospital, Clermont-Ferrand university hospital, Diaconesses hospital, Dijon university hospital, Limoges university hospital, North university hospital of Marseille, Institut Mutualiste Montsouris, Montpellier university hospital, Saint-Antoine university hospital, Saint-Louis
university hospital, Bichat university hospital, Cochin university hospital, Institut Gustave Roussy, Reims university hospital, Rennes university hospital, Rouen university hospital, Strasbourg university hospital, Toulouse university hospital and Tours university hospital.

10. Statistical evaluation and sample size

The hypothesis of this phase III study is that the use of EN nutrition will improve the fistula closure rate at 30 days after randomization. According to Klek et al. [16], the 30-day fistula closure rate is expected to be 35% in the TPN group and 55% in the EN group. According to Rutegård M et al.[28], we expect a 10% mortality rate within 30 days.

Considering a 35% fistula closure rate in the TPN group and an expected 55% rate on the EN group (absolute difference of 20%, relative risk of 1.57), a two-sided test, a type I error of 0.05, a 90% power, an allocation rate of 2:1 for the EN group and the TPN group respectively, taking into account a 30-day mortality rate of 10%, 214 patients are needed in the EN group and 107 in the TPN group, leading to a total number of 321 patients to be recruited.

The intention-to-treat (ITT) population will comprise all randomized patients, whether or not they satisfy the eligibility criteria and irrespective of the study treatment actually received. Unless otherwise indicated, all efficacy and safety analyses (including the primary outcome) will be conducted on the ITT population.

The per protocol (PP) population will consist of all ITT patients who complied with the protocol requirements. Compliance with protocol requirements will be addressed through the review of protocol deviations/violations at the time of a blind data review meeting, just prior to database lock. Any significant issues may warrant patient exclusion of all part of their assessment data. The PP population will be applied only for the primary outcome, to be considered as a secondary analysis.

No interim analysis will be planned.
Statistical analyses will be independently performed by the Biostatistics Department of University of Lille under the responsibility of AD. Data will be analyzed using the SAS software (SAS Institute Inc, Cary, NC, USA) and all statistical tests will be performed with a 2-sided alpha risk of 0.05. A detailed statistical analysis plan will be written and finalized prior to the database lock. The data analysts will be blinded to the treatment arm. Any deviation from the protocol specified analysis will be documented within a protocol amendment or statistical analysis plan, as appropriate, and described within the clinical study report.

Patient accountability will be summarized by treatment group and overall for all randomized patients. In addition, patient accountability information for screen failure patients will be collected and reported. The number of patients randomized will be summarized along with the number of patients within each patient population. In addition, the number of patients completing/not completing the study will be presented along with the primary reason for withdrawal from the study.

Deviations that warrant patient exclusion from the PP population will be determined just prior to database lock and documented within the relevant patient listing.

Some subgroup analyses, considered as exploratory, will be performed according to some well-known factors linked to the primary outcomes and considered in the randomization per minimization technique: (i) Type of fistula: high versus low input fistula (high output fistula defined as effluent greater than 200mL /24h, (ii) malignant/non-malignant disease, (iii) Somatostatin analogue use or not.

Baseline characteristics will be described for each arm for the ITT population. Quantitative variables will be expressed as mean (standard deviation), median (interquartile range) and range. Qualitative variables will be expressed as frequencies and percentages. Normality of distributions will be assessed graphically and using the Shapiro-Wilk test.
11. Medico-economic analysis

Considering the clinical design, a full economic evaluation will be performed taking into account both benefits and costs. The analysis will be conducted in concordance with HAS guidelines [29]. Cost-effectiveness analysis will be performed according to ITT principle and from a societal perspective. A PP complementary analysis is planned as many patients are expected to switch from TPN to EN. The following costs will be considered in the economic analysis: (i) hospitalization (inpatient and home settings); (ii) nutritional products; (iii) management of early (before 30 days after randomization) and late (over 30 days) complications occurring during follow-up.

