

## **The ACBC- trial    June 17<sup>th</sup> 2020**

Acute Colon resection versus Bridge to Colon surgery with stent or stoma: a prospective cohort study

### **ABSTRACT**

P patients with acute obstructive colon cancer

I resection or bridge to surgery with stent or stoma

C emergency procedure

O morbidity and mortality within 30 days, 90 day mortality and 3 & 5 years overall survival

### **INTRODUCTION**

#### **Study committee**

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Ingvar Syk Department of Surgery, Skåne University Hospital Malmö (on the part of the study that is included in the Ph.D. thesis of Tobias Axmarker)

The committee decides on the final version of the protocol, changes in the protocol as well as data analyses. The committee can include other researchers at will.

#### **Study group**

All surgical departments in Sweden treating patients with acute colon cancer obstruction may participate in the study. The study is available for foreign departments as well.

#### **Writing committee**

The results of the ACBC-study are planned to be published in international peer reviewed scientific journals. The members of the study committee together with some participating researchers in the study group handling the enrolment and follow up of patients locally, fulfilling the Vancouver criteria will be part of the writing committee. The final decision on participation in the writing committee will be left to the PI and vice PI based on the researchers' contribution to the study. All papers will be written on behalf of the ACBC-study group and the names of all study group members will be published and indexed.

### **Study secretariat**

The study secretariat will be situated at SUS Malmö, Department of Surgery, Lund University 205 02 Malmö. A study specific e-CRF form has been created and is currently being linked to the INCA platform. Supplementary clinical data will be retrieved from the Swedish ColoRectal Cancer Registry (SCRCR). The clinical data will be collected prospectively by the researches at each centre and will be registered in the e-CRF, linked to the INCA platform. The study will be registered at Clinicaltrials.gov.

## **PROTOCOL**

### **Background**

Colorectal cancer is a major cause of cancer-related mortality worldwide. In Sweden approximately 4.500 patients are diagnosed with colon cancer annually and the numbers are increasing [1, 2]. Disease stage according to AJCC is the most important prognostic factor. Emergency presentation of colon cancer including obstruction, perforation, and haemorrhage comprises 17-26% of colon cancer cases in Sweden and in other countries [1, 3]. Roughly 70% of all emergencies are due to colonic obstruction, hereafter referred to as malignant obstruction. Patients who undergo emergency surgical resections for colon cancer have a higher overall 30- day morbidity (33%) and spend more days in the hospital [1, 4-5]. Furthermore, they have an increased 30- day (5%) and 90- day mortality (11%) compared to elective cases 1.3 and 2.5%, respectively [1]. Other concerns about acute colon cancer resections are the short term and long term oncological outcomes. Long term oncological outcomes are significantly worse in terms of recurrence and death [6-8] where adjuvant chemotherapy does not appear to make a difference. Furthermore, decision making in the acute situation may be challenging for the individual surgeon, since it is not only the immediate postoperative morbidity and mortality to consider but also the oncological results.

Colon resection has been gold standard for acute malignant obstruction due to colon cancer [1]. The concept of bridge-to-surgery for colon cancers was introduced assuming temporary decompression would improve postoperative and oncological outcomes. Stoma and self-expanding metallic stent (SEMS) are two options for bridge-to-surgery [9-12]. It is theoretically appealing to create an elective procedure out of an emergency before cancer resection to allow decompression, treatment of unfavourable physiology and improve nutritional status. Moreover, this would concede qualified colorectal surgeons to perform the resection possibly with an increased use of minimally invasive surgery. From an oncological point of view this would allow better surgical specimens in terms of R0-resection, total mesocolic excision and higher lymph yield etc in the short term [12] and possibly lower recurrences and better survival in the long term. Another attainable advantage of decompression would be that patients recover faster and would be accessible for adjuvant chemotherapy when needed. The safety of an anastomotic procedure in the emergency setting with unfavourable physiology is another issue. Many studies have evaluated primary anastomosis in the emergency setting with reassuring results in selected patients even in presence of peritonitis [13-16]. A stoma avoids the risk of anastomotic leakage and lowers the perioperative risk in the emergency setting but there is a high risk of the stoma turning into permanent eventually [10, 17, 18]. There is also the cumulative morbidity and mortality of the stoma reversal procedure to consider.

Initially reported as a palliative measure for non-resectable malignant colonic tumours SEMS was later suggested for initial bowel decompression with delayed elective resection in malignant left colonic obstruction [10, 17, 18]. Pioneer data suggested that SEMS was associated with a lower stoma formation rate and more successful primary anastomosis [17]. However, there were issues regarding technical and clinical success rates as well as clinical and silent perforations and subsequent oncological results [19]. More recent reports imply that long-term oncological data using SEMS is not impaired at least in experienced hands [20, 21].

