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EMERGENT SURGERY VS. STENT AS A BRIDGE TO SURGERY IN PATIENTS WITH ACTUTE MALIGNANT LEFT COLONIC OBSTRUCTION. A RANDOMIZED CONTROLLED TRIAL.

FINAL DEGREE PROJECT

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I would like to express my gratitude to all the Service of Abdominal Surgery of the CHU of Liège for welcoming me in the service and especially to Dra. Coimbra Marques, for her patience and attention.

Ever tried, ever failed.
No matter, try again.
Fail again, fail better.
S. Beckett

INDEX

1- ABREVIATIONS

CRC	Colorectal cancer
CRO	Colorectal ostruction
LBO	Large bowel obstruction
SEMS	Self expandable metal stents
BTS	Bridge to surgery
MBO	Malignant bowel obstruction
OLCC	Obstructed left colon cancer
QOL	Quality of life

2- ABSTRACT

EMERGENT SURGERY VS. STENT AS A BRIDGE TO SURGERY IN PATIENTS WITH ACTUTE MALIGNANT LEFT COLONIC OBSTRUCTION. A RANDOMIZED CONTROLLED TRIAL.

Background: Malignant left-sided large bowel obstruction is a common complication among patients with colorectal cancer.
There is still debate regarding which is the best method to treat these patients.
Conventionally emergency surgery has been the elected treatment option but self-expanding metal stents as a bridge to surgery has been advocated as an acceptable alternative.
Self-expanding metallic stents may decrease mortality and morbidity in comparison with emergency surgery and may decrease the stoma rate, which supposes a benefit in quality of life for the patients.

Objective: The aim of this protocol is to compare the rates of mortality and morbidity of the self-expanding metal stents used as a bridge to surgery with emergency surgery in the treatment of acute malignant left colonic obstruction in short term and long term. And also compare the quality of life of the patients included in the study.

Design: A randomized controlled trial that include 130 patients.
Non probabilistic sampling will be performed in order to obtain our patients. The study is planned to last six years, during the first three years we will recruit the patients and in the course of the following three we will collect data of quality of life and complications from that patients.

Setting: This protocol of study will take place in the Centre Hospitalier Universitaire de Liège.

Participants: Adult patients with an acute left colonic obstruction due to an obstructing tumor between the splenic flexure and rectosigmoid juntction that consult in the emergency department. The patients are randomized in the emergency department in two groups of treatment, the group of emergency surgery or the stent as a bridge to surgery. $\chi 2$ (Chi Square) test will be used to prove statistical association between interventions and the diminution of mortality and morbidity.

Key words: Colorectal cancer. Colorectal obstruction. Self-expanding metallic stents. Hartmann. Colostomy.

3- INTRODUCTION

3.1. Epidemiology

Colorectal cancer (CRC) is a global health problem. It is one of the most prevalent cancers worldwide. Nowadays, it represents approximately 10-15% of all cancers. The recently available data placed it in the world's fourth most deadly cancer (after lung, liver and stomach cancer). It is estimated that it kills 700.000 people every year (1).
According to what Occhionorelly *et al.* state in their work, CRC is the most common cancer in Europe, with a mortality rate of almost 50% (2).
It is though, one cause of high mortality and morbidity worldwide.

In woman, CRC is responsible of 614.000 cases of cancer, which represents the 9.2% of the total. It is the second most common cancer affecting women after breast cancer.
In men, with 746.000 cases of CRC are reported, representing the 10.0% of the total cancers affecting that gender, after prostatic cancer and lung cancer globally.

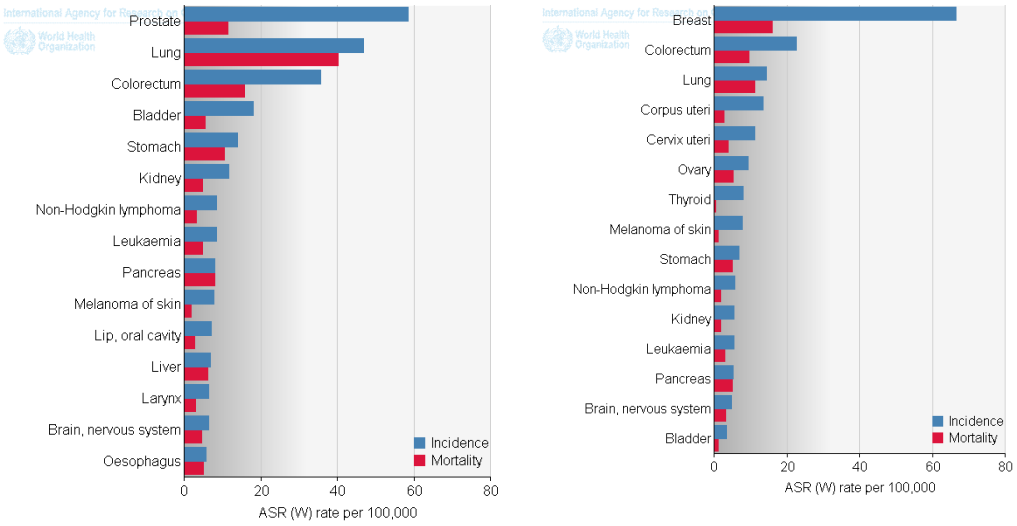


Figure 1. ***Estimated age-standardised incidence and mortality rates men and women*****. (3)**

Despite its high frequency, there is a wide variation in the incidence of this type of cancer across the world. Colorectal cancer is mainly found in the developed countries. As reported by GLOBOCAN, almost the 55% of the cases occur in more developed regions.

In Spain, according to the data of the oncological medical Spanish society, the colorectal cancer follows the same patterns that worldwide and it ranks the third place in prevalence in men and the second place in women. But again, when considering both genders together, colorectal cancer was the most frequent type of cancer affecting Spanish population in 2012.

Nevertheless, contrary to what we might expect, and contrary to the stabilizing rates observed in Western and North-western European countries; an increase of the rates have been reported in Spain (3). This is probably related with the increasing prevalence of obesity that had occurred in the last years in our country.

If we consider both sexes together CRC is the one with the highest incidence. In terms of mortality, it is the second cause of death in men and in women when both sexes are considered together.

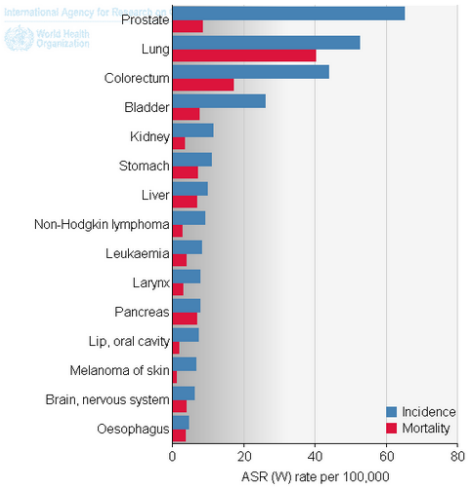


Figure 2. ***Estimated Cancer Incidence, Prevalence and Mortality Worldwide in 2012 (3)***

3.2. What is colorectal obstruction

A bowel obstruction is a blockage of the intestine that prevents passage of food or liquid through it.

When an obstruction occurs, liquids and food ingested and also the digestive secretions accumulate above the obstruction.

It is the first clinical manifestation in 15-20% of left colon cancers, especially the ones affecting the splenic angle and the recto-sigmoid junction (4). Colorectal obstruction (CRO) it is frequently encountered in abdominal surgery (5). Furthermore, colonic obstruction is one of the most common causes of emergency surgery in CRC (6).

The colonic obstructions have a higher incidence in the left side compared to the right side. There is an anatomical explanation for this. The diameter of the lumen is narrowest in the pelvic brim, between the splenic flexure and the rectosigmoid junction(7), that is why most of the blockages are placed there.

In literature, when talking about obstructions, we often find the concept of Malignant Bowel Obstruction (MBO).

MBO refers to the clinical syndrome with obstructive symptoms, that affects patients with intra-abdominal malignant neoplastic disease due to their malady (8).

This term has been used interchangeably for both patients with potentially curable single site of obstruction as a result of colorectal cancer and for those patients with advanced intra-abdominal cancer with incurable disease (8). In this protocol when we talk about malignant obstruction we will be referring to obstructions caused by malignant colorectal tumors.

Colorectal obstruction involves a high number of admissions in emergency surgical departments and it is recognized to be a major cause of morbidity and mortality as well as a financial expenditure all around the world (5).

3.3. Physiopathology of the obstruction

When a bowel obstruction occurs, it triggers a series of reactions which are responsible for the clinical patient's presentation.

Firstly, bowel distension is produced as a consequence of the accumulation of intestinal contents. In order to solve the blockage there is an increase of the peristaltic contractions which in turn raise the endoluminal pressure.

The increment of the pressure may result in an epithelial damage which activates an inflammatory response with oedema and hyperaemia and the corresponding liberation of inflammatory factors as prostaglandins, vasoactive intestinal polypeptide and nociceptive mediators (9).

An up regulation of serotonin is also produced, causing a release of substance P, nitric oxide and somatostatine. In turn, all this substances have a natural inhibitory effect on gut motility further complicating the situation (10).

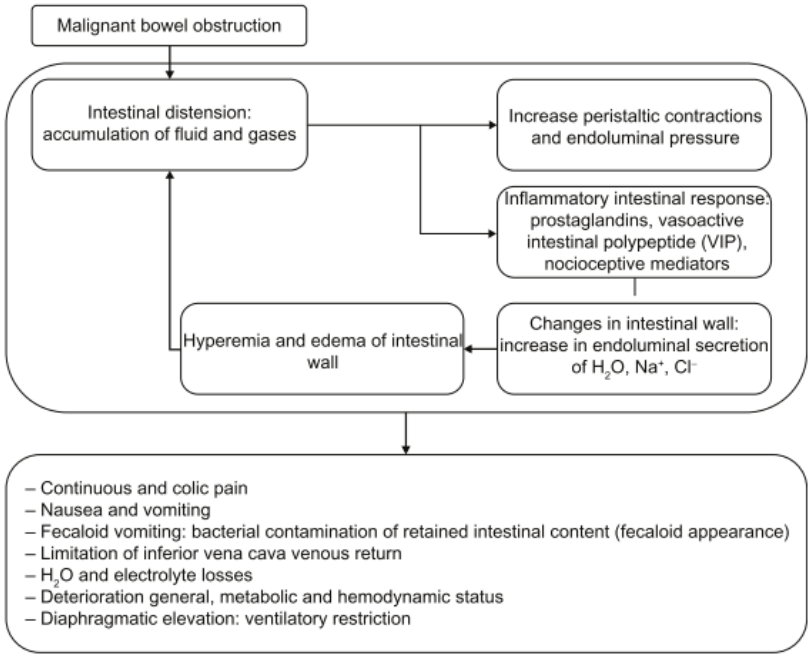


Figure 3. Physiopathology of MBO. (13)

Besides, we have to add to the decreased peristalsis a poor dietary intake and possible neural dysfunction what aggravates the situation (4,11).

