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**RESEARCH PROJECT**

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## Title

**Robotic versus laparoscopic intracorporeal anastomosis in right colon cancer surgery: a randomized controlled prospective study.**
***Analysis of the operative outcomes of the patients and evaluation of the stress of the surgeons.***

## Introduction

In western countries, the current standard of surgical treatment for right colon cancer is the laparoscopic right hemicolectomy (LRH) with extracorporeal anastomosis (EA)[1]. This technique consists of a wide laparoscopic mobilisation of the colon, its extraction through a median laparotomy, the resection of the pathologic segment, and the creation of the anastomosis outside the abdominal cavity.

However, in spite of the standardisation of the technique and the introduction of fast recovery protocols[2], randomized studies and national registers have shown that LRH with EA is still associated with a hospital morbidity of about 30%[2-4].

Today, the progress in mini-invasive surgery allows surgeons to perform a LRH with intracorporeal anastomosis (IA). According to this technique, the ileo-colic anastomosis is performed inside the abdominal cavity by means of a mechanical stapler and completed with a laparoscopic suture. The colon dissection needed is less extended than in the LRC with EA, and the colon resected is usually extracted by a suprapubic incision, which is associated with a lower rate of incisional hernias than midline laparotomy (less than 2% vs. 8-12%).

Between 2013 and 2018, five systematic reviews with meta-analysis comparing short term outcomes of patients undergoing LRH with EA and IA have been published[1,5-8]. All authors have reported a faster post-operative recovery and a significantly shorter hospital stay. According to van Oostendorp[1] and Ricci[8], patients who have undergone LRH with IA have also a significantly lower rate of post-operative complications. No author has shown differences in mortality, conversion and quality of surgical resection, which proved LRH with IA to be a safe technique.

However, even though some advantages have been demonstrated for post-operative recovery and hospital stay, the laparoscopic IA is still considered a challenging procedure and it still performed by a small number of experienced surgeons[9-12]. For this reason, LRH with EA is still the most common operation performed for right colon cancer[13-14]. In this context, robotic surgery may overcome the technical difficulties of the laparoscopic AI and allow to a greater number of surgeons to perform AI more easily. The robotic right hemicolectomy (RRH) with IA might assure to patients suffering from right colon cancer the advantages demonstrated for IA compared to EA in laparoscopy, representing a new progress in the surgical treatment of this oncological pathology.

To this day, a few studies comparing operative outcomes of RRH and LRH with IA are available in literature. They are all retrospective and have a limited statistical significance[12,15].

The aim of this research project is to carry out a randomised controlled prospective study comparing RRH and LRH with IA, which would represent the first randomized trial on this subject in literature.

Moreover, the interest in robotic surgery depends not only on improved view and dexterity, but also on the better working conditions it offers.

At present, there are a few studies comparing the stress of the surgeons during robotic and laparoscopic operations on real patients[16]. In addition, none of these studies concerns crucial surgical procedures such as the creation of a digestive anastomosis in colorectal surgery. Thus, the stress of the surgeons has largely been excluded from the criteria of choice of surgical operations.

In this regard, this research project aims to measure surgeons' stress during RHH and LRH with IA objectively, in order to evaluate how much stress is caused by each type of operation. Also this aspect of the project would give interesting information about a subject not largely explored and it would be an uncommon line of research potentially attracting the attention of several hospitals with large volumes of robotic and laparoscopic surgery.

## Aims of the study

This research project develops along two lines:

- to evaluate the operative outcomes of patients with right colon cancer undergoing RRH with IA and LRH with IA
- to evaluate the stress of the surgeons.

On what concerns the first research line, this project intends to carry out a randomised controlled prospective study, whose primary aim will be the length of hospital stay, often considered in clinical trials as suggestive of the evolution of post-operative recovery.

The secondary aims will be represented by the main operative outcomes:

- operative time
- conversion rate
- time to flatus and stools
- time to oral intake
- post-operative complications
- 90-day mortality
- incisional hernias rate.

On what concerns the second research line, the evaluation of surgeons' stress will be based on two main parameters, which will represents the primary aims of this branch of the study:

- heart rate of operators and its variation
- salivary levels of cortisol of surgeons.

A score of perceived difficulty of the surgical procedure, specifically developed, will represent the secondary aim.

## Materials and methods

With regard to the line of the project concerning the comparison between RRH and LRH with IA, the randomised controlled prospective study that will be carried out will consider an experimental group represented by RRH with IA and a control group represented by LRH with IA.

