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***ReAL trial (Rectal Anastomotic seal)***

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PROTOCOL

Full title:

**Prevention of anastomotic leak in colorectal surgery by glue reinforcement. A prospective randomized trial.**



Developed by Department of Emergency and Organ Transplantation (DETO),  
University of Bari, Italy

*Clinicaltrial.gov* ID number: **NCT03941938**

Date of protocol: 09/01/2019

## ReAL Trial Management Group

## **Surgery**

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## **Randomization**

Simple randomization will be centralized and carried out by assigning the 2 treatment options to consecutive computer generated random number obtained through the website  
<http://www.randomizer.at>

The randomization code will be obtained by contacting the number or the Tel number +39 3287586007 / +39 3397593066 or by the e-mail address [arcangelopicciariello@gmail.com](mailto:arcangelopicciariello@gmail.com) , or [donatofrancesco.altomare@uniba.it](mailto:donatofrancesco.altomare@uniba.it)

Clinical queries during office hours should be directed to one of the clinical coordinators or to an appropriate member of the ReAL trial Management Group

## **Data Monitoring and Ethics Committee**

Clinical data monitoring will be carried out by Ms Angela Accettura: Dept of Emergency and Organ transplantation, University of Bari e-mail: [angela.accettura@uniba.it](mailto:angela.accettura@uniba.it) Tel +39.0805592235

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Protocol approval n. 4555/2014

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## **ReAL Study Office**

For general queries, supply of trial materials, and collection of data:

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### **1. Background**

Colorectal cancer (CRC) is the second most common cause of cancer-related death in male and the third in females in Western Countries accounting for more than 500,000 deaths in 2013 worldwide(1).

One of the most worrying postoperative complication in colorectal surgery is the anastomotic leak which can occur in about 10-15% of the cases(2).

This complication severely impact clinical outcomes with increased risk of death or permanent stoma, higher risk of local recurrence) and relevant increase in hospital costs (length of hospital stay, admission to intensive care, re-interventions)(3).

The problem of anastomotic leak is particularly relevant in rectal surgery. The more distal the anastomosis, the higher the likelihood of failure, with resection of a distal rectal cancer having almost a five-fold increased risk of anastomotic leak compared with resection for colon cancer(4).

In fact, anastomotic Leakage (AL) is the most severe complication after Low anterior resection of rectum for cancer, occurring between 3 and 24 % of patients(5).

Many risk factors have been recognized in the onset of this complication(6), including gender (male patient have a higher anastomotic leak rate)(7), malnutrition, obesity an diabet, ASA score, tobacco use, cardiovascular disease, immunosoppression, use of NSAID(8), preoperative pelvis radiation.

Other intraoperative risk factors considered are the splenic flexure mobilization with proximal ligation of the IMA(9), positive intraoperative Air-Leak Test(10) and the perfusion of the anastomosis (11).

Temporary fecal diversion has also been suggested (although a diverting stoma mitigates the clinical consequences of an anastomotic leak but does not prevent it(12).

Other intraoperative technical factors include the use of single or double stapled anastomotic techniques, with or without transanal reinforcing sutures(13).

Therefore, preventing the anastomotic leak can bring benefits to the patient and the health system.

All the risk factors described above rapresent the rationale that justifies the use of intraoperative procedures to prevent the anastomotic leak, such as additional manual stiches to the mechanical suture and / or patches of collagen (proper reinforcement or buttressing) or of sealants.

Several attempts have been proposed to reduce the risk of AL in low rectal cancer surgery including

suture protection with omental flap and external suture reinforcement by biological glue or mesh (14-16).

Some Authors have reported good results of reinforcement of the colon anastomosis with cyanoacrylate glue. in a porcine model(17, 18).

Cyanoacrilate is a synthetic glue with sealing, adhesive and hemostatic properties widely used in surgery. Furthermore the sealing effect creates an antiseptic barrier against bacteria (19).

Several clinical studies have described the utility of cyanoacrylate glue mainly in vascular surgery, urology(20, 21) and bariatric surgery (22).

Considering its mechanical, physical, biological properties and its safety, cyanoacrylate glue could facilitate the healing of the colorectal anastomosis reducing leak rate, without negative effects on perfusion(23).

## **2. Study hypothesis**

The hypothesis is that the application of nebulized cyanoacrylate to the colo-rectal anastomosis in open or laparoscopic/robotic rectal surgery can prevent the leakage

### **3.1 General Design**

Prospective, multi-centre, parallel-arm randomized controlled superiority trial. Eligible patients will be randomized to cyanoacrylate reinforcement arm and no reinforcement arm, following rectal anastomosis.