The costs of hospitalization (inpatient) will be computed using the French hospital production costs study (Echelle Nationale des Couts à la Methodologie Commune Medecine Chirurgie Obstetrique (ENCC-MCO)). The average cost will be adjusted to the length of stay (secondary endpoint) and the number of days in intensive care units which are known to be the main cost drivers. Home hospitalizations will be valued by reference to the French home hospitalization production costs study (Echelle nationale des Couts-Hospitalisation à Domicile (ENC HAD)). All hospitalizations will be recorded in the electronic Case Report Form (eCRF) (gathered data: hospital in which patient were admitted, main diagnosis, date of admission, date of discharge) at each scheduled clinical examination. Information on Diagnosis Related Groups (Groupe Homogène de Malades (GHM), inpatient setting) or Management Related Groups (Groupe Homogène de Prise en Charge (GHPC), home care setting) information will be requested at the end of the study by the study coordinator to hospitals in which patients were admitted. Nutritional products will be valued at their current price.

Quality Adjusted Life Years (QALY) will be computed using the French value set by a linear interpolation between dates of measurement (inclusion, D30, D60, D90 and D180) [30].
Considering follow-up, costs and QALY will not be discounted.

12. Ethical approval

This study protocol was approved on 02th of November 2018 by the national ethic board and written informed consent will be obtained from all participants in the trial by the study investigators in each centers. The results will be presented at scientific meetings and published in periodicals.

13. Confidentiality

Information about study subjects will be kept confidential. All data will be entered into a dedicated data study management system, and as in all data documents studies, subjects will be assigned an individual identifying code which does not contain identifying information.

Comment

Despite considerable improvements in surgical techniques, PUGIF remains a worrying problem and there is an urgent requirement for improving outcomes after PUGIF normally associated with high mortality and morbidity rates. Nutritional support is mandatory to accelerate healing of the fistula. However, the best route to deliver nutrition is still subject to debate in literature. EN and TPN are already used in daily practice, but some surgeons are often reluctant to use EN in PUGIF.

Nutrients via the GI tract stimulate a complex response which has implications on body composition and on immunologic integrity. The mechanisms include nonspecific luminal stimulation provided by nutrients, “functional workload”, potential stimulation of pancreaticobiliary secretions, secretion of humoral mediators, and induction of intestinal hyperaemia [12, 13].

EN has been shown to be efficient in the prophylactic setting [1,15] leading to a high probability of efficiency in the curative setting when the fistula is in place. In a well-
designed randomized trial, EN was associated with significantly higher closure rates and shorter closure time of postoperative pancreatic fistula [16]. EN was identified as an independent factor significantly associated with fistula closure. (OR=6.136; 95% CI: 1.204 - 41.623; \( P =0.043 \)).

The transversal approach, in this trial, with inclusion of various upper GI surgery will help to validate the concept of the use of EN after fistula across different surgical sub-specialities. The trial results could modify national and international guidelines and practices worldwide offering a high level of evidence.

To conclude, in the NUTRILEAK study, we aim to test the hypothesis of the superiority of EN versus TPN in PUGIF in a large multicentered, phase III, prospective controlled, open label trial. This trial will also assess patients’ quality of life and medico-economic effects of the different treatment strategies.

**Trial Status**

The Protocol Version is 2.0 (1th February 2019). The trial is registered at ClinicalTrials.gov with identifier number NCT03742752. This trial is currently on going. The recruitment of subjects is expected to finish in 2022.

**List Of Abbreviations**

AE: Adverse Event, ALAT: Alanine Amino-Transaminase, ALP: Alkaline Phosphatase, ASA: American Society of Anaesthesiologists, ASAT: Aspartate Transaminase, CBC: Cell Blood Count, ct-scan : Computerized tomography scans , CRP: C-Reactive Protein, eCRF: Electronic Case Report Form, EN: Enteral Nutrition, ENC-HAD: Echelle nationale des Couts-Hospitalisation à Domicile, ENCC-MCO: Echelle Nationale des Couts à la Methodologie Commune Medecine Chirurgie Obstetrique, EQ5D : EuroQoL5D; GGT: Gamma Glutamyltransferase, GHM: Groupe Homogène de Malades, GHPC: Groupe Homogène de
Prise en Charge, GI : Gastro Intestinal, HRQOL : Health Related Quality Of Life, ITT: Intention To Treat, PP: Per Protocol, PUGIF: Postoperative Upper GastroIntestinal Fistula, SF36 : short form 36, SAE: Serious Adverse Event, TPN: Total Parenteral Nutrition, QALY: Quality adjusted Life Years, WBC : white blood count, WHO PS: World Health Organization Performance Status

Declarations

1. Ethics approval and consent to participate

This study protocol was approved by the national ethics board (the Committee for the Protection of People) on 02/11/2018 under the registration number ID-RCB 2018-A01625-50. The study is registered on the Clinicaltrials.gov website under the identifier NCT03742752.