Surgical procedures will be performed in a centre with high volume of colorectal surgery of the University of Palermo, with the collaboration of the digestive surgery department of Henri Mondor University Hospital, Créteil, France.

Operations will be performed by means of DaVinci technology for the experimental group and standard laparoscopic instruments for the control group. The surgeons involved will be at least two

surgeons with experience in laparoscopic and robotic colorectal surgery and two surgeons completing their formations.

This research will include patients suffering from right colon cancer, staged according to the staging manual of the American Joint Committee on Cancer (AJCC), VIII edition[17].

The inclusion criteria of the patients will be:

- 18 years of age or older
- diagnosis of right colon carcinoma confirmed at histology
- stage 0-III (with the exception of subcategory T4b)
- elective surgery
- surgical approach (RRH with IA, LRH with IA)
- primary anastomosis, without diverting stoma.

The exclusion criteria of the patients will be:

- subcategory T4b (locally advanced disease)
- stage IV (metastatic disease)
- emergency surgery (occlusion, perforation, digestive bleeding)
- colon carcinoma with double localisation
- familial polyposis.

Eligible patients will be assigned to one of the two groups by means of a computerized draw system. The overall number of patients needed to reach an adequate statistic power is 200, 100 for each group.

After the operation, the patients assigned to both experimental and control groups will be involved in the same fast recovery protocol, developed according to ERAS (enhanced recovery after surgery) principles[18].

Data will be collected from each patient in a prospective way and will include:

- demographic data (sex, age)
- clinical data (BMI, pre-operative haemoglobin, leukocytes and albumin, diabetes, cardiovascular and respiratory diseases, renal failure, ASA score, AJCC-TNM stage, neo-adjuvant chemotherapy)
- surgical approach (RRH with IA, LRH with IA)
- operative outcomes (operatory time, haematic loss, conversion, time to flatus and oral intake, post-operative complications, hospital stay, 90-day mortality)
- histological findings (resection margins, number of lymph nodes retrieved, tumour size, differentiation class).

Conversion is the prosecution of the operation with open technique. In case of robotic surgery, also the prosecution in laparoscopic way will be considered as conversion.

The post-operative complications considered will include; ileus, anastomotic fistula, intra-abdominal abscess, surgical wound infection, digestive bleeding. They will be classified according to their gravity and to the treatment needed, according to Dindo-Clavien's classification.

With regard to the evaluation of the stress of the operator during RRH and LRH with IA, this research project will consider as surgeon stress indicators the following parameters:

- surgeon's heart rate (HR) and its variation
- cortisol salivary levels of the surgeon.

Heart rate and its variations will be measured by means of a heart rate monitor with thoracic strip, worn by the surgeons during the whole surgical operation and intended not to interfere with their movements.

For each operation of both experimental and control groups, measures will concern average and maximum HR value, heart rate variability (HRV), and HR values at the beginning of the operation, during dissection, while performing the anastomosis, and at the end of the operation.

Salivary cortisol levels will be measured by means of specific salivary tests kits. Salivary samples will be collected at the beginning and at the end of any operation.

Surgeons will be handed out a questionnaire to evaluate the perceived difficulty of the surgical procedure performed, from which a specific score will be calculated.

Lastly, the costs of surgical equipment used will be registered for each operation.

For what concerns statistical analysis, in order to compare categorical variables, $\chi^2$ and exact Fisher tests will be used. In order to compare two groups of continuous variables, Student and Mann-Whitney tests will be used. The threshold of statistic significance will be set out at a p-value inferior to 0,05. Statistical analyses will be performed with the computer program SPSS (Statistical Package for Social Science, IBM SPSS Statistics, version 22 for Macintosh).

## Organisation of the study

After the examination of the ethical and scientific committee of the hospital, it is presumed that a preliminary phase of about three months will be necessary to improve methods. Then, it would be possible to focus on the elaboration of the randomisation list and to start data collection. A first analysis of data concerning patients and surgeons will be carried out when 100 operations (50 for each group) will be performed. It is presumed that the planned number of 200 patients will be reached by the first half of 2021. Once this number reached, the final data analysis will be carried out.

## Expected results

With regard to the operative outcomes of the patients undergoing RRH and LRH with IA, it is hypothesized that data analysis will confirm better results for the experimental group in terms of both primary and secondary aims. With regards to the evaluation of the stress of the operators, it is presumed that the study will show a significant improvement of the working conditions of the surgeon in the robotic group.

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