### **3.2 Endpoints**

#### **3.2.1 Primary**

The aim of the trial is to observe a significantly lower number of anastomotic leak of a colorectal anastomosis in the group of patients treated with cyanoacrylate glue

### 3.2.2 Secondary

**SAFETY:** Demonstration that the new treatment will not add related morbidity

**EFFICACY:** Demonstrate that anastomotic reinforcement with cyanoacrylate decrease the rate of anastomotic leakage

### 3.2.3 SWOT analysis

<p style="text-align: center;"><b><u>STRENGTHS</u></b></p> <ul style="list-style-type: none"> <li>- Applicable to anastomosis located over 7 cm from the anal verge</li> <li>- High risk of stoma-related complications</li> <li>- Psychological impact of a stoma</li> <li>- Possibility to improve patient's outcome and reduce hospital costs</li> <li>- Low cost of the new treatment</li> </ul>	<p style="text-align: center;"><b><u>WEAKNESS</u></b></p> <ul style="list-style-type: none"> <li>- High number of patients to be recruited</li> <li>- Variability of the techniques</li> </ul>
<p style="text-align: center;"><b><u>OPPORTUNITIES</u></b></p> <ul style="list-style-type: none"> <li>- Applicable to a relevant proportion of patients affected by Rectal cancer which is one of the most frequent human cancer.</li> <li>- Reduce number of stomas, stoma related complications and new operations for stoma closure</li> <li>- Reduce hospital costs</li> <li>- Improvement of the patients QoL</li> </ul>	<p style="text-align: center;"><b><u>THREATS</u></b></p> <ul style="list-style-type: none"> <li>- Risk of sepsis for anastomotic leakage (?)</li> </ul>

### 3.3 Randomization

Written informed consent will be obtained prior to surgery by the operating surgeon. Computer-generated randomization will be used to create an allocation sequence to assign patients to the different study arms. Randomization will be computer generated and centrally controlled by an operator not involved in the study. Patients will be randomized only after completion of neoadjuvant chemo radiation (when indicated) and before surgery.

#### **3.4. Subject Recruitment and Screening**

Each patient referred for elective resection found eligible per stated inclusion and exclusion criteria will be approached by the operating surgeon. The patient will be informed about the study as per IRB protocol and consent. Patients will be given information about the risks, discomforts, and potential benefits of both treatments. The randomization protocol will be explained to the patient before consent is obtained.

#### **3.5 Participating Institution and Surgeons**

This multicenter trial is opened to the contribution of surgeons across Europe in order to achieve the required number of patient recruitment in the shortest period.

- All surgeons must have prior experience in performing colorectal cancer surgery either in open or laparoscopic route.
- All participating institutions must have IRB (Institutional Review Board)/Ethics Committee approval in order to enroll patients in the trial.
- As part of educational interventions, all participating surgeons will preview a video of the surgical technique of the application of nebulised cyanoacrylate glue.
- Recruitment of Centers will be by direct invitation or spontaneous proposal of Colorectal Units interested in the study.

#### **3.6 Definition of Outcome Measures**

Please use the following definitions:

- estimated blood loss (ml) recorded by the anaesthesiologist (not by the surgeon)
- duration of hospital stay (defined as from beginning of surgery to time of discharge, measured in days)
- Anastomotic leak will be confirmed by one or more that the following conditions
  - fecal discharge from the pelvic drainage at any time after surgery
  - rectovaginal fistula defined as fecal or mucus discharge from the vagina
  - pelvic sepsis as defined by the collection of pus/ fecal material in the pelvis documented by CTscan
  - Two sides X- Ray proctography performed by introducing 100 ml of hydro soluble liquid contrast medium (Gastrographin NOT barium sulphate) through the anus over the anastomotic line, by a Foley catheter (with an empty balloon) with the patient in standing position. The Foley catheter must be withdrawn after injection of the contrast medium and before the X Rays in order to prevent false-negative results.

**Classification of the anastomotic leak:** Grade A anastomotic leakage results in no change in patients' management, whereas grade B leakage requires active therapeutic intervention but is manageable without re-laparotomy. Grade C anastomotic leakage requires re-laparotomy (according to Rahbari NN, et al. Surgery 2010)

### **3.6.1 Definition of Adverse Events**

- Primary ileus will be defined as bowel dysfunction occurring after surgery for a duration greater than 10 days and that requires intervention including nil per os (NPO) status, naso-gastric tube, medication, or surgery.