The study complies with the Declaration of Helsinki and the principles of good clinical practice guidelines.

Informed consent is obtained from each patient in written form prior to randomization. Patients will be informed about the objectives, the nature, the duration and the possible adverse consequences of the trial, by a surgeon familiar with the study, orally and with the help of an information letter, approved by the Ethic Committee. Patient safety and all potential threats to the patients are monitored at each consultation. A Data and Safety Monitoring Board (DSMB) is not necessary because the aim of the study is to compare treatments already used in practice. Sponsor representatives will regularly review data collected on e-CRF at each participating site and on the basis of patients files present in those sites – in the conditions defined by a monitoring plan. Any information deemed to potentially affect the safety of the trial will be brought to the attention of the sponsor.

2. Consent for publication: not applicable

3. Availability of data and material:
The datasets used or analysed during the current study will be available from the corresponding author upon reasonable request.

4. Competing interests: The authors declare that they have no competing interest

5. Funding:

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6. Authors' contributions

CG wrote the manuscript, CG, CC, BD, CL, CM, GP were involved in the study design and assisted in writing the manuscript, AD was the statistical advisor, CG, CC, BD, CM, AD, GP, FRENCH group DC, DV, JMR, JJ, JT, GL, JV, AV, POD, FP, MM, JP, LBB, DF, PR, JL, PC, SD, BM, JJT, PP, NC, ES, NCB, BD, SM were involved in the study design and inclusion of patients in the trial, GP is the study coordinator, obtained the grant and is responsible for the present paper; All authors read and approved the manuscript.

7. Trial sponsor

The trial sponsor is Centre Hospitalier Universitaire de Lille / Direction de la Recherche et de l’Innovation avenue Oscar Lambret 59037 LILLE Cedex, France Tel : +333 20 44 59 69

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Additional Files

Additional file 1: SPIRIT 2013 checklist: recommended items to address in a clinical trial protocol and related documents.

Additional file 2: Consent form

Figures
| STUDY PERIOD | Enrolment | Allocation | Post-allocation |
|--------------|-----------|------------|----------------|
| **TIMEPOINT**| -\(t_1\)  | 0          | \(t_1\)       |
|              | \(t_2\)   | \(t_3\)    | \(t_4\)       |
|              | \(t_5\)   |            | 450-day       |
| **ENROLMENT:**|           |            |                |
| Eligibility screen | X          |            |                |
| Informed consent  | X          |            |                |
| Allocation        |            | X          |                |
| **INTERVENTIONS:**|           |            |                |
| Enteral nutrition |            |            | *              |
| Parenteral nutrition |            |            | *              |
| Nutritional route placement for EN or TPN | X          |            |                |
| **ASSESSMENTS:**  |           |            |                |
| Demographic data  |            | X          |                |
| Medical history    |            |            |                |
| Clinical examination |            | X          | X X X X X X X X |
| Laboratory tests   |            | X          | X X X X X X X X |
| CT scan with ingestion of contrast product | X          | X** X** X** X** X** X** |
| Nutritional assessment | X          |            |                |
| Assessment of fistula closure status | X          | X X X X X X X |
| Quality of life questionnaires (SF-36, EQ5D) | X          | X X X X X X X |

EN: enteral nutrition, TPN: total parenteral nutrition
* EN or TPN will be continued until the oral intake reach at least 60% of daily requirements
** CT scan with injection of contrast product for patient who do not show any output of fluid during 48 hours in wound or drainage

Fig. 1 Schedule of the trial interventions and assessments

**Figure 1**

Schedule of the trial interventions and assessments.
Figure 2

Flowchart of the trial.

Supplementary Files

This is a list of supplementary files associated with the primary manuscript. Click to download.

2. Etude NUTRILEAK - Avis favorable initial_English - final.pdf
   additional file 1.pdf
   NUTRILEAK study - Certificate for funding.pdf
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