

# PROLOGUE RECTAL CANCER

*Improving Outcomes  
After Surgery*

M I L A D F A H I M



# COLORECTAL CANCER

*Improving Outcomes  
After Surgery*

MILAD FAHIM

## **Colorectal Cancer; Improving Outcomes After Surgery**

PhD thesis, Utrecht University, The Netherlands

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*Improving Outcomes After Surgery*

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*Verbeteren van Uitkomsten na Chirurgie*  
(met een samenvatting in het Nederlands)

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**Milad Fahim**  
geboren op 11 oktober 1991  
te Kabul, Afghanistan

**Promotor:**

Prof. dr. D.H. Biesma

**Copromotoren:**

Dr. L.M. Dijkman

Dr. A.B. Smits

**Beoordelingscommissie:**

Prof. dr. N.D. Bouvy

Prof. dr. I.Q. Molenaar

Prof. dr. H.M. Verkooijen

Prof. dr. A.M. May

Prof. dr. B.L.A.M. Weusten



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01

# Introduction and outline of thesis







## INTRODUCTION

Good quality healthcare is imperative for a properly functioning society and affects people from all walks of life. Healthcare enables children to excel in the educational system, adults to be productive members of society, and the elderly to enjoy longer and healthier lives. Unfortunately, healthcare expenditure has risen sharply. With the aging of the population, it is very likely that the pressure on the healthcare sector will increase even more in the future. This has led to the formulation of the outline agreement in 2018 by the Dutch government and healthcare stakeholders (1). The outline agreement states that the yearly growth of healthcare expenditure should be reduced to 0% in 2022 to ensure accessible healthcare in the future while at the same time improving the quality of healthcare.

Efforts in the past to reduce costs and improve quality focused on doctor-centered measures of quality, and have had limited effect. To truly improve quality, a shift must be made from doctor-centered quality measures to patient-centered quality measures. One of the first persons to define quality as value for the patient was Michael Porter, who defined it as the health outcomes achieved that matter to patients relative to the costs of achieving those outcomes. As described in the paper “The Strategy That Will Fix Health Care” by Porter et al. (2), improving quality or value, will also reduce costs. For example, the Affordable Care Act in the United States aimed to expand healthcare coverage and increase the patient-relevant quality of care. After its introduction, healthcare quality improved and healthcare spending in 2019 alone was \$160 billion less than previously projected (3)

Despite the importance of the healthcare system, data collection for quality assessment has long been scarce, fragmented between hospitals, and poorly coordinated. Since that time, several nationwide clinical audits have been implemented successfully, such as the United States National Surgical Quality Improvement Program and the United Kingdom National Clinical Audit and Patient Outcomes Programme (4,5). Following these international examples, the nationwide Dutch Surgical Colorectal Audit (DSCA) was launched in 2009, leading to a reduction of practice variation and improved clinical outcomes in colorectal cancer patients (6). The DSCA provides reliable patient-level data on case-mix variables (i.e., age, sex, comorbidity), process variables (i.e., diagnostic tests done, waiting times, multidisciplinary team meeting), and outcome variables (i.e., 30-day complications, mortality, length of stay). It was initiated to allow quality of care evaluation within each hospital and benchmarking between hospitals. But it also provided a wealth of reliable data that was used for several studies in this thesis.

Worldwide and in the Netherlands, colorectal cancer is the third most common form of cancer in terms of new cases per year (7,8). In the Netherlands, 4750 patients died due to

this disease in 2020, making it the second most common cause of death due to cancer (8). Optimal treatment of colorectal cancer patients requires a multidisciplinary team. However, surgery remains the cornerstone of curative treatment for colorectal cancer. More than 60% of colorectal cancer patients will undergo at least one major surgical resection (9). Despite these improvements, colorectal cancer surgery is still associated with a much higher rate of postoperative complications than general surgery (10). In 2018, postoperative mortality and morbidity rates in the Netherlands ranged from 1.2-3.1% and 14-21% respectively (11). This means that the quality of care is not consistent and that there are considerable differences between hospitals. Quality improvement is therefore imperative, and hospitals should learn from each other using patient-relevant outcomes. As matters stand, much work is still to be done to move to high quality and affordable surgical care for all colorectal cancer patients. The studies in this thesis focus on the three phases of surgical treatment of colorectal cancer patients i.e., pre-operative, intra-operative, and postoperative.