Tumour location matters when choosing therapy for malignant obstruction. Current opinion may advocate resection +/- primary anastomosis in most tumours proximal to the splenic flexure while the optimal treatment for left colonic cancers remains debated [16]. However, emerging data suggests that at least high-risk patients with obstructing right sided cancer may benefit from a staged surgical management [17] although there is conflicting data whether SEMS is recommendable on right sided cancers [22].

There are studies evaluating treatment of obstructive left-sided colon cancer at a national level. All studies demonstrate that surgical resections are performed in most of cases and these are associated with high morbidity and mortality particularly in frail patients [9, 11,22, 23]. A recent Dutch retrospective nation-wide analysis of 2587 patients (2013 emergency resection, 229 SEMS and 345 defunctioning stomas) treated between 2009-2016 showed a decreased 90-day mortality rate for patients defunctioned by stoma explained mainly by a lower anastomotic leakage rate [24].

In summary, there is a need for a prospective study regarding malignant colonic obstruction to evaluate how these patients are best dealt with. This study will collect data on all colon cancer causing acute obstruction regardless of location. To date we do not know how many patients that are treated with a bridge-to-surgery intent that eventually undergo a resectional procedure.

#### **AIM AND HYPOTHESES**

The aim of this prospective observational study is to evaluate primary resection for malignant obstruction of the colon compared to only decompression as first intervention regarding postoperative outcomes. We hypothesize that patients with malignant obstruction benefit from avoidance of emergency cancer resection, by a two-stage procedure, with decompression by a stoma or stent as first intervention, leading to decreased short-term morbidity and mortality and improved long-term oncological outcome.

#### **PRIMARY ENDPOINTS**

- 30-day and 90-day mortality
- Total 30-day severe morbidity (>Clavien Dindo 3a), including resection and decompression with subsequent resection and anastomotic leakage
- Overall survival after 3 and 5 years

## SECONDARY ENDPOINTS

- Locally radical resections
- Number of examined mesenteric lymph nodes
- Proportion of patients receiving neoadjuvant or adjuvant treatment
- Proportion of patients with stomas after 3 years
- Recurrence rate after 3 after years
- Disease-free survival after 3 years
- Proportion of patients not being subjected to resection of initially decompressed
- Procedure related factors (bridging interval, laparoscopic resection, primary anastomosis, stomas after resection and type of stoma, total hospital stay, qualification of operating surgeon)
- Number of stent complications (perforations, migration, bleeding, success rate etc)
- Number of stoma complications
- Morbidity and survival and impact of tumour location

## STUDY DESIGN

This is an exploratory, prospective, longitudinal, non-interventional, multicentre study aiming to the evaluation of treatment of malignant colonic obstruction due to colon cancer. Baseline characteristics at diagnosis, first line treatment (resection, stoma or stent), complications, proportion of patients ultimately subjected to resectional surgery, type of operation, proportion of permanent stomas and short and long term oncological outcomes will be registered. All cases are to be registered on an intention-to-treat bases, *i.e.* if patients are allocated to stent or stoma initially but this fails, and the patient is resected instead, the patient is to be registered according to first objective and the reason for change registered.

Patients will be identified at participating emergency departments or hospital wards. For patients with suspected malignant colon obstruction a routine medical history will be taken, and the patients will

undergo a clinical examination. Routine laboratory test such as haemoglobin, white blood cell count, creatinine, C-reactive protein, albumin and CEA will be obtained. CT abdomen will be performed before the acute surgical procedure. If findings are consistent with malignant colon obstruction the patient will be included according to the hospital's routine for inclusion in the SCRCR. CT chest should preferably be performed preoperatively. The e-CRF admission form will be linked to SCRCR. In case of urgent surgery preventing that informed consent can be achieved preoperatively informed consent may be retrieved later during the same hospital stay. Prospective registration additional to SCRCR on base line characteristics and certain long-term outcomes will be performed. A screening list of all eligible patients at participating centres will be compulsory to allow analyses of demographics and registry data of the cohort of missed cases.

#### **STUDY POPULATION**

A national cohort study where all patients treated for malignant obstruction are invited to participate. All patients at participating centres who fulfil the inclusion criteria shall be evaluated for participation in the study. To achieve high coverage all potentially eligible patients will be registered continuously along with information on why they were not included. After completion of the study inclusion a retrospective search in SCRCR will be performed for acute procedure and elective procedures with temporary decompression at each participating hospital to identify all not included potentially eligible patients.

#### **INCLUSION CRITERIA**

- Age >18 years
- Symptomatic large bowel obstruction requiring acute intervention
- CT-verified colon obstruction due to colon cancer independent of presence of metastases

## EXCLUSION CRITERIA

- Colonic perforation or bleeding
- Colonic obstruction of other origin than colon cancer

## CRF

e-CRF will be filled out during patients' primary hospital stay.

e-Operation-form will be filled out if bridge-to-surgery is used with either decompressing stoma or stent.

30 days follow up form will be filled out from primary procedure either surgical resection, SEMS or decompression stoma and after resection surgery in case of two-stage procedure.

90-day mortality will be cross checked via Swedish Cause of Death Registry

Follow up at three years via SCRCR (recurrence and survival) + stoma yes/no

Follow up at five years via SCRCR (recurrence and survival)

## STUDY VARIABLES

Baseline characteristics CRF

Age, gender, single household (yes/no), post-secondary education (yes/no), comorbidity (WHO/ECOG performance status, ASA), immunosuppressing medication, time from admission to surgical procedure, prior abdominal surgery. Biochemistry at admission (albumin, CRP, WBC, creatinine), Clinical presentation; duration of symptoms (hours), day of admission, body temperature (C), abdominal pain (tender, local peritonitis, generalised peritonitis), caecum diameter (cm), small bowel dilation (yes/no)

Intervention performed (resectional surgery/stent/stoma) *if stoma* what type, operation date, surgical entry (minimal invasive surgery/open), bleeding, operation time (as xx.xxH-yy.yyH), surgical procedure started after office hours, surgical competence, length of hospital stay, *if stent* procedure date,

technique used, technical success, clinical success, perforation, migration, bleeding, re-stenting, length of hospital stay

All patients preoperative radiological staging (rTNM)

Resectional details from SCRCR: type of operation, histopathological details from the resection incl TNM, date of surgery to calculate bridging interval, laparoscopic resection, primary anastomosis, stoma after resection and type of stoma, total hospital stay, qualification of operating surgeon and if adjuvant chemotherapy is given

30-day morbidity Clavien Dindo  $\geq 3a$

Follow up data: 90- day mortality, recurrence rate after 3 years, survival after 3 and 5 years, remaining stoma after and 3 years, number of patients not being subjected to resection.

Reviewing of medical charts may be necessary for data missing in the SCRCR or e-CRF.

For patients in Skåne there will be a possibility to collect tissue for a biobank (STABB).

## **ETHICS**

The study has received ethical approval (Dnr 2020-01161). KVB has been applied for in Region Skåne. The study is granted by the steering committee of SCRCR. All patients will be informed according to clinical routine for SCRCR. All patients that fulfil the inclusion criteria will receive oral and written information at their local hospital. Written consent will be required for participation and GCP principles will be followed at the inclusion. Data handling will apply to GDPR standards.

Demographic data from the SCRCR on patients not asked or not giving consent to the study but consenting to participate in SCRCR will be used for comparisons of demography for participants and non-participants. Comparing data will only be handled as group data and no individual data will be analysed.

## **STATISTICS**

This is a population –based observational study on patients with malignant colonic obstruction. Power calculations are not suitable for this study. In a randomized setting, 432 patients would have to be



included in each group, in order to detect a reduction by half in the 90 day mortality of 11% when comparing resection versus bridge-to-surgery (significance level 5%, power 80). Since this is not a randomized study, an additional number of patients is necessary, because of the need to control the analysis for potential confounders. We aim to include an evaluate 1000 patients. Approximately 500 patients are subjected to emergency resections due to malignant obstruction annually in Sweden.

Analysis will be carried out in an intention-to-treat basis. When the database is complete a detailed analysis plan will be worked out prior to the statistical analyses. When all data is collected data analyses will be carried out as depicted in the study protocol. In addition, interim analyses will be performed after 250 and 500 recruited patients to evaluate preliminary results. If large differences between the groups at interim analyses, the study might be terminated. More details will be given in the statistical analysis plan. Statisticians at Clinical Studies Sweden – Forum South have been involved in the study protocol and will conduct the analyses.

#### **TIME SCHEDULE**

Ethical approval has been granted in May 2020. The e-CRF is currently being linked to INCA with expected finishing date August 2020. The study will commence in September 2020. All hospitals in Sweden that treat malignant colon obstruction has been invited to join the study. All hospitals in Sweden are welcome to participate. The follow up period is five years. There will be at least two publications; one of short term morbidity and oncological outcomes and one of long term results.

#### **FINANCING**

The study is at the moment supported by the regional agreement on medical training and clinical research ALF between Region Skåne and Skåne University Hospital Malmö and Crafoord foundation. We are currently applying for further funding.

#### **SIGNIFICANCE**

This national prospective study namely the ACBC-trial, will hopefully provide evidence if Bridge to Surgery is a valid option to improve outcomes of malignant colon obstruction. The results of the present study will be accounted for in national and international guidelines.

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