3.4. Clinical features of the colorectal obstruction

Colorectal obstruction is the first clinical manifestation in 15-20% of left colon cancers, especially the ones affecting the splenic angle and the recto-sigmoid junction.

According to other studies; is one in five patients with CRC that presents acutely obstruction (12).
It is not uncommon that the onset of the symptoms may be subacute. Patients often describe a set of symptoms like abdominal cramps, abdominal distension, and a change in bowel habits, that are presented periodically but spontaneously cease, when the gas or stool get through the blockage. This clinical manifestation corresponds to the progressive luminal narrowing. Progressively, these episodes of obstruction become more frequent and last longer; until the complete obstruction results (9).

When the lumen is completely blocked, the most frequent signs and symptoms found are:

- Colicky abdominal pain 72-80% as a consequence of the peristaltic waves and spasms in the bowel with incremented endoluminal pressure without effective transit (13).
- Pain reported in 56-90% of the cases, due to the intestinal distension and tumoral infiltration of the abdominal structures (13).
- Absence of stools or emission of flatus in the previous 72h in 85-93% (10).
- Nausea and vomiting when the iliocecal valvula is incompetent.

We have to take in account, that large bowel obstruction is an emergency. It is very important to choose and establish the treatment as fast as possible, because if not, the obstruction could lead to several dangerous complications (13) as follows:

- Ischemia of the bowel due to dilatation which means the gradually necrosis of the intestinal wall. And so necrotic tissue is very weak and could easy be perforated.
- If the LBO progresses, particularly when the iliocaecal valve is competent, may result in caecal perforation (14).
- Peritonitis. If a perforation occurs, the risk of developing peritonitis is truly high with a high mortality and morbidity accompanied.
- Septic shock. Because of intraperitoneal bacteria translocation (7).
- When the ileocaecal valve is not competent, fecaloids vomits can also appear, although is not the most common sign.

3.5. Diagnosis of the obstruction

Given the fact that colorectal obstruction is an emergency it is necessary to carry out the crucial tests for its quick and correct diagnosis in order to provide an effective therapy as soon as possible (5).

For proper diagnosis it is essential to make a good physical examination.The physical examination including inspection, auscultation, percussion, palpation of the abdomen and bimanual pelvic and rectal palpation is essential but it is not sufficient to establish the diagnosis. The signs found in the exploration would be suggestive of obstruction. For an accurate diagnosis we need the imaging tests which would be imperative in order to detect the site of the obstruction and if possible the thereof etiology (7)**.**

a) In the **physical examination**, we often find:

- Remarkable abdominal distension.
- Fighting peristalsis in the auscultation and in cases where the obstruction is consolidated metallic sounds are often found because of the hydroaerial tension (13).
- In the percussion, when we precut the abdominal wall we obtain a tympanic sound resulting of the air that is trapped inside of the bowel which as it is said, distends the abdominal cavity.
- In some cases we can palpate abdominal masses.

b) Imaging tests

- **Plain radiograph**. Shows a dilatation of the large-bowel loops (15).

The signs are distension of the intestinal loops, fluid retention, and gases with the presence of air-fluid levels in the zone proximal to the occlusion as well as a reduction in gas and stools in the segments distal to the obstruction. (13)

But it is notoriously difficult to differentiate pseudo-obstruction from mechanical obstruction with only plain abdominal radiology (14).

- **Abdominal CT scan**.

The imaging modality of choice for the diagnosis of the cause of LBO is the CT scan (16).

The advantage of CT scan is that it can also give information about additional abdominal pathology, ascites or solid-organ parenchymal abnormalities (17).

Regarding the tumour, it can help assessing the tumour extension, if adjacent structures are involved or if associated lymphadenopathy is present along with intraperitoneal metastasis (15). Additional abdominal pathology is also easily detected; ascites, nodal or liver metastasis, and so on.

3.6. Options of treatment

The left acute colonic obstruction, as it has been said, is a medical emergency in which urgent decompression is needed (18). The importance of urgent decompression lies in the elevate risk of colonic necrosis and perforation due to the colonic mucosal friability that is produced when there is a big colon distension (19). The aim of the treatment is to restore the digestive permeability.

For many years, the patients with acute left colonic obstruction, received emergency surgery to restore the luminal patency (20). The surgical procedures that can be performed include:

- Resection of the obstructive tumor and primary anastomosis.
- Loop colostomy.
- Hartmann's procedure.

But the introduction of the self-expanding metallic stents (SEMS) in 1991 by Dohmoto et al. for palliation in cases of malignant bowel obstruction and three years later the use of SEMS as a bridge to surgery (BTS) by Tejero *et al.*, changed the scenario (2,21).

Nowadays, there are several options of treatment for obstructive left colon cancer (OLCC)(22):

- **Surgical approach**

The management of the obstructed colon distal to the splenic angle does not have consensual surgical criteria. Among surgical options for treatment we can distinguish different types of procedures which differ between them for the number of stages they have.

Primary resection and anastomosis. The intestinal anastomosis is a surgical procedure to establish communication between two formerly distant portions of the intestine. This procedure restores intestinal continuity after removal of a pathological condition affecting the bowel, in our case a colorectal obstruction due to colorectal cancer. This type of approach

would be the ideal choice for treatment if it were not for the high rate of dehiscence of the anastomosis and the difficulties of performing this kind of surgery in emergency conditions.

The surgeons in favor of the technique maintain that the alleviation of the faecal load in the colon proximal to the obstruction practically annuls the risk of dehiscence of the suture. In addition, the morbido-mortality and the economic costs (only one hospitalisation required) are less than the 2-stage procedure and, obviously, a colostomy is precluded. Besides, the proponents of the technique highlight the low incidence of reconstruction following the two-stage surgery(23).

In the **loop colostomy and subsequent resection**, the obstruction is solved by a colostomy, which is the first stage. A few weeks later when the emergency situation is controlled, it is the time for the second stage, which consists in the resection of the tumour and closing the colostomy. The closing of the stoma could also be done in a third stage (22).

Finally, the **Hartmann procedure (HP)** is the more commonly performed technique in emergency settings.

HP consists of a sigmoidecotomy with rectal stump closure and a terminal colostomy (24).

Henri Albert Hartmann was the French surgeon who described the technique that became eponymus with his name. The first time he described the surgery was in 1921 at the 30th Congress of French Surgical Association. The creation of this technique resulted from the high mortality rate (aronund the 40%) that the abdominoperineal resection described by Miles in 1908 had (25).

Nowadays, it is a common operation for pathologies affecting left colon, especially for emergency cases. This is explained by the fact that it is a technically simple intervention in comparison with other techniques; also because is rapid, minimally traumatic and the effect is immediate.

And also, as it is reported in some articles, when is performed through a midline laparotomy, allows exploration of the abdominal cavity which helps to exclude perforation or peritoneal carcinomatosis (7).

The advantages that this approach offers include: immediate resection of the diseased colon, avoiding the anastomosis which in emergent situation has elevated risk of dehiscence, shorter convalescence and therefore shorter hospital stay (26). On the other hand, one of the biggest disadvantages this technique has is the low reversal rate of the colostomy. Approxymately 40-60% of patients do not have their colostomy reversed (27).

The 2-stage operation with segmental resection of the obstructed colon and closure of the distal stump is popular among those who are aware that a resection and a primary colocolonic or colorectal anastomosis with an obstructed left colon that is distended and with a considerable faecal load, presents a high risk of dehiscence. Further, as it has been exposed it is a rapid and simple technique(23).

Endoscopic stent

Early attempts at colonic decompression with a nasogastric tube or chest were unsuccessful as the tubes were prone to obstruction.

The first case reported of colorectal stenting date back to 1991, when Dohmoto *et al.* first described the use of a metallic stent for palliation in a malignant rectal obstruction (2,6,16,17).

This was followed by sporadic similar reports predominantly for the palliation of obstructing lesions. Shortly after, two further cases of stenting of inoperable rectosigmoid carcinoma were described by Itabashi *et al* (28). The stents described were those used originally for relief of esophageal obstruction.

Subsequently, Spinelli *et al*. first reported endoscopic placement of a self-expandable metal stent (SEMS) for treatment of malignant rectal obstruction in 1992. Since then, there have been numerous publications on the use of SEMS for management of malignant colonic obstruction. Also three years later, Tejero *et al* published their work using SEMS as a bridge to surgery (BTS).

The use of *Wallstent enteral endoprosthesis*, designed specifically for colonic use was first reported by Soonawalla *et al.* Seven patients underwent stenting, with successful stent deployment in five. The two failures were due to inability to negotiate the stricture. The five cases have subsequent uncomplicated surgical resection of the obstructing lesions.

Thereafter, the use of metallic stents as a bridge to surgery for treating colorectal obstructions became a reality.

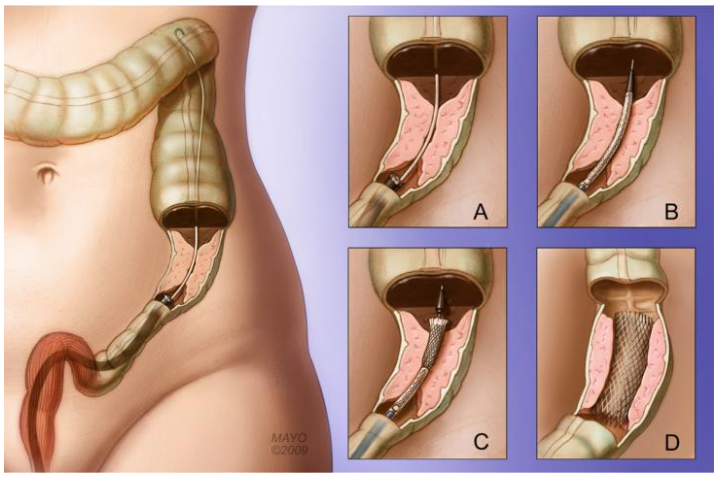


Figure 4 Illustration of placement of a through-the-scope colonic stent (29)

SEMS are expandable metallic tubes that are advanced to the site of endoluminal obstruction along a guidewire in a collapsed state (30). They are placed under fluoroscopic and/or endoscopic guidance.