## OUTLINE OF THESIS

**Table 1.** Main Study questions of this thesis

	Chapter	Study questions
Part 1: preoperative	2	Narrative review: when and how should surgery be performed in elderly colorectal cancer patients?
	3	Does emergency surgery increase the long-term mortality in colon cancer patients who underwent surgery?
	4	Does open surgery increase the long-term mortality in colorectal cancer patients who underwent surgery?
	5, 6	Can the obstruction protocol prevent emergency surgery in bowel obstruction patients and prehabilitate them before elective surgery?
Part 2: intraoperative	7	Are current temperature management measures sufficient in preventing hypothermia and related surgical site infections?
	8	Does prevention of Trendelenburg position by the Endosponge reduce postoperative length of stay in colorectal cancer patients?
Part 3: postoperative	9	What is the effect of routine postoperative ICU admission after colorectal cancer surgery for patients aged 80 years or older on adverse outcomes and costs?

## Part 1, preoperative: optimizing patients for surgery

Colorectal cancer patients are often not fit for surgery and several domains, such as physical and nutritional condition, should be optimized prior to surgery to improve postoperative outcomes. The mean age at time of diagnosis is 70 years, and the incidence of other comorbidities is typically high (8). Furthermore, malnutrition, poor physical condition, and the risk of emergency surgery due to acute complaints are all risk factors that occur frequently and are associated with increased postoperative morbidity and mortality (12–14). Fortunately, these are modifiable risk factors, which can and should be addressed prior to surgery (15). In **chapter 2**, a narrative review was performed to provide an overview of colorectal cancer surgery optimization in elderly patients.

In the last decades several intraoperative risk factors, such as emergency surgery and open surgery, have been identified, which increase the risk of postoperative adverse outcomes. However, the long-term effects of these risk factors have been scarcely studied. Population-based studies are the preferred research method to answer the question of long-term effects. These studies include high-risk patients with higher rates of events, reflecting daily practice. The association between open surgery and emergency surgery with long-term outcomes in CRC patients who underwent surgery was assessed in **chapter 3 and 4**.

In elective surgery, there is time to optimize the patient's physical and nutritional status prior to surgery. Still, when patients have sepsis, near blowout, or signs of perforation, there is no time as emergency surgery might be the only option. Luckily, this is not the case for the majority of patients who present with acute complaints, with bowel obstruction being the most frequent acute presentation (16). These patients present with clinical signs such as pain, intermittent stool passage, anorexia, and prestenotic bowel dilatation on imaging. In these patients, physicians can take measures to prevent emergency surgery and optimize the patient's condition before elective surgery. The implementation of a protocol that aimed to avoid emergency surgery and optimize the patient before surgery is reported in **chapters 5 and 6**.

## Part 2, intraoperative: improving intraoperative surgical care

Intraoperative hypothermia was the first area of interest in the intra-operative domain. Several surgical guidelines, including the Guidelines for Safe Surgery published by the World Health Organization, recommend maintaining perioperative normothermia to reduce the risk of surgical site infections (17). These guidelines are mainly based on randomized controlled trials conducted more than 20 years ago, and since that time, many hospitals have implemented temperature management measures. However, postoperative complications remain common

in patients undergoing colorectal cancer surgery (10). Therefore it is crucial to assess whether current temperature management measures are sufficient in preventing hypothermia and related surgical site infections. The results are reported in **chapter 7**.

Another factor that plays a role in surgical risk is the Trendelenburg position, which surgeons often use to obtain an adequate visual working field during laparoscopic surgery. This position leads to hemodynamic changes that may increase the risk of cardiopulmonary complications and prolonged hospital stay. In recent years, an intraoperative retractor sponge was introduced as an alternative to the Trendelenburg position. The effect of this retractor sponge on length of stay was researched in the randomized controlled SPONGE trial and reported in **chapter 8**.