- Secondary ileus will be defined as bowel dysfunction that occurs after the patient has resumed oral nutrition after surgery, and that requires intervention including NPO status, naso-gastric tube, medication, or surgery.
- Urinary tract infection (UTI)
  - Symptomatic urinary tract infection must meet at least 1 of the following criteria:
    - fever (>38°C), urgency, frequency, dysuria, or suprapubic tenderness *and* patient has a positive urine culture, that is,  $\geq 10^5$  microorganisms per cc of urine with no more than 2 species of microorganisms.
- Urinary retention will be defined as the condition of urinary dysfunction that occurs following surgery and requires intervention, including placement of urinary catheter.
- Pyrexia will be defined as any documented patient temperatures >38.0 C that require any treatment intervention such as antipyretics or that result in an increase in hospital stay.
- Wound dehiscence is defined as a delayed opening of the abdominal scar, without evidence of infection.
- Rectovaginal fistula defined as fecal or mucus discharge from the vagina
- Surgical site infection purulent discharge from the wound with positive culture
- Pulmonary infection documented by Chest X Ray

### **3.6.2 Classification of the postoperative complications**

- The Clavien Dindo Classification for postoperative complications will be adopted (see attached form 9.2)
- The Comprehensive Complication Index

## **3.7 ELIGIBILITY CRITERIA**

### **3.7.1 Inclusion Criteria**

- Resectable, histologically proven primary adenocarcinoma of the High-medium rectum without internal and/or external sphincter muscle involvement.
- Distal margin of the tumor at least 8 cm from the anal verge
- Staged as follows prior to neoadjuvant chemoradiation:
  - Stage T2 - T4 at MRI
- Patient classified T3-T4 will undergo neoadjuvant chemoradiation if the cancer is located in the extraperitoneal rectum

### **3.7.2 Exclusion Criteria**

- Squamous cell carcinoma
- Adenocarcinoma Stage T1,
- T4 with one of the following:
  - with pelvic side wall involvement
  - requiring sacrectomy
  - requiring prostatectomy (partial or total)
- Unresectable primary rectal cancer or Inability to complete R0 resection.
- Rectal cancer under 8 cm from the anal verge requiring colo-anal or ultra low rectal anastomosis
- Recurrent rectal cancer
- Previous pelvic malignancy
- Inability to sign the informed consent

### **3.8 Withdrawal Criteria**

Study participants will be informed of their ability to withdraw from the study or refuse initial enrollment at any time. Patients may withdraw without explanation.

## **4 STUDY INTERVENTION**

### **4.1 Preoperative work-up**

Patients will be seen for preoperative evaluation within 2 weeks prior to surgery. All tests and evaluations should be completed prior to surgery.

- All subjects will receive bowel prep per institutional routine.
- The entire colon should be investigated by a colonoscopy.
- Proctoscopy should be performed to assess the localization of the tumor and the distance from the anal verge.
- Histological confirmation of the tumor prior to surgery is mandatory.

Preoperative Tumor and nodal staging should be done by MRI and /or endorectal ultrasonography

#### **4.1.1 Timing of surgery after Neoadjuvant Chemoradiation**

Surgery must occur within 8-12 weeks (56-84 days) after completion of neoadjuvant therapy when indicated

### **4.2 Operative protocol**

- Anesthetic care will include general endotracheal anesthesia with gastric and bladder catheterization.
- Epidural catheter may be used for post-operative pain control.

#### **4.2.1 Technique**

Patient preparation to rectal surgery will follow the general Rules for Good Clinical Practice. Mechanical bowel preparation using oral PEG solution will be used according to surgeon preference, antibiotic and antithrombotic prophylaxis will start immediately before surgery.

Patient Position: Lithotomy position for abdominal and perineal procedures.

Abdominal procedure (open or laparoscopic) will be carried out according the oncological guidelines included total mesorectal excision with adequate lymph-node retrieval, at least 1 cm of distal clearance. A termino-terminal, latero-terminal, colorectal knight-Griffen anastomosis.

Both groups of patients will have a pneumo-hydraulic test after the completion of the anastomosis.

#### **4.2.1.1 NO CYANOACRYLATE GROUP**

Patients selected in the no cyanoacrylate glue arm will not have anastomotic reinforcements

#### **4.2.1.2 CYANOACRYLATE GROUP**

Patients selected in this group will receive the anastomotic reinforcement with nebulized cyanoacrylic glue using the special short catheter device for open surgery or the laparoscopic catheter.

### **4.3 Post-Operative Management**

Postoperative care will be according to current standards as directed by the operative surgeon.

- Pain control will initially be provided using parenteral (intramuscular, intravenous or epidural) administration of narcotics or analgesics.
- Oral analgesics will be offered ad lib when the patient has resumed oral intake.
- The initiation of oral intake and dietary advances will be made according to individual patient tolerance.
- Intravenous fluids will consist of maintenance crystalloid solution in addition to blood products as needed until the patient is able to sustain oral intake.
- Hospital discharge will occur only after the patient has shown diet tolerance, return of bowel function and ability to resume self-care with minimal assistance.

Subjects will return to the PIs ambulatory clinic for a post-op 30-day follow-up visit in order to collect the post-operative data and the post-operative proctography to document the integrity of the anastomosis. If

the subject does not come for the follow-up, the research nurse will contact him/her by all means available (phone, email, mail) to ascertain whether the patient had any complications and/or adverse events that were treated at another institution. If the research nurse is unsuccessful in contacting the patient, this subject will be considered 'lost to follow-up'.

**5. DATA MANAGEMENT:** Data will be collected by a combination of the study investigators, nurse research coordinators, and trained residents and fellows. Baseline characteristics and clinical data, procedural data, and postprocedure outcomes will prospectively entered into a secure database available to each participating center.

## **6 STATISTICAL ANALYSIS**

### **6.1 Sample Size Determination:**

The mean percentage of anastomotic leak after rectal cancer is 16% and its reduction to 10% is considered to be clinically significant. Therefore, the interval of confidence calculated is 12. A sample size calculation shows that 67 subjects per arm will suffice for accepting of the hypothesis with a power of 0.8 and a type I error probability of 0.05, with a Confidence level of 95% (sample size calculated by R Studio Version 1.1.419 – © 2009-2018 RStudio, Inc.). Accounting for a predicted 5% estimated loss to follow-up, a total of 138 (134+4) patients will be included in the study.

### **5.2 Statistical Methods:**

All statistical analysis will be done in an intention-to-treat fashion. No interim analyses are planned. For all statistical tests, a P value of .05 will be considered significant. A Student t-test will provide an unadjusted estimate of the difference between treatment arms. Analysis of covariance, a more robust method that allows control for key differences in baseline characteristics, will be used to provide adjusted comparisons.

Like the primary outcome, continuous secondary outcomes (such as safety and efficacy) will be modeled by t-tests and analysis of co-variance.

Any relationship of the anastomotic leakage with other possible adverse factors will be evaluated by univariate and multivariate regression analysis

When the complete case analysis will exclude more than 5% of patients due to missing data, exploratory analyses to investigate the effect of missing data will be performed. In order to explore the mechanism of the missing data and the validity of a complete case analysis for each end point, patient characteristics will be compared between those with and without missing data and multilevel logistic regression models will be used to identify any associations between prognostic variables and to inform if data are missing at random.

Multilevel logistic regression will be used to estimate the odds ratios (ORs) for conversion to laparotomy, intraoperative complications, and postoperative complications between treatment groups.

### **5.3 Subject Population for Analysis**

Data analysis will be performed in accordance with the intention to treat principle. If a violation of randomization occurs, all patients will be analyzed according to the original allocation.

The following information will be prospectively collected and reported:

- All-randomized population: Any subject randomized into the study, regardless of whether they receive the intervention.
- Protocol-compliant population: Any subject who was randomized and received both the study intervention and received the required protocol processing.

## **6. ETHICS**

### **6.1 Risks of Participation**

Patients in both study arms will be informed of standard risks of anterior resection surgery, such as ileus, surgical site infections, thrombotic complications, cardiac, or pulmonary complications. In addition, the risk of anastomotic dehiscence will be discussed and the two randomized options to prevent them (suture reinforcement or not) will be carefully described

### **6.2 Institutional Review Boards**

This study will be conducted in accordance to the principles of the Declaration of Helsinki and good clinical practice guidelines. The study protocol will be approved by the Ethics committee of all participating institutions. Prior to randomization, written informed consent will be obtained from all patients.

### **6.3 Data Safety Monitoring Committee**

A data safety monitoring board (DSMB) will be established with experts independent of the authors. The chairman of the DSMB will receive the clinical data forms continuously from the coordinating center and will review data. The DSMB chair may at any time suggest to the Study Chair to terminate the study in case of ethical concerns such as unacceptable complication rates and others.

## **7. AUTHORSHIP AND PUBLICATION**

The rules described herein apply to any presentation of this study. Members of the Protocol Writing Committee as well as Study Chairs qualify for authorship of this study. Vancouver Authorship Guidelines rules shall apply (for full document please see full article at <http://www.icmje.org/index.html>). Surgeons that include patients will attain authorship through a group authorship where names of surgeons will be mentioned. The order of the authors in the group authorship according their active contribution to the trial. The study results may only be published and/or presented as final analyses after the completion of the study, and needs authorization by the study chairs. Publication and/or presentation are defined as any

article, podium presentation, poster, abstract, or any other public presentation of this research. As is generally accepted, members of the DSMB should be independent and not involved in the study in any way including authorship.

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