Once they are located in the site of obstruction, they expand radially to their maximum diameter allowing the opening of the bowel lumen.

The aim of using SEMS as a BTS is to decompress the colon acutely obstructed and gain time for stabilization of the patient until the surgery. This period of time between the stent implantation and surgery, is used to stabilize the patient, staging the tumour and bowel cleansing (31). At the time of resection, the tumour and the stent are resected *en bloc* (29).

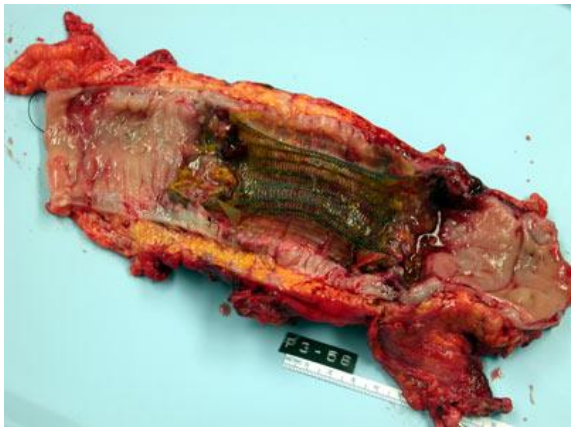


Figure 5. Resected specimen showing stent in sigmoid colon. A successful one-stage operation with primary reanastomsis was performed (29)

Nevertheless, this technic is not exempt from complications. The complications are divided in early complications (within 30 days from stent placement) and delayed complications (thereafter 30 days) (2,6). The most frequent problems resulting from the placement of metallic stent are:

- Perforation. It may occur early, when the implantation is carrying out, due to excessive manipulation of the guidewire, rapid expansion of the stent, closed loop obstruction with subsequent cecal distension from excessive air insufflation or related to balloon predilatation also (2). It is the most feared complication owing to that could lead tumour dissemination. In most of the cases, emergency surgical intervention is required.

- One problem that could also appear is the inability of introducing the stent. In some cases, technically the stent cannot be placed because the obstruction is very severe and the colon is too much dilated and therefore the risk of perforation would be high.

- Colonic reobstruction. Is the most common late complication, caused essentially because of the tumour ingrowth (6). It usually occurs when stent is used for palliation.

- Stent migration. Occurs mainly as an early complication, specially within several hours after SEMS insertion (6). Stent typically migrate distally and can pass through the anus spontaneously (2).
- Other complications related with the stent insertion are: rectal bleedings, tenesmus and abdominal pain. Although this are not very common complications (30).

The placement of the stent is not always possible. In some selected cases the use of stents is absolutely contraindicated (32):

- When there is a radiological evidence of perforation.
- Low rectal tumours within (5 cm) of the anal verge where stenting is liable to cause severe anal pain.
- When tenesmus or incontinence are affecting the patience.

Relative contraindications are (32):

- Anatomical difficulties, for example long stricture segment or strictures positioned in tortuous colonic segments.
- Bowel isquemia.

This figure summarizes the treatment options described above:

Comparison of indications, advantages, and disadvantages of different techniques.

TECNICHE	INDICATIONS	ADVANTAGES	DISAVANTAGES
Resection-Anatomosis	-Low risk patients	No diverting colostomy (in theory).	-Risk of anastomose dehiscence. - Availability of skilled personnel. - Risk of fistula
Hartmann procedure (HP)	-High risk patients -Inexperienced surgeon	-As safe as segmental resection.	-2nd intervention to restore continuity. -Risk of permanent colostomy. -Patient discomfort.
Stent	-Left colon obstruction -Palliation -Preoperative decompression	-Fewer colostomies -Decreased mortality -Elective 2nd stage colectomy.	-Contraindicated if perforation. -Technical failure -Risk of perforation. -Availability of skilled personnel.

Adapted from (7)

4- JUSTIFICATION

As it has been reported, CRC is commonly presented with an acute obstruction as a first manifestation (18) . Although its high frequency there is still significant debate regarding which is the best treatment option. For that reason we believe it is necessary to clarify which is the best way to address the acute left colonic obstruction in order to achieve better results for our patients.

Conventionally, the surgical treatment has been the option selected for patients with LCO, especially the Hartmann's technique. HP has been recommended in high risk patients in the emergency situation (33) because it offers some advantages as the fact that there is no risk of anastomotic dehiscence since a colostomy is performed instead of an anastomose; and also that it could be executed by less experimented surgeons.

Despite it is considered an effective treatment, the main problems are the mortality and morbidity that ensues its application and also the low rate of reintegration of the colostomy. The need of a secondary intervention is a well know disadvantage of HP and only 40%-60% of the patients have their colostomy reversed with the repercussion in the quality of life that it carries (33).

The introduction of SEMS not with palliative purpose but as a bridge to surgery seems a feasible option and it allows transforming an emergency surgery in an elective one, with the advantages that it entails.

The introduction of a stent in an obstructed colon aims to reopen the lumen and restore patency of the obstructed bowel and allows the stabilization of the patient's condition before surgery. It supposes an advantage with a view to the surgery, being that patients with acute malignant bowel obstruction have a bad general medical condition (2).

Some authors have reported that mortality and morbidity are low with the stenting technique and also, as expected, that a smaller rate of colostomies are performed when SEMS are used as a bridge to surgery (18). If the use of SEMS could delay the emergent surgery and avoid the creation of stomas that would suppose a benefit for the patients in terms of mortality, morbidity and quality of life.

Some authors suggested that stenting is safer because the complications found after emergency surgery would be non-existent and the hospital stay would be shorter. A shorter hospital stay allows earlier adjuvant treatment with chemotherapy (6).

One aspect we consider crucial in the management of this patients is the rate of colostomies. As it is asserted in some systematic reviews (18,34), with the use of SEMS as a bridge to surgery the rate of colostomies descends which implies a better quality of life for those patients.

The major part of the literature concerning this topic does not focus on the impact in the QOL that a colostomy has and that is why we also consider necessary to asses in our protocol the quality of life of our patients depending on the applied treatment. Besides comparing the surgical and the endoscopic treatment we also aim to include in the protocol the assessment of the QOF years after the treatment.

We also plan to assess the quality of life of the patients after six years from the surgery because we wanted to assess the impact of this technique in long term. Only a few of the consulted studies have reported information about the situation of the patients in the long term and we consider that assess the long terms results is also as long as we are investigating a recently new technique and we do not know yet what to expect from it. Moreover, we believe that further studies with bigger samples and with longer follow-ups are needed to prove the possible differences in mortality, morbidity and quality of life between the approaches.

However, in spite of the fact that we might think that stenting reports more advantages that surgical treatments, concerning have emerged regarding low technical success rates and possible high rates of perforation associated with stent implementation in some studies (12).

While it is true that recent meta-analysis have demonstrated lower overall postoperative morbidity, higher primary anastomosis and lower rate of stoma creation when comparing stenting with emergency surgery in left CRC obstruction (6) no significant differences in overall postoperative mortality were reported.

Moreover, the long-term oncological outcome understood here as a recurrence was worse in the group of SEMS as a bridge to surgery than in the group of emergency surgery in some publications (6).

The major concern of stenting, as it has been said, is perforations. It is important to keep in mind that if a perforation occurs, can cause tumor spill and provoke the dissemination of the disease(12) with high risk of peritoneal carcinomatosis.

As well as stenting can suppose an advantage transforming an emergency surgery in an elective one; it can also be the responsible of convert a local disease in a spread/disseminated one, in other words, stenting can convert a potentially curable cancer into a non-curable one (31).

A great part of the literature found and revised consists of systematic reviews and meta-analysis (35). We think that the study we are proposing is beneficial comparing with this meta-analysis because a randomized controlled trial will be the best method to perform the investigation. We consider that we will be contributing to the research with new data and information.

For the reasons exposed we think it is necessary to elucidate if the use of stents as BTS are as promising as they seem or if indeed, they do not offer a benefit for our patients when compared with HP.

The aim of this project is to clarify whether the SEMS truly offers an improvement in the management of left colonic obstruction when comparing with classic surgical treatments.

5- HYPOTHESIS

Primary hypothesis

The use of SEMS as a bridge to surgery will decrease the rates of mortality and morbidity in patients with acute left colonic obstruction as compared to classical surgical treatments.

Secondary hypothesis

The use of SEMS improves the quality of life of our patients due to the absence of colostomy.

6- OBJECTIVES

Primary objectives

General: This study aims to compare the morbidity and mortality in patients who underwent either surgery or SEMS as BTS for obstructive left colon cancer.

Specific:
Compare the disease free survival and overall survival with the follow-up at three years.
Compare the stoma rate between the two groups.
Compare the amount of days the patients spend in the hospital between the two options of treatment.

Secondary objectives

The intention is to compare the QOL between the two groups in the short term (at 3o days) and in the long term (after one year and after three years).

Moreover, the use of stents as a bridge to surgery, will report a better quality of life to the patients that have been treated with SEMS as a BTS in comparison with the classical surgical treatment due to the absence of colostomy.

7- MATERIAL AND METHODS

7.1 Study design

In order to be able to confirm or refuse our hypothesis with the level of evidence expected, we propose a randomized controlled open-label clinical trial.

The patients will be randomly divided in two groups. The first group will be included in the ***Stenting as a bridge to surgery group*** and, the second group of patients will form part of the group of ***emergency surgery***.

7.2 Setting and population of the study

The study will take place in the Centre Hospitalier Universitaire de Liège, Belgium.

The study population is based in patients attending the emergency department of the hospital who are diagnosed of acute left bowel obstruction. The diagnosis would be confirmed by abdominal TC.

7.2.1 Inclusion criteria

- Patients > 18a.
- Malignant acute obstruction confirmed by TC scan.
- Obstruction distal or in the splenic flexure.
- Obstruction caused only by malignant colorectal cancer.
- Patients who have read the Information sheet for participants and have signed the Informed consent form.

7.2.2 Exclusion criteria

- Obstruction proximal to the splenic flexure.
- Obstruction due to a non-malignant cause.
- Functional or extrinsic mechanical large bowel obstructions.
- Signs of peritonitis or perforation.
- Patients with metastatic lesions.
- Patients with evident signs of peritoneal carcinomatosis on the CT scan.
- Rectal cancers.
- Life expectancy < 1 year (judged by the investigator)
- Known allergy to any device component

7.2.3 Randomization methods

We will randomize the patients of our study in order to avoid the selection bias, therefore each patient admitted in the study will be assigned in a group randomly. An external researcher will be the person in charge of distributing the patients and the tool we will use for the randomization will be the SPSS software after the patients have signed the consent form (annex 1).

7.3 Sampling

7.3.1. Patient selection

The sample recruitment will take place at Centre Hospitalier Universitaire de Liège during three years and a half approximately. A consecutive non-probability sampling will performed.

Patients with acute malignant left colonic obstruction will be potential candidates for our study. If the patients meet all the inclusion criteria, they will receive an information sheet which describes the study. If the patient accepts to participate in our study we will proceed to give the informed consent form.

7.3.2. Sample size

To conduct our study, a non-probabilistic consecutive sampling will be done during a period of three years and a half.

Accepting an alpha risk of 0.05 and a beta risk of 0.2, 65 subjects for the emergency surgery and 65 patients in SEMS as a bridge to surgery will be needed;, (130 patients in total) to recognize a statistically significant relative risk greater than or equal to 0.2 with a reason between the samples equal 1. It is estimated that the drop-out rate will be 10%.

We have calculated the necessary sample with the program GRANMO calculator. The Poisson approximation has been used.

We estimate a relative risk of 0.2 according to the data published in previous studies and also according to clinical experience of the surgeons of our hospital.
In the most of the consulted publications, the mortality in the group of emergency surgery ranges from 15% to 35% (7,20,21,36–39) whereas in the SEMS as BTS group the mortality ranges from 1%-5%.
The reduction of incidence is surprisingly high according to this data and we estimated to have similar results with our patients in our centre.

Estimated time of recruitment

We calculate that to manage to reach the required number of patients to carry out our study, we will need three years and a half approximately.

We rely in the information provided by our hospital to state that estimation. According to data accessed by the researchers of this protocol, the *Centre Hospitalier Universitaire de Liège* treats about 35 to 40 patients with malignant colorectal obstruction per year. We need 130 patients and therefore we will need three years and some months more to reach the above mentioned figure.

First year study	40 patients with MLCO	20 ES	20 SEMS
Second year study	40 patients with MLCO	20 ES	20 SEMS
Third year study	40 patients with MLCO	20 ES	20 SEMS
Fourth year study	40 patients with MLCO	20 ES	20 SEMS
Total amount of patients	160 patients with MLCO	80Emergency surgery	20 SEMS as a bridge to surgery

7.4 Variables

7.4.1 Independent variables

The independent variables are ***represented by the two compared approaches***. Independent variable in our study is to be allocated in the Stenting as a bridge to surgery group or in the Emergency surgery group for the treatment of the left colonic obstruction. This is a dichotomous qualitative nominal variable and therefore it will be expressed in proportions or percentages.

7.4.2. Main dependent variables

The dependent variable in our study will be ***whether or not the mortality rates are lower*** after the use of SEMS as a bridge to surgery. It is a qualitative nominal variable and we will express it also in proportions or percentages.

7.4.3 Secondary dependent variables

- **Quality of life.** QOL will be measured using the SF-36 questionnaire. The questionnaire will be administered to patients from both groups of treatment and we can define it as a quantitative discrete variable.

- **Reduction of hospital stay.** Cumulative hospital stay is defined as the total number of days spent in the hospital. It is a quantitative continuous variable.

- **Morbidity.** As shown as complications after surgery as: surgical site infection, in- hospital mortality or anastomotic leak.
  It will be measured as dichotomous qualitative variable. We will record this event in the case report form and express it with percentages.

- **Rate of colostomies.** As it is a qualitative nominal dichotomous variable, it will be expressed in proportions or percentages. We want to compare the rate of colostomies between the two groups. We are certain that the rate will be smaller in the stent as a bridge to surgery but we do not know how big will be the difference expected.

- **Overall survival.** As it is a qualitative nominal variable it will be expressed also in proportions

7.4.3. Covariates

The covariate variables are other factors that can influence our result as they are related with our independent and dependent variables. We will include them in the multivariate analysis in order to assess its impact in the future results.

- *Concerning the patients:*
  - **Gender** (male or female) dichotomous variable.
  - **Age** (measured in years) continuous variable.
  - **Tumor stage** is an ordinal categorical variable.

- *Concerning the surgery*
  - **Previous surgical treatment**. Whether the patient has been operated before or not because of the colorectal cancer. It is a nominal categorical dichotomous variable.
  - **Obstruction location**. We are interested in knowing if the site of obstruction has any consequence or effect in the results. We will describe it as a qualitative categorical variable. Splenic flexure, recto sigmoidal junction or other location will be the three options we will collect in our case report form.
  - **Surgeon or endoscopiste:** We will classify the surgeons and the endoscopistes as: surgeon 1, surgeon 2, surgeon 3, surgeon 4 and endoscopiste 1, 2, 3 and 4; in order to include them in the multivariate analysis. It is a categorical nominal variable.

- *Concerning the medical care:*
  - **Total follow-up appointments in three years**: it is a quantitative discrete variable.

7.5 Data collection

For the process of data collection, the communication between the emergency department and the departments of abdominal surgery and gastroenterology services will be very important. All the personal will have to work together for data collection; the surgeons will inform the rest of the members of the unit about the study that is being carried out. Also the patients will play an important role in our study as long as we need them to help us complete the case report form and they must fill in the QOL questionnaires.

SF-36 which consists of nine scaled scores including: general health, limitation of activities, physical health problems, emotional problems, social activities, pain, energy and emotions, social activities, general health.
Assuming that each question carries equal weight, each scale is transformed into a 0-100 scale. The lower score the patients gets, the more disability.

For gathering the information concerned with our study, we will proceed as described below:

Trial entry in the emergency department.

The patients who visit the emergency department and meet the inclusion criteria will be asked if they want to participate in our study. An information sheet and the consent form will be given.

If they agree to engage in, we will proceed to collect the data needed for our investigation.

We will use a case report form (annex 1) in which all the variables of our study will be included. The first distinction we will have to do is to indicate in which approach is the patient randomly assigned.

We will use a CT scan to confirm and locate the obstruction. We will have to describe in the case report form the exact place of the obstruction.

It would be very important to record if a patient is diagnosed intra-operatory of perotineal carcinomatosis, since in these cases the features of the patient would be different in comparison with other patients.

During the postoperative period

The short term complications will be detected during the post-operative period.
After the surgery, we will evaluate our patients daily in order to control the possible complications. As immediate complications we consider: infections, dehiscence , migration or reobstruction…
Before the patient is discharged we will have to annotate in the case report form the total amount of hospitalization days. For the patients from the group of SEMS, the total amount will be completed when they have they operation. And for the group of emergency surgery the total amount will be the sum of the first hospital stay and if they have a colostomy the days they spent in the hospital for the reversal of the colostomy.
These two variables must be recorded in the case report form.

At 30 days post-op appointment

We will assess the general condition of the patients. We will ask the patient if he/she suffers from constipation or diarrhea as the intestinal habits after the surgery may have changed.
We will also seek if there are complications in urination and/or in the sexual function.

The quality of life of our patients will be valued with the SF-36 questionnaire for the first time and the results will be reflected in our Case Report Form.

If the patient belongs to the surgery group and carries a colostomy, we will decide with him or her the optimal date for the reversal of the colostomy.

Long term surveillance: after six months, after one year, after three years.

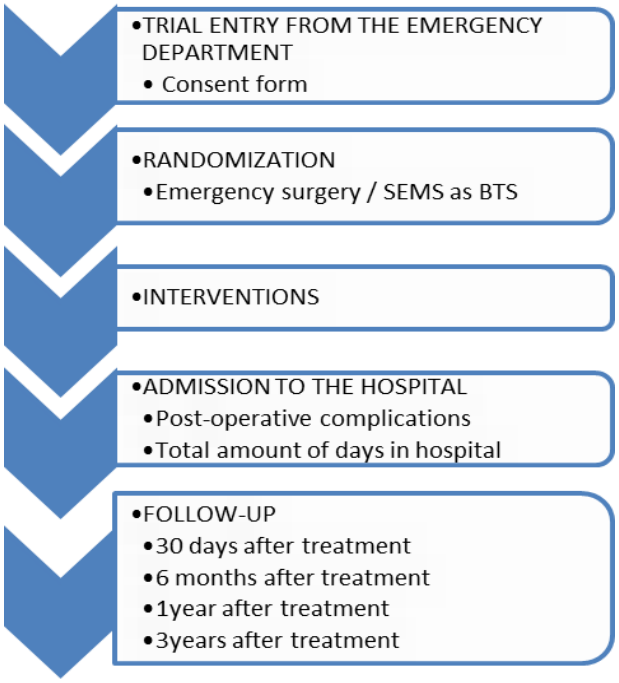
Inasmuch as the patients have their visits with the oncologist and general practitioner for the follow-up, we will take advantage from this situation, and we will use these consultation appointments for collecting the data for our study.
Thus the inconveniences for the patient will be minor, as we use the same appointment for collecting information and they will not have to come back to the hospital exclusively for our follow-up. Hence, the follow-up data will be obtained during routine clinical appointments defined according to the Belgian programs of colon cancer management.

We will contact by phone with the oncologist or the physician in charge of our patient before the six months to ask when the appointments are. This way, a researcher of our team can go to the consultation the day of the patient's visit in order to collect the data needed.

We will proceed alike at the following visits, after one year and after three years.

We also have to take in account that maybe some of the patients included in the study die during the following up. For the deceased patients, the date of death will be established after telephone contact with the personal doctor who also will report the cause of death and also after contacting the Office of Vital Statistics in the patient's place of birth.

The case report form will be filled by the physician and for a member of the research team. In each appointment, the person who will collect the data will have to write his/her surname and the date when the data is collected. All data must be introduced to a computer database after each appointment in order to have two copies of the patient's case report form.



7.6 Interventions

As we have expounded above, the patients participating in our study will be divided in two groups depending on the applied treatment.
One group will be treated with emergency opened surgery while the other group will be treated with a stent as a bridge to surgery.
Both procedures will be briefly explained below:

Emergency open surgery

Patients who were randomized to the open surgery group undergo emergency laparotomy on the same day of admission. The type of surgery will be performed according to the intraoperative findings and the surgeons' judgment.
A defunctioning stoma will be constructed if the surgeons considered it appropriate.

All the patients will be operated-upon under emergency conditions by the general surgeons. The surgery will be performed under general endotracheal anaesthesia, in supine decubitus position and with standard monitoring. Intravenous electrolyte replacement will be routine together with prophylactic antibiotics.

Immediate tumour resection for obstruction left-sided colonic lesions.

In general terms, the mobilization of a left-sided tumour may be divided into six basic phases:

- Phase 1: division of arterial supply and venous drainage and visualization of the left ureter.
- Phase 2: mobilization of the left colon.
- Phase 3: mobilization of the splenic flexure.
- Phase 4: complete distal mobilization.
- Phase 5: division of the bowel.
- Phase 6: consideration of immediate anastomosis.

a) Primary resection or anastomosis

Intestinal anastomosis is a surgical procedure to establish communication between two formerly distant portions of the intestine. This procedure restores intestinal continuity after removal of a pathological condition affecting the bowel. Intestinal anastomosis is one of the most commonly performed surgical procedures, especially in the emergency setting, and is also commonly performed in the elective setting when resections are carried out for benign or malignant lesions of the gastrointestinal tract.

Intestinal anastomosis can be performed by a hand-sewn technique using absorbable or nonabsorbable sutures or stapling devices. Sutured anastomosis (hand-sewn technique) is the commonly used option because of the availability and affordability of suture materials and familiarity with the procedure. The increased availability of stapling devices for intestinal anastomosis has provided an alternative option to perform a rapid anastomosis. Higher cost, limited availability, and less familiarity are the main drawbacks of stapling devices. Less common techniques for intestinal anastomosis use compression devices (biofragmentable anastomotic rings), glue (tissue or synthetic), and laser welding

b) Loop colostomy

This is the most usually formed temporary colostomy. Its side depends on the reason for its construction.
In principle, a loop of colon is brought to the surface, secured by mucocutaneous suture and held in place by a rod until it becomes adherent (usually 5-8 days) when the rod can be removed.
This kind of stoma will divert the stool and gas completely from the proximal portion of the colon while the distal portion is ventilated.
Loop stomas are now less commonly constructed in cases of obstruction than in the past, as more surgeons embark on immediate intestinal resection in the treatment of these conditions.

c) Hartmann's procedure

1.Incision and inspection of abdomen

Usually the surgical approach is made by a median pubo-umbilical incision, prolonged above the umbilicus. Turning the blade around the umbilicus, could result in an irregular and cosmetically displeasing incision. In order to avoid this problem, the umbilicus must be retracted laterally after grasping it with tissue forceps and then making a straight incision.
When the umbilicus is released, the incision will curve smoothly around the umbilicus.

Subsequently, the incision is carried down to the fascia. If the patient is obese, and a large amount of subcutaneous tissue is found, the midline may be difficult to find. To make it easier to find the midline, the surgeon and assistant should each place a large laparotomy pad on either side of the incision and exert strong lateral traction. This will cause a relatively avascular plane to open up in the midline.

After access to the peritoneal cavity is gained, the abdomen is examined to confirm the diagnosis. We will place a large self-retaining retractor. Care must be taken to pad the abdominal wall when placing the retractor.

A complete abdominal exploration is mandatory before considering the resection.

Once the abdomen is opened there is always some free fluid present, some of which should be placed in a sterile screw-capped pot and sent for aerobic and anaerobic culture as well as cytological analysis (40).

2. Exposure of sigmoid colon and pelvis

Next, the patient will be placed in a mild Trendelenburg position to facilitate exposure of the sigmoid colon and the pelvis. The small bowel has to be retracted upward and then placed in the right upper quadrant in order to keep it out of the way. The simple way of doing it is wrapping the small bowel in a warm towel and retracting it with one of the Bookwalter retractor.

The sigmoid colon is then mobilized. With the colon held in the surgeon's left hand, the lateral peritoneal reflection (the white line of Toldt) is incised, and dissection is carried out proximal and distal to the affected area. To produce a tension-free colostomy, it is usually necessary to mobilize the descending colon and the sigmoid colon; the splenic flexure is not routinely mobilized.

At this point, the surgeons will have to identify the ureter. It can usually be found as it crosses over the aortic bifurcation. The gonadal vessels can be a helpful landmark: once they are identified, the ureter can usually be found slightly medial and deep to them (40).

3. Transection of bowel

The next step is to select the proximal point of bowel transection, after the sigmoid and the descending colon are completely mobilized. Usually, this point lies at the junction between the descending colon and the sigmoid colon. Taking the ascending branch of the left colic artery as a reference, it can be identified.

Using a linear cutting staple, the descending colon has to be divided. The sigmoide vessels will be divided up to the rectosigmoide junction. The loss of taeniae coli, will serve as an indication that were the rectum is. Immediately after its identification, the rectum is similarly divided through healthy tissue (40).

4. Creation of colostomy

The next step is to create the colostomy. The colostomy must function optimally and must be capable of remaining in place for a long time.

Colonic mobilization at this point should be sufficient to allow bringing up a segment of descending colon about 2-3 cm above the skin, without any tension. It is not recommended to do a more extensive mobilization, because an increased risk of prolapse (28).

A 3-cm circular disk of skin is then removed at the colostomy site followed by a longitudinal incision through the subcutaneous fat to expose the rectus sheath. The rectus sheath is incised longitudinally, and the muscle is bluntly split to expose the posterior sheath and peritoneum. At this point, the laparotomy sponge is visible under the peritoneum (40).

Then the peritoneum is opened; the laparotomy sponge prevents injury to the abdominal contents. A Babcock clamp is advanced through the skin incision and into the abdominal cavity, then used to grasp the stapled proximal bowel. The stapled bowel is brought out through the abdominal wall, with care taken to ensure that it is not twisted or under tension (40).

5. Closure and stoma maturation

The midline incision must be closed before the colostomy is matured. Two sutures will be used, one starting from the superior portion of the wound and the other from the inferior aspect. The two sutures meet in the middle of the wound, ensuring adequate length and avoiding the use of a short suture at the distal end of the incision.

The midline incision is then protected with a towel or laparotomy pad while the stoma is matured. The staple line is excised from the stoma. Stitches are placed, one at each aspect of the stoma (superior, inferior, lateral, and medial). The objective in creating a colostomy leaving the bowel flushed against the skin. The skin is then closed with skin staples, and an ostomy appliance is placed over the colostomy (28).

Complications

Potential complications of the Hartmann's procedure include the following:

- Wound infection (most common).
- Rectal stump leak
- Abscesses around the rectal stump
- Fistula from the rectal stump to the bowel
- Retraction of the colostomy
- Parastomal hernia
- Skin irritation around the colostomy
- Paralytic ileus
- Wound dehiscence
- Ureteral injury

Colostomies

Generally, the stoma creation begins with an incision on the left side of the rectus abdominis projection area, followed by the dissection of the subcutaneous layer and incision of the anterior sheet of the rectus abdominis.

After the dissociation of the muscular fiber, an incision is made on the posterior sheet of the rectum abdominis and peritoneal sheet, and the sigmoid or the descending colon (depending on the anatomic and clinical findings for each patients) is exteriorized.

A series of discontinuos and reabsorbable sutures are then placed around and exteriorized bowel to ensure its fixation to the tegument.

When the patient is recovered the reinsertion of the colostomy could be done. In order to restore continuity an anastomose between the descendent colon and the rectum is performed.

Stent as a bridge to surgery

The stent placement will be performed using a combination of direct endoscopic visualization and fluoroscopic guidance. An expandable uncovered metallic colonic stent that passes through the working channel of a standard adult colonoscope with midbody diameters and proximal flange diameters of 22/27 and 25/30 mm respectively, and with length of 6, 9 and 12 cm (WallFlex, Boston Scientific) will be used.

First of all the endoscope will pass to the site of the obstruction. Contrast material will be injected directly through the working channel of the endoscope in order to define the stricture. Immediately after, a guidewire will traverse the stricture. Then, the predeployed stent will be passed through the channel of the endoscope and positioned across the lesion.

The stent will be deployed by withdrawing the constraining sheath. It is important that the SEMS has a suitable length to bridge the stricture. It must extend at least 2 cm on each side of the lesion, once it is deployed.
After deployment, we will perform a radiography in order to assess the proper positioning of the SEMS.
One must also account for the degree of shortening that occurs during deployment and stent movement away from the endoscopist as the sheath is withdrawn.

In patients who present with complete colonic obstruction, consideration should be made to leave the guidewire in place after stent deployment to pass a colonic decompression tube through the stent and into the proximal bowel if immediate passage of stool does not occur after stent placement.

Contraindications for stenting

Contraindications to placement of SEMS in the upper gastrointestinal tract are:

- Free perforation with signs of peritonitis or tension pneumoperitoneum.
- Documentation of multiple sites of obstruction not within an area that could be covered by one or two stents.
- Documented peritoneal carcinomatosis is a relative contraindication to stent placement.
- Known benign disease, including strictures and adhesions, is considered a contraindication to stent placement.

8- STATISTICAL ANALYSIS

All statistical analysis will be performed with Statistical Package for the Social Sciences (SPSS) for Windows®.

Univariate analysis

In the univariate analysis, the variables will be defined as categorical or continuous.

On the one hand, for the categorical variables, the results will be expressed in percentages. One the other hand, for quantitative continuous variables, if a normal distribution could be assumed, we will use mean and standard deviation; whereas if a normal distribution cannot be assumed, the median and the quartiles will be estimated.

Bivariate analysis

In our study, both the independent and dependent variables are categorical and for realize the comparison between them, we will use a Chi-square test.

In other words, to prove statistical association between the interventions and the diminution of mortality and morbidity, a $\chi 2$ (Chi Square) test will be required.

While for the comparison between the independent variables with the secondary dependent variables, Student's t-test will be needed as the independent variable is a categorical variable and the secondary dependent variables are quantitative.

Multivariate analysis

A multivariate analysis will be accomplished to adjust our variables for co-variables, thus we will try to avoid potential confounders that could modify the results. It will be done using a logistic regression model.

In order to include the amount of days in hospital also in the multivariate analysis, as it's a quantitative continuous variable, a generalized lineal model will be used.

Missing data

During the post-operative period patients could die. The data of the lost patients will be used until last observation carried forward

9- ETHICAL ASPECTS

This study protocol will be evaluated by the Ethics Committee of the University Hospital of Liège. This committee shall ensure that the study respects the ethical principles for medical research involving human subjects established by Helsinki's Declaration, and that the privacy of all the participants is protected and confidential as well as their personal information. Any further recommendation from the Committee will be taken into account in order to improve the procedure.
Previous to the inclusion, information sheet will be provided to all candidates by presenting the risks, benefits and alternatives to the both different approaches using the best update data available at that point. It is imperative that they understand the information before they are asked to sign the informed consent. Thus the principle of autonomy will be respected.

The subjects will participate voluntarily in the study after giving their informed consent. In the case that a potential research subject could not give us the permission to include him or her in our study, we will seek informed consent from the legally authorized representative. If the representative is not available we will proceed without informed consent and obtain the consent to remain in the research as soon as possible from the subject or a legally authorized representative.

Moreover, all the data collected from our study will be kept strictly confidential ensuring the compliance of the Act of 8 December 1992 on the protection of privacy in relation to the processing of personal data in Belgium. This law intends to guarantee and protect the public liberties and fundamental rights of natural persons. What is more, to maintain confidentially of personal data, an identification number will be used instead of the patient's name.

Finally, in cases that SEMS involves a high risk for the patient in SEMS group of treatment, the managing surgeon is able to decide whether to include or not the patient in the study. That way no patient is being subjected to a worse intervention and there is not an ethic violation.

10- STUDY LIMITATIONS

Several limitations to this study need to be accepted:

The main limitation in our opinion will be to recruit the patients. It is probable that many patients refuse to participate in our study because they will be scared of the surgery and they prefer the stent and an elective surgery.
Patients may prefer to be in the stenting group instead of in the group of emergency surgery because they will understand that there is a risk of ending up with a colostomy if the emergency surgery is the approach elected, which for most of the patients would be a _____

At this juncture, it is possible that we meet patients who want to be changed from the treatment group or may want to withdraw from the study.
The medical team will have to explain to these patients that they are not able to change the group of treatment because the randomization is a crucial part of the study.
In addition, they will have to explain to the patients that if they do not want to take part in the study, they will also be treated with the surgical approach which it is so far the treatment option in the *Centre Hospitalier Universitaire de Liège.*

It is probable that the emergency context also hinders the process of selection of the patients or the participation of everyone needed for the application of the protocol. The physicians, nurses, nursing assistants and all the medical staff, will have to learn to work as a big team to solve this problem. Synchronised work and communication between practitioners will be essential.

Secondly, other limitation of the protocol is the fact that the study presented is an open-label trial. That means the patient, doctors and the research team will know in which approach is the patient included. With the intention to overcome this limitation, the statistician will be blind and will not be aware of which participant belongs to which group.

A third evident limitation is the extrapolation of our study to other populations. The results obtained, will be valid for our population, but it is possible that this results may or may not coincide with other centers population. Especially because the two compared treatments are both dependent of operator experience. The experience and technique of the surgeons and of the endoscopists, can be a factor that may be determinant of the results. With a major experience a better results will be achieved. A way to avoid inter-surgeon variation or inter-endoscopist variation would be randomize also the physicians that will participate in the study but given the fact that we are developing the study in an emergency context, we have to take in account that the personnel on guard could not be controlled. We will try to minimize the possible bias including the different physicians in the multivariate analysis.

Another limitation that we need to keep in mind is the possible loss of patients. We have described that we consider a loss follow-up the patients who die, but could be that patients may not come to visit and the results of the study may be biased.

However we expect that the lost follow-up will be minimum as most of the appointments are part of the medical care. In case that the patients do not come to the appointments with the doctors, the administrative workers participating in the study team, will try to contact them via phone, text message or email during the following days. Intention-to-treat analysis will be used for missing data.

Finally, the time estimated to recruit all the patients will be three years and a few more moths approximately. With the intention of reducing the time needed for obtaining all the patients maybe considering a multicenter study would be a good solution. The problem of the multicenter study is that the variability of the approaches increases and also the realization will be more difficult and the costs higher.

11- WORK PLAN

This study is expected to last 6 years. All the activities carried out during this period of time by the researcher team, will be organized in 5 phases which are detailed below:

1- Preparation and coordination phase (4 months).

This first phase of the study will consist in the elaboration of the protocol from September 2015 to November 2015. A detailed definition of the study variables will be done.

The entire team participating; investigators, collaborators, nursing staff, administrative staff and statisticians, will meet in order to specify which will be the tasks of every member of the team. The chronogram will be arranged in collaboration with the other members of the research team and the methods for data collection will be discussed and set up.

Once the protocol is ready, we will present it to the Ethical Committee for its evaluation and approval.

As the study is longitudinal and it will last about 6 years, the researchers decide to organize meetings every three months in order to control the data collected and to assess the progression of the study. The aim of this is to identify deficiencies of the study design and correct the methodological flaws.

2- Field research

- Sample collection (3 years): patients who come to the emergency department and that meet the inclusion criteria for our study will be collected and distributed randomly into different study groups. Inclusion period will last 3 years and it could be prolonged in case of not achieving the predefined sample.

- Interventions (during 3 years): Each patient incorporated in the study will be immediately given the surgical or endoscopic treatment depending on the group assigned.
  If the endoscopic treatment fails or it cannot be done, the surgeons will proceed to perform an emergency surgery.
  If a patient of the surgery group has a dehiscence during the postoperative days, he/she will be re-operated.

- Follow up (3 years): every patient will be followed during six years counting from the day of the inclusion in the study.
  We are going to set our first appointment after the 30 days after the first approach and then after the three months.
  After the first month, the control visits would be scheduled at three months, after one year and after three years.

  As our patients are affected for colon cancer and the normal follow up for these patients is five years, we will use the mandatory visits for our data collection also.

3- Data collection (6 years).

While the trial is taking place, the data collected from each patient will be registered in our database.

This collected data, will be periodically evaluated and analysed by our statistician to control if the protocol is being followed.

4- Data analysis and final evaluation (6 months).

After processing the database, all data will be analysed using the appropriate statistical test by a statistician.

5- Results interpretation (6 months).

An interpretation of the results will be performed and of the results found are what we expect, the corresponding articles will be written.

6- Publication and dissemination (1 year).

The researchers will write and edit a scientific paper to publish.

12- FESIABILITY

The study proposed, will take place in *Centre Hospitalier Universitaire de Liège*, where all the means necessaries for the study development will be available and provided.

The abdominal surgery service and the gastroenterology unit of the hospital, in coordination with the emergency department, will work together in order to achieve the marked objectives. The emergency department will serve as a gateway to our patients to the study and afterwards, the patients will receive the surgical or endoscopic (as a bridge to surgery) treatment.

The hospital also has a service of statistics. We will hire a statiscian who will be the responsible of the statistical analysis and processing of the data collection.

For the patients in the group of emergency surgery, operating room will be always available as it is an emergency situation and as it is the standard treatment in this center for MLCO. The emergency operating rooms will be used in this study.

In the group of stents as a BTS, since the surgery becomes elective, and also because is a usual surgery performed, the operation rooms would be available for the interventions.

To carry out the study, the hospital will supply the necessary means. Personnel salaries, surgeries, cures and following up are covered by the hospital.
The informatics equipment needed for processing the database for the study development and statistical analysis will be also dispensed by the hospital.

In *Centre Hospitalier Universitaire de Liège*, around 35-40 patients presenting an acute malignant left colonic obstruction are admitted per year. According to that, in three years, we will have our sample completed.

13- BUDGET

For our budget we have done the following estimations:

The appointments and surgeries will not be included in the budget because they are part of the National Belgian Health System. Since the hospital has a statistical service, we will hire a statistical specialist who will randomize and code the patients of our study control the data quality, the statistical analysis and who will help us with the discussion and publication of the results if needed. The salary is 50€ per hour and approximately we believe that we will need his or her services for 80 hours, which means that the estimated cost will be 4000€.

In order to help us with the data collection, we will also hire two administrative workers from the hospital who will be responsible of making the necessary phone calls and a freelance clinical research professional who will be the person in charge of the study registration

information and who will attend the appointments with the patients in order to collect the data needed.

We will also need insurance for the patients and also for the researchers which is about 4000€.

The appointments and surgeries will not be included in the budget because they are part of the National Belgian Health System.

The Belgian health system includes the stents in the public health but due to the fact that we have to budget all the elements of the study we will need 2925€ because each stent costs 450€.

We will also include the extra hospitalization days for the group of patients treated firstly with the stent and secondly with the surgery. If we only count one day in hospital which is about 500€, and we have 65 patients the total amount for one extra day will be 32500€. It is mandatory to clarify this point and to average a number of days in hospital for this group of patients.

Finally, in case the results are relevant and we decide to publish them, we can approximate that 3000 euros will be needed, knowing that the costs of publications are around 2000 euros and the national dissemination in the next congress will be around 1000 euros.

	BUDGET PROPOSAL	
	Description	**Total cost**
STAFF		
Statistical specialist	50€/h x 80h	4.000€
Administrative workers	350€/year x 6 years	2.100€
Freelance clinical researcher	30€/h x 80h	2.400€
MATERIAL		
Stent	450€ unit x 65 stents	29.250€
Extradays in hospital	1 day 500€ x 65 patients	32.500€
Insurance	Insurance patient's for 130 patients.	4.000€
PUBLICATION AND DISSEMINATION		
Cost of publications		2.000€
National congress		1.500€
TOTAL		
		77.750€

14- IMPACT

The main aim of this project is to achieve more information about the indication, safety and utilization of colonic stents as a bridge to surgery in patients with left colonic obstruction.

Due to the high frequency of the obstruction among patients affected by colorectal cancer, we consider that the necessity of assess this treatment is evident and that is the reason why we decided to propound this protocol.

If the results obtained are relevant enough and our hypothesis is validated, at least, for our population of study, we will be confident in the implementation of this technique for the management of left colonic obstruction. This can suppose a change in the routinely treatment.

Firstly, because the rates of mortality will be lower and secondly because the morbidity, understood in this project as the amount of complications derivate from the emergency surgery will be also less frequent.

As a whole, it will be a positive change in the way we treat this patients.

As far as we could confirm that the use of stents is not harmful for the patients, (even six years after the treatment) we will be offering our patients a general improvement in the management of their disease, that is to say, we will be presenting them a series of benefits in comparison with the classical surgical treatment as for example our patients will not need colostomy anymore. It is important for us to note this concrete point as far as we are aware of the psychological distress the colostomy entails and that 40-60% of patients treated with emergency surgery carrying a colostomy, will not have their colostomy reversed.
Also the expenses related to the colostomy care will be reduced.

Although this technique works in our center, further studies with bigger samples will be needed in order to make a step forward in the establishment of the best treatment.

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16- ANNEXES

Annex 1: CASE REPORT FORM (CRF)

CASE REPORT FORM

Project title: EMERGENT SURGERY VS. STENT AS A BRIDGE TO SURGERY IN PATIENTS WITH ACUTE MALIGNANT LEFT COLONIC OBSTRUCTION. A RANDOMIZED CONTROLLED TRIAL

Patient's number identification					

Instructions:

- Please write the patient's identification number in the boxes above.
- Read carefully and marc with "X" in the most suitable option in the boxes.
- Please mark all the boxes. Verify you have marked the right box and that the X is clear.
- Write your surname and the date before you start collecting the data in every appointment.
- Mark X if the patient has attended or answered your call.
- If you have doubts or you have problems with some answer or item, please contact with the investigators by phone at +34696000000.

Patients information:

NAME _____ DATE OF BIRTH _____

SURNAME _____ TELEPHONE _____

DIRECTION _____ EMAIL _____

DATE OF INCLUSION ____ / ____ / ____ SEXE: MALE ☐ FEMALE ☐

The patient has read the information sheet: YES ☐ NO ☐

The patient has signed the consent form: YES ☐ NO ☐

Investigator's name and ID _____

1- Phase 1. Trial entry in the emergency department

Group of treatment:

EMERGENCY SURGERY ☐ **SEMS as a Bridge to surgery** ☐

Preoperative information

Age (years): BMI (kg/m2):

Height (cm): Blood pressure:

Weight (kg): Heart rate:

Allergies:

Regular medication:

Toxic habits

Obstruction confirmed by CT scan ☐

Tumour stage if known:

Localization of the obstruction:

Previous surgical interventions:

Other concomitant diseases:

2- Phase 2. Postintervention.

EMERGENCY SURGERY TYPE		**SEMS as a BTS**	
Primary anastomosis	☐	**Successful stent placement**	☐
Loop colostomy	☐	**Impossible stenting and conversion to surgery**	☐
Hartmann's technique	☐		

Localization of the obstruction: Splenic flexure ☐ **Recto sigmoidal junction** ☐ **other location** ☐
Peritoneal carcinomatosis found: Yes ☐ **No** ☐
Other findings _____

Colostomy Yes ☐ No ☐

3- Phase 3.

Number of days of hospital stay:

Date of discharge ___ /___ / ___

Inhospital stay complications:

4- Phase 4. Follow-up

FIRST APPOINMENT - 30 days after treatment

- **Postoperative complications:**

- **SF-36**
  - Answered Yes ☐ No ☐
  - Punctuation ☐

SECOND APPOINMENT - 6 months after treatment

- **For patients with colostomy only.**

Reversal of colostomy: Yes ☐ No ☐

Date of reversal ___ / ___ / ___

- **SF-36**
  - Answered Yes ☐ No ☐
  - Punctuation ☐

THIRD APPOINTMENT - 1 year after treatment

- **Long term complications:**

☐

- **SF-36**
  - Answered Yes ☐ No ☐
  - Punctuation ☐

FOURTH APPOINMENT - 3 years after treatment

- **Long term complications:**

☐

- **SF-36**
  - Answered Yes ☐ No ☐
  - Punctuation ☐

Annex 2: INFORMATION SHEET FOR PATIENTS AND CONSENT FORM

INFORMATION SHEET FOR PARTICIPANTS

Project: EMERGENT SURGERY VS. STENT AS A BRIDGE TO SURGERY IN PATIENTS WITH ACTUTE MALIGNANT COLONIC OBSTRUCTION. A RANDOMIZED CONTROLLED TRIAL".

Investigators:

You are being invited to take part in a research study.
Please take time to read the following information about the study carefully. It is important for you to understand why the research is being done and what it will involve. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.
Thank you for reading this.

This Informed Consent Form has two parts:

- **Information Sheet (to share information about the research with you)**
- **Certificate of Consent (for signatures if you agree to take part)**

You will be given a copy of the full Informed Consent Form.

What is the purpose of the study?

The purpose of this study is to compare the effectiveness in reducing mortality rates between two different approaches for the treatment of left colonic obstruction.
We aim to compare the surgical treatment in an emergency setting with another one that consists in the introduction of a stent to solve the obstruction and a few days after perform the surgery.

We also want to assess, if the SEMS increase the quality of life of our patients, if the recurrence are minor when we treat the patient with SEMS before surgery and if they offer a shorter hospital stay.

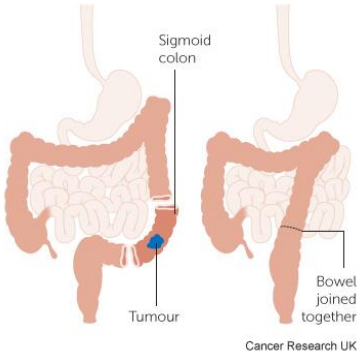
Due to the fact that colonic obstructions are very frequent and that we have different option for treatment our intention is to find out which is the most recommended.

Type of Research Intervention

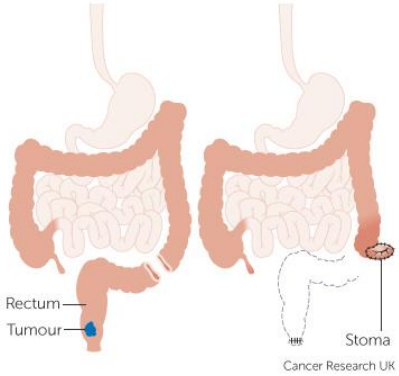
In this study, two options of treatment are proposed. One the one hand, we have a surgical treatment and on the other hand an endoscopic procedure followed by a surgery.

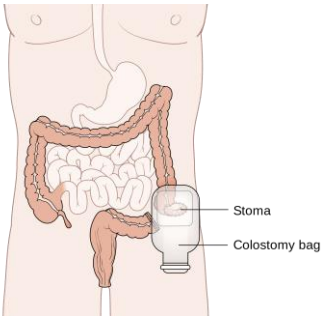
- *What kind of surgery intervention?*

The emergency surgery is done in order to remove the blockage of your bowel and restore the continuity of your colon.
The first intention of the surgeons is to eliminate the cause of the obstruction and anastomose, which means to join again the two parts of the bowel that have been cut.



In some cases anastomosis cannot be done in the emergency situation and surgeons will have to do a colostomy.
A colostomy is a surgical procedure that brings one end of the large intestine out through an opening (stoma) made in the abdominal wall. Stools moving through the intestine drain through the stoma into a bag attached to the abdomen.
After a period of time estimated of 3 months, when you have recovered from the first intervention; you will be submitted to the second intervention which consists in the reintegration of the colostomy with the intention to attach the two sides of your bowel.





- *What is endoscopic technique?*

The stent is a metallic tube that will be introduced in your colon under laparoscopic guidance When the stent is placed in the obstruction site, it will be opened and with that action the obstruction is solved.

After 7-10 days you will be operated and the tumor together with the stent will be removed.

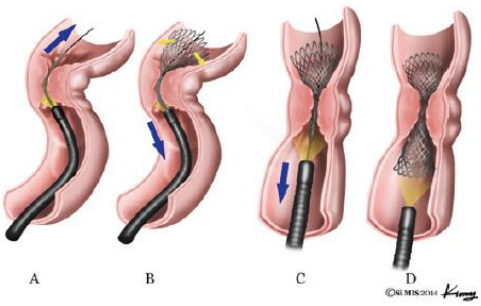


Figure 1 Technique of SEMS placement in acute colorectal obstruction. A: Passing stent and guide wire through lesion with contrast injection. B: Partial stent deployment. C: Pull back stent and scope until fair part of stent reach upper border. D: Fully deployment of SEMS.

This picture shows how the metalic stent is implanted in the large bowel.

This technique will be performed with the patient under general anesthesia.

You should also know that the stent placement it is not always possible. Sometimes, the type of obstruction, the bad conditions of the bowel or the big dilatationof the large bowel, prevent this approach.
If this happens, you will need a surgery in order to remove the blockage and if possible reanastomose the two sides of the bowel cuted. If the anastomose is not possible to make, you will receive a colostomy. Although the percentatges of unsuccesful placement of the stent are low, you should be aware that it is a risk.

This technique also implies other risk, which is the bowel perforation. It could happen that during the stent insertion a perforation occurs. In this case you will be immediately operated concerning the risk the perforation means.

Randomization

Because we do not know if the option of treatment with the stents as a bridge to surgery for treating the left colonic obstruction is better than emergency surgery, we need to compare the two approaches. To do this, we will put people taking part in this research into two groups. The groups are selected by chance, as if by tossing a coin.

Participants in one group will be treated with a stent and then a few days later they will be subjected to a surgery while participants in the other group will treated with emergency surgery. We will then compare which of the two has the best results.

The healthcare workers will be looking after you and the other participants very carefully during the study. If there is anything you are concerned about or that is bothering you about the research please talk to me or one of the other researchers

Duration

The study is estimated to last two years for recruit all the patients and if you participate we will follow you during three years.

When you come to your following up consultations and after this period of time, the information will be collected by phone call.

Voluntary Participation

Your participation in this research is entirely voluntary. It is your choice whether to participate or not. Whether you choose to participate or not, all the services you receive at this clinic will continue and nothing will change.
If you choose not to participate in this research project, you will be offered the treatment that is routinely SURGERY offered in this hospital for acute left colonic obstruction.
You may change your mind later and stop participating even if you agreed earlier

What are my responsibilities if I take part in the study?

-To go to all the study's appointments and other appointments asked by the study team.
- To follow all the study's instructions.
- To inform about any problem or doubt during the study.
- To answer all the questionnaires when asked by the study team during the appointments.

What are the possible benefits of taking part?

The information we get from this study may help us to treat future patients with a similar condition better. However, it is not guaranteed that your condition will be better as a consequence of participating in the study.

What happens when the research study stops?

Once the study has finished, you will receive the medical care you need depending on your condition without affecting having or not participate in the study.

Confidentiality

The information that we collect from this research project will be kept confidential. Information about you that will be collected during the research will be put away and no-one but the researchers will be able to see it. Any information about you will have a number on it instead of your name. Only the researchers will know what your number is and we will lock that information up with a lock and key. It will not be shared with or given to anyone except Student researcher Mireia Bauzá and Dr. Coimbra.

Sharing the results

The knowledge that we get from doing this research will be shared with you through community meetings before it is made widely available to the public. Confidential information will not be shared. There will be small meetings in the community and these will be announced. After these meetings, we will publish the results in order that other interested people may learn from our research

Right to refuse or withdraw

You do not have to take part in this research if you do not wish to do so and refusing to participate will not affect your treatment at this clinic in any way. You will still have all the benefits that you would otherwise have at this clinic. You may stop participating in the research at any time that you wish without losing any of your rights as a patient here. Your treatment at this clinic will not be affected in any way

Who can I contact to for Further Information, doubts or problems?

If you have any questions about your rights as a research subject, about your participation in the study or any complains about the study, please contact with your research doctor

CONSENT FORM

This Informed Consent Form is for men and women who attend Centre Hospitalier Universitaire de Liège.

Project: **EMERGENT SURGERY VS. STENT AS A BRIDGE TO SURGERY IN PATIENTS WITH ACTUTE MALIGNANT COLONIC OBSTRUCTION. A RANDOMIZED CONTROLLED TRIAL".**

I have read the foregoing information, or it has been read to me. I have had the opportunity to ask questions about it and any questions that I have asked have been answered to my satisfaction. I consent voluntarily to participate as a participant in this research and I understand that I am free to withdrawal at any time without giving any reason, keeping my medical care and legal rights.

Print Name of Participant_____

Signature of Participant _____

Date _____

Day/month/year

The researchers declare,

I have accurately read out the information sheet to the potential participant, and to the best of my ability made sure that the participant understands the study will be done.

I confirm that the participant was given an opportunity to ask questions about the study, and all the questions asked by the participant have been answered correctly and to the best of my ability. I confirm that the individual has not been coerced into giving consent, and the consent has been given freely and voluntarily.

A copy of this ICF has been provided to the participant.

Print Name of Researcher/person taking the consent____ **Mireia Bauzá Collado**

Signature of Researcher /person taking the consent_____

Date _____

Day/month/year

Annex 3: SF-36 QUESTIONNAIRE FOR QUALITY OF LIFE

SF-36 QUESTIONNAIRE

Name:_____ **Ref. Dr:**_____ **Date:** _____

ID#: _____ **Age:** _____ **Gender: M / F**

Please answer the 36 questions of the **Health Survey** completely, honestly, and without interruptions.

GENERAL HEALTH:

In general, would you say your health is:

☐ Excellent ☐ Very ☐ Good ☐ Good Fair ☐ oor

Compared to one year ago, how would you rate your health in general now?

☐ Much better now than one year ago

☐ Somewhat better now than one year ago

☐ About the same

☐ Somewhat worse now than one year ago

☐ Much worse than one year ago

LIMITATIONS OF ACTIVITIES:

The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports.

☐ Yes, Limited a lot ☐ Yes, Limited a Little ☐ No, Not Limited at all

Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf

☐ Yes, Limited a lot ☐ Yes, Limited a Little ☐ No, Not Limited at all

Lifting or carrying groceries

☐ Yes, Limited a lot ☐ Yes, Limited a Little ☐ No, Not Limited at all

Climbing several flights of stairs

☐ Yes, Limited a lot ☐ Yes, Limited a Little ☐ No, Not Limited at all

Climbing one flight of stairs

☐ Yes, Limited a lot ☐ Yes, Limited a Little ☐ No, Not Limited at all

Bending, kneeling, or stooping

☐ Yes, Limited a lot ☐ Yes, Limited a Little ☐ No, Not Limited at all

Walking more than a mile

☐ Yes, Limited a lot ☐ Yes, Limited a Little ☐ No, Not Limited at all

Walking several blocks

☐ Yes, Limited a lot ☐ Yes, Limited a Little ☐ No, Not Limited at all

Walking one block

☐ Yes, Limited a lot ☐ Yes, Limited a Little ☐ No, Not Limited at all

Bathing or dressing yourself

☐ Yes, Limited a lot ☐ Yes, Limited a Little ☐ No, Not Limited at all

PHYSICAL HEALTH PROBLEMS:

During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

Cut down the amount of time you spent on work or other activities

☐ Yes ☐ No

Accomplished less than you would like

☐ Yes ☐ No

Were limited in the kind of work or other activities

☐ Yes ☐ No

Had difficulty performing the work or other activities (for example, it took extra effort)

☐ Yes ☐ No

EMOTIONAL HEALTH PROBLEMS:

During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

Cut down the amount of time you spent on work or other activities

☐ Yes ☐ No

Accomplished less than you would like

☐ Yes ☐ No

Didn't do work or other activities as carefully as usual

☐ Yes ☐ No

SOCIAL ACTIVITIES:

Emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

☐ Not at all ☐ Slightly ☐ Moderately ☐ Severe ☐ Very Severe

PAIN:

How much bodily pain have you had during the past 4 weeks?

☐ None ☐ Very Mild ☐ Mild ☐ Moderate ☐ Severe ☐ Very Severe

During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

☐ Not at all ☐ A little bit ☐ Moderately ☐ Quite a bit ☐ Extremely

ENERGY AND EMOTIONS:

These questions are about how you feel and how things have been with you during the last 4 weeks. For each question, please give the answer that comes closest to the way you have been feeling.

Did you feel full of pep?

☐ All of the time

☐ Most of the time

☐ A good Bit of the Time

☐ Some of the time

☐ A little bit of the time

☐ None of the Time

Have you been a very nervous person?

☐ All of the time

☐ Most of the time

☐ A good Bit of the Time

☐ Some of the time

☐ A little bit of the time

☐ None of the Time

Have you felt so down in the dumps that nothing could cheer you up?

☐ All of the time

☐ Most of the time

☐ A good Bit of the Time

☐ Some of the time

☐ A little bit of the time

☐ None of the Time

Have you felt calm and peaceful?

☐ All of the time

☐ Most of the time

☐ A good Bit of the Time

☐ Some of the time

☐ A little bit of the time

☐ None of the Time

Did you have a lot of energy?

☐ All of the time

☐ Most of the time

☐ A good Bit of the Time

☐ A little bit of the time

☐ None of the Time

Have you felt downhearted and blue?

☐ All of the time

☐ Most of the time

☐ A good Bit of the Time

☐ Some of the time

☐ A little bit of the time

☐ None of the Time

Did you feel worn out?

☐ All of the time

☐ Most of the time

☐ A good Bit of the Time

☐ Some of the time

☐ A little bit of the time

☐ None of the Time

Have you been a happy person?

☐ All of the time

☐ Most of the time

☐ A good Bit of the Time

☐ Some of the time

☐ A little bit of the time

☐ None of the Time

Did you feel tired?

☐ All of the time

☐ Most of the time

☐ A good Bit of the Time

☐ Some of the time

☐ A little bit of the time

☐ None of the Time

SOCIAL ACTIVITIES:

During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

☐ All of the time

☐ Most of the time

☐ Some of the time

☐ A little bit of the time

☐ None of the Time

GENERAL HEALTH:
How true or false is each of the following statements for you?

I seem to get sick a little easier than other people

☐ Definitely true ☐ Mostly true ☐ Don't know ☐ Mostly false ☐ Definitely false

I am as healthy as anybody I know

☐ Definitely true ☐ Mostly true ☐ Don't know ☐ Mostly false ☐ Definitely false

I expect my health to get worse

☐ Definitely true ☐ Mostly true ☐ Don't know ☐ Mostly false ☐ Definitely false

My health is excellent

☐ Definitely true ☐ Mostly true ☐ Don't know ☐ Mostly false ☐ Definitely false

Annex 4: CHRONOGRAM

TASKS	2015		2016				2017				2018				2019				2020				2021				2022				Researchers
	Sep -Oct	Nov -Dec	Jan-Mar	Apr-Jun	Jul-Sep	Oct-Dec	Jan-Mar	Apr-Jun	Jul-Sep	Oct-Dec	Jan- Mar	Apr- Jun	Jul- Sep	Oct – Dec	Jan - Mar	Apr- Jun	Jul- Sep	Oct- Dec	Jan- Mar	Apr- Mar	Jul- Sep	Oct- Dec	Jan - Mar	Apr- Jun	Jul- Sep	Oct – Dec	Jan - Mar	Apr- Jun	Jul- Sep	Oct- Dec	
PREPARATION AND COORDINATION PHASE																															
Protocol elaboration and evaluation																															MB, CC
Coordination of reaserch team																															All reseacrh team
FIELD RESEARCH AND DATA COLLECTION																															
Recruitment of patients, intervention																															Clinical researchers
Coding and data collection																															Researchers
Data cleansing, quality assurance and control																															FR
DATA ANALYSIS																															
Statistical analysis																															Statistician
Interpretation and discussion of the results																															Statistician
PUBLICATION AND DISSEMINATION																															
Scientific publications and National congress.																															Surgery team.