### **Part 3, postoperative: improving postoperative surgical care**

In 2001, the ERAS Study group was established to further develop concepts of multimodal postoperative surgical care. The efforts of the study group resulted in many ERAS guidelines, including colonic surgery. In the present day, these guidelines have become standard practice in the vast majority of hospitals and have done much to improve postoperative surgical care. However, the current shift in the colorectal cancer population towards older patients requires a new approach. Elderly colorectal cancer patients are more prone to developing postoperative complications. They are at increased risk of postoperative mortality, even in the current climate where ERAS guidelines have become the standard of care (16,18–20). The basis for postoperative complications in these elderly patients might lie in the patient's hemodynamic status in the first 12-18 hours after surgery. As the hemodynamic status of the elderly patients is less stable, better monitoring is helpful as it leads to fast interventions before the patient deteriorates. Routine ICU admission of the elderly colorectal cancer patient for the first postoperative night might, therefore, be a valuable addition to the use of ERAS guidelines in daily practice. This hypothesis was assessed in **chapter 9**.

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# PART I



*Improving preoperative  
surgical care*







02

# When and how should surgery be performed in senior colorectal cancer patients?



S.H.J. Ketelaers, M. Fahim, H.J.T. Rutten, A.B. Smits, R.G. Orsini

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## **ABSTRACT**

Older studies reported high rates of postoperative morbidity and mortality in the senior population, which lead to a tendency to withhold curative surgery in the older population. However, more recent studies showed impressing developments in postoperative outcomes in seniors. Probably, these improvements are due to enhancements in both surgical and non-surgical aspects in the pre-, peri- and postoperative period, such as minimally invasive techniques and anesthesiological insights. The postoperative survival gap seen earlier between younger and older patients is fading. For optimal treatment in the older population, special awareness and care on several aspects is needed. As only a minority of the seniors are frail, a quick frailty assessment is crucial to distinguish the fit from the frail in the decision-making process. In addition, it could be valuable to improve the lacks in physical condition in the preoperative period with the use of prehabilitation programs. Furthermore, it is important to evolve an emergency to an elective setting by postponing emergency surgery to prevent any high-risk situation. In conclusion, based on modern insights, surgery is a valid option in the curative treatment of colorectal cancer in seniors, however individual attention and care is required.

## INTRODUCTION

Colorectal cancer (CRC) is mainly a disease of the older population, with the highest incidence around the age of 80 years old [1]. With increasing life expectancy of the worldwide population, this will result in aging of the population and higher rates of CRC in the oldest population [1]. Therefore, it is not unthinkable that clinicians have to deal more and more commonly with these senior CRC patients.

In older papers, after introduction of TME surgery, seniors did not seem to benefit as much as their younger counterparts [2]. It had been postulated that higher postoperative mortality rates were mainly responsible for this lack of benefit. However, the tide has turned recently. Population-based cohorts from Belgium, Denmark, Sweden and The Netherlands showed that short-term mortality rates are improving over time [3]. Other recent studies show that fit senior patients can be treated the same as younger patients and, when operated on, they have the same outcomes as their younger equivalents [4,5]. Unfortunately, senior patients are less likely to undergo surgery and intensive treatment regimens than their younger counterparts [5-7]. They are believed that they cannot deal with these treatment regimens, due to comorbidities or age [2,4,6]. However, these assumptions are based on older studies who reported worse outcomes than nowadays [8,9].

With growing evidence that fit senior patients can deal the stress of curative treatment regimens and increasing numbers of seniors that are affected by CRC, there is a need for clarity about the areas of concern during treatment of these patients [10-12]. Age itself should not lead to withhold curative treatment before the physical status of the senior patients is assessed [4-6]. As senior patients are not included in most clinical trials, evidence is based on younger patients [5,6]. Fortunately, there are expert recommendations on how to treat this senior population, as standard guidelines focus particularly on middle aged patients [6,13].

In this paper a surgery-focused recommendation is outlined why, when and how we should treat the senior CRC patient.

## **WHICH CHANGES HAVE BEEN MADE OVER THE YEARS TO IMPROVE OUTCOMES AFTER COLORECTAL CANCER SURGERY?**

### **Minimally invasive surgery**

Laparoscopic colorectal cancer surgery is safe and has comparable oncological results as open surgery [6,14]. There is no difference between laparoscopic and open surgery in harvested lymph nodes, circumferential resection margins, recurrence rates, and overall and disease-free survival [14,15]. In addition, minimal invasive surgical techniques evoke less intensive immune response than open surgery, thus reducing the surgical stressor [16]. This could be an explanation for the improved recovery seen after laparoscopic surgery with less postoperative pain, shorter hospital admissions and less postoperative and cardiopulmonary complications [5,15,17,18]. Also in the older population, laparoscopic CRC surgery is safe and goes with less postoperative morbidity [18-20].

In select cases, organ-sparing techniques like polypectomy, transanal excisions (TAE) and transanal endoscopic microsurgery (TEM) can be the solution [6]. Organ-sparing techniques have less morbidity and excellent functional results, with acceptable oncological results [6]. For rectal cancer, good oncological outcomes with local excisional techniques are achieved in T1 tumors with minimal submucosal and no lymphovascular invasion, when no poor differentiation, mucinous histology and budding is present [6]. For malignant colorectal polyps in general, similar oncological results after radical polypectomy were seen as after surgical resections [21]. It is important to weigh balances between both oncological and surgical outcomes before choosing for these local techniques. As some senior patients are frail or could prefer good functional outcomes over survival benefit, it is important to discuss this with the patient using shared decision making.

### **Organ preservation in rectal surgery**

In about 20% of the patients treated with neoadjuvant treatment, complete pathological response is observed [22]. When complete response is achieved after neoadjuvant rectal cancer treatment, there is a possibility for a watch-and-wait approach [23]. Complete responders of neoadjuvant chemoradiotherapy are assessed and followed with MRI and endoscopy [22]. With this more conservative approach with intensive surveillance, acceptable rates of local recurrence and high rates of survival are found in clinical responders [22,24,25]. About 10-30% need delayed salvage surgery to resect regrowth and only a small percentage of them had unresectable recurrences, so in highly selected patients it could be an effective method to avoid surgery [23,25].

The standard for treating rectal cancer remains surgery with or without neoadjuvant treatment [22]. Although watch-and-wait procedures have similar cancer-specific and overall survival rates, surgery is associated with higher rates of disease-free survival and a smaller risk of technically unresectable recurrences [25]. However, in patients who are at risk to undergo surgery or when functional outcomes and the avoidance of a permanent stoma are important, it could be better to have a more conservative approach that only consists of neoadjuvant treatment followed by the watch-and-wait protocol [22,25]. In short, in selected patients with clinical complete response, the watch-and-wait protocol could be an adequate surrogate to surgery [22].

### **Effect of colorectal differentiation on outcome**

One of the effects seen of subspecialization in surgery is improved surgery-related outcomes [26]. Higher CRC volumes and colorectal subspecialization improves outcomes and survival [27-29]. Specialized and high-volume surgery is also related to less anastomotic leakages, lower postoperative mortality and recurrence rates [28,30,31]. Especially in more complex surgery, like advanced rectal cancer surgery, high-volume and specialized surgery is associated with more sphincter-preserved surgery, lower rates of permanent stoma formation, better local control and increased survival [26,32]. Only those senior patients with advanced cases, or seniors in whom an increased risk of morbidity or mortality is expected, a referral can be considered.

### **Need for changing the perspective of surgical treatment of the senior patient with colorectal cancer**

The current belief that seniors could not manage curative treatment regimens is based on older studies that show associations between senior patients and high rates of postoperative morbidity and mortality [2,33]. These outcomes lead to a decrease in older patients receiving curative surgery, enlarging the risk of undertreatment [6,34]. Fortunately, there is increasing evidence showing seniors who are fit for surgery, have the same benefit from curative treatment as younger patients do [9,11,35]. With improving the surgical circumstances over the years, declining rates of postoperative morbidity and mortality have been described for this population [8,9,36]. In earlier studies high rates of one-year mortality in senior patients of about 19-26% were reported and were much higher than in younger patients [37-39]. A population based study from The Netherlands showed an improvement in short-term mortality after CRC surgery in the senior population between 2009 and 2013 [36]. For colon and rectal cancer patients 75 years 1-year mortality decreased from 18.5% to 15.0% and from 15.3% to 11.7%, respectively. Nevertheless, these rates were still much higher than in younger patients [36]. Another populationbased study across four North-European countries and also other population-based studies showed improvement in short-term mortality rates over time [3,40,41].



Possible explanations for this major improvement in short-term mortality rates for seniors are better staging, increased use of minimally invasive techniques, perioperative care, awareness of complications, expertise and high-volume care [9,36]. Other possible contributing factors are insights in perioperative anesthesiological factors, which include administration of antibiotics, preservation of body temperature and adequate fluid balances [42,43].

More recently, a study using Dutch population-based data analyzed the developments of postoperative mortality and 1-year relative survival in CRC patients between 2005 and 2016 [8]. Improvements in 30-day mortality for senior patients to 4.0% and 2.7% were seen, for colon and rectal cancer, respectively [8]. The relative 1-year survival rates improved to 94.6% and 97.2%, for colon and rectal cancer respectively [8]. (Fig. 1) These rates were almost comparable to those in younger patients [8]. In addition, a recently published study from a high-volume center for complex cases showed 30-day mortality rates for senior CRC patients of 1.2% (1.1% for senior colon and 1.4% for senior rectal cancer patients) and 1- year relative survival rates of 94.3% [9]. These rates were also comparable to younger patients [9]. (Table 1).

While one-year mortality after CRC surgery has been a major concern in the past for seniors, recent studies show a major increase in survival, both for specialized and general CRC surgical centers [2,8,9]. The earlier reported mortality rates in seniors should no longer be used to form a basis to withhold CRC treatment in older patients [8,9]. However, we are aware that special care and attention is needed in this population and that individual differences in frailty levels need to be assessed preoperatively.

## **WHEN AND HOW TO TREAT?**

### **Staging**

Treatment for all colorectal cancer patients starts with adequate staging of the primary tumor and an estimation of the patient's performance status. Primary diagnosis is done by colonoscopy and biopsy for histological examination on the characteristics of the tumor [44]. A Computed Tomography (CT) is advised for tumor staging and to examine the possibility of lymph node involvement and/or (extra)hepatic metastasis [44]. In rectal cancer, the Magnetic Resonance Imaging (MRI) provides detailed views of dissection planes, pelvic organs and mesorectal fascia and circumferential margins (CRM) [45].

### **Frailty assessment**

In senior patients an estimation of their performance status is important to reveal frailty. Frailty is defined as a state of diminished physiological reserve capacity across multiple organ systems



[46]. As a result of frailty the capacity to withstand stressors, such as intensive treatment, is reduced, which is associated with postoperative complications, hospitalization, and reduced survival after surgery [6,47-49].

It has to be clear that only a small percentage of the senior population is considered frail. Therefore, in the older population it is important to distinguish the frail from the fit senior. But it is not clear how to identify frailty in the individual patient, as no one tool is accurate enough to include all differences between older patients [6,50]. Extensive and comprehensive assessment of frailty on a routinely basis is time-consuming and resource intensive, as many geriatricians are needed to be involved to evaluate every older patient who undergoes CRC surgery [12,45]. For most hospitals it is difficult to implement this as standard care. Therefore, other less time-consuming tools are needed in daily practice to screen for frailty and to distinguish those patients that benefit from an assessment by a geriatrician prior to treatment [6]. In the most recent published expert opinion on how to treat senior rectal cancer patients, the focus should lie on identifying the main predictors of frailty and postoperative complications such as functional status, nutritional status, and comorbidities [6].

Functional status is easily assessed during the patient's visit with the timed-up-and-go test (TUG), since a high TUG is able to predict the risk of postoperative complications [51]. Also a history of falls in the last 6 months before surgery is associated with a higher risk of postoperative complications [12]. Other possible tools given by the expert group are the G8 score to determine health and nutritional status and medication use and the Mini-Cog score for the evaluation of cognitive status [6]. Since 2012, as part of a National Patient Safety Program, all patients over 70 years in the Netherlands should be screened for frailty by assessing the following domains: undernutrition, physical impairment, delirium risk and fall risk [52]. Other important factors to evaluate could be the mental status, alcohol and smoking habits, supporting system and the willing to fight for recovery of the patient. As it could be possible that some seniors tend to give up earlier when feeling bad, discussing that some symptoms like fatigue, nausea or weakness are normal during recovery after colorectal surgery, could be of significance.

If no frailty is expected the patient should be offered an optimal treatment. When after the previous mentioned quick and easily applicable screening methods, the patient is at risk, the selected patient should be referred to a geriatrician to perform a full comprehensive geriatric assessment. This full assessment evaluates the multiple domains of frailty, such as physical, nutritional, functional and psychosocial health status, cognition and polypharmacy [50]. When after this geriatric assessment the patient seems fit, standard curative care can be performed. However, in case the patient is considered frail, prehabilitation programs should be started to increase the patient's condition before surgery is performed or the treatment regimen should

be fine-tuned to the health status of the individual patient. In addition, when the patient is considered frail, it could be of importance to discuss the patient in a regional multidisciplinary team meeting (MDT) with incorporated geriatricians for the whole decision-making process.

## **Prehabilitation**

Older patients who undergo CRC surgery are at risk for delayed recovery, and prehabilitation could enhance the capacity to tolerate surgery and to recover earlier [53]. It seems to be a promising method to increase the physical condition of the senior patients prior to surgery, and reductions of about 50% in postoperative complications are seen in intra-abdominal surgery [54]. Although, clear evidence on postoperative outcomes in colorectal cancer surgery is still lacking [49].

Especially in selected patients, improvement of preoperative physical status could be beneficial in improving postoperative outcomes [55]. Seniors with lack of physical condition and muscle strength have an increased risk for postoperative complications, and therefore these are targets for prehabilitation programs [12,49]. In particular senior patients with the lowest baseline fitness benefit most from these programs [56]. Until now, it is still not exactly known which aspects the best prehabilitation programs should include and what the optimal timing and duration of these programs should be [6]. Probably, these programs should contain multimodal interventions such as physical training, smoking cessation, nutritional support and psychological support [53,56,57].

The prehabilitation program should start with assessing where the patient is lacking in condition and what the situation and possibilities of the patient are. As home-based training has shown some good results in prehabilitation programs, training at home could be considered if preferred by the patient [58]. While in other cases, it could be preferred to train with a physiotherapist. Ideally, these programs should take place in the waiting period between diagnosis and surgery. This period can be used optimally by letting patients participate in prehabilitation programs to improve their condition. In case of advanced rectal cancer where neoadjuvant treatment is needed, this period is often longer and can extend up to 12 weeks, which makes it feasible to perform a longer and possibly more effective prehabilitation program to improve the patient's condition. Although prehabilitation needs time to take its effect, until now it is not clear whether long prehabilitation programs are more effective than short programs [59]. However, it is believed that these programs should be given to patients where there is at least about 2 weeks, and ideally 4-6 weeks, prior to surgery [59]. Participating in prehabilitation programs can help to lower the impact of neoadjuvant regimens on physical condition [60]. In patients that are considered frail, response to prehabilitation can also help to determine if they can receive curative treatment with surgery or it is better to perform best supportive/palliative treatment.

## **Nutritional status**

About one in five CRC patients is malnourished before surgery [61]. Poor nutritional state is associated with adverse postoperative outcomes, while good nutritional status is important for muscle gain and recovery [49,53,62]. So, improving nutritional status preoperatively seems important to create an anabolic instead of a catabolic state. Supplementation of proteins in addition to physical training could be beneficial to increase muscle gain [57]. Additionally, some proteins have shown some anti-inflammatory and immune-modulating effects [53]. Supplementation of vitamin D and multivitamins, which are often deficient in seniors, could be beneficial as vitamin D is associated with muscle mass and strength [57,63]. Although the use of nutritional interventions has not yet been proven, it seems that when nutritional interventions are integrated with other prehabilitation modalities, clinically meaningful enhancements could be made in outcomes [62,64].

## **Comorbidity**

Older patients with CRC often have other chronic diseases to deal with, about 60% of CRC patients over 70 years suffer from any comorbidity [65]. Each comorbidity has a different impact on physical function and postoperative outcomes, but patients with comorbidities in general do not especially develop more surgical complications than those without comorbidities [65,66]. As having comorbidities is not the same as frailty and frailty is influenced only by a few specific comorbidities, it is important to know the impact of each comorbidity on postoperative outcomes [65,67]. Most seniors with CRC have comorbidities like cardiovascular and pulmonary diseases, which both increase the operative and postoperative risk of morbidity and mortality [67,68]. Patients with colorectal cancer and a preoperative diagnosis of deep venous thrombosis (DVT) also have an increased risk of developing postoperative complications [65]. Therefore, when patients suffer preoperatively from a DVT, it is important to give extra attention to regulate their hemostasis both pre- and postoperatively to prevent complications and to increase survival [65,68]. Also neurological comorbidities in the presence of CRC increases the risk of negative postoperative outcomes [68]. Other prevalent comorbidities seen in CRC patients are hypertension, diabetes and previous malignancies, but these have minimal impact on frailty and postoperative outcomes [65,69]. However, some comorbidities do play a role in survival and must be taken into account during the decision-making process. Preoperative treatment and regulation of the patients' comorbidities is important and may reduce the peri- and postoperative morbidity and mortality [70].

## **Emergency surgery**

About 15% of colon cancer patients present with acute obstruction [71]. Emergency surgery is considered as a major risk factor for postoperative mortality in comparison to elective surgery, especially in the senior CRC patient [71]. In addition, they died earlier after surgery and had

higher rates of complications compared to younger patients [71]. However, it has been shown that relative survival rates do not differ between older and younger obstructed colon and rectal cancer patients, which implicates that curative treatment of these seniors is beneficial [9,71]. Even in emergency cases, age itself should not be the most important factor in decision-making [9,71].

In obstructed colon cancer, surgery is also the primary treatment modality [71]. However, it is still not known which surgical technique is the best and whether stent as bridge to surgery should be performed or not [71]. The rationale behind stenting as bridge to surgery is to initially decompress the distended colon to transform an emergency resection into an elective procedure with optimized circumstances [72]. Although guidelines even recommend the use of stent placement as bridge to surgery for seniors who are at risk, it is not frequently performed because of safety concerns [72]. Recently it is shown that the use of a stent as bridge to surgery is safe and provides an alternative to emergency resections, especially in high-volume centers [72]. In addition, it is associated with higher rates of laparoscopy and lower rates of postoperative morbidity and permanent stomas than after emergency resection [72,73]. Although not statistically significant, a meta-analysis showed a tendency to higher tumor recurrence rates in the stent group than after emergency surgery. However, short-term mortality and overall and disease-free survival rates were not impaired in the stent-group [72,73].

Another alternative to emergency surgery is the obstruction protocol, which has been developed by some of the authors (M.F., A.S.) [74]. (Fig. 2) This protocol aims to postpone surgery for several weeks allowing proper prehabilitation. Especially in the older patient who is in an emergency situation and thus depleting their physical reserves, prehabilitation is important to reduce postoperative morbidity. The obstruction protocol consists of reduction of prestenotic dilatation and abdominal pain, thus preventing emergency surgery and providing time for prehabilitation, both in regards to physical and nutritional status. The prestenotic distention of the bowel wall and the stenosis of these patients causes pain and malabsorption leading to chronic insufficient intake and lethargy which in turn causes suboptimal physical and nutritional condition [75]. In this obstruction protocol, patients that present with obstructed colon cancer receive dietary adjustments and oral laxatives to reduce the amount of stool produced. The reduced volume of stool can more easily pass the obstructive bowel. This will reduce prestenotic bowelwall distension and consequently abdominal pain. In the absence of bowelwall distension and abdominal pain the need for emergency surgery disappears. Surgery can be postponed, planned electively after preferably 3 weeks and conducted by a specialized colorectal surgeon, laparoscopically or robot-assisted. It also provides time for proper prehabilitation of the patient such as improving physical status, smoking cessation and reduction of alcohol consumption prior to elective surgery. The dietary measures that

were given to reduce the amount of stool also covered all the nutritional needs of the patient and subsequently ensured adequate caloric intake which resulted in the patient leaving the catabolic state. According to the severity of obstruction the patients are given diets ranging from residue-low diet to total parenteral nutrition. In the senior patient these measures that can enhance nutritional and physical condition can make an important difference. Promising results have been shown in a pilot study and are now further investigated in a multicenter setting [74].

In obstructed rectal cancer with an impending cecum blow-out, it seems necessary to perform a deviating stoma first and to perform resectional surgery in an elective setting after adequate staging and neo-adjuvant treatment when needed [45]. During this period it could also be possible to use the obstruction protocol to improve the circumstances and the patients' condition as a bridge to definitive surgery.

## CONCLUSION

The poor outcomes in the past of colorectal surgery do not reflect daily practice anymore. Colorectal surgery can be performed safely without increased postoperative morbidity and mortality and without excess one-year mortality. Several changes in the management have contributed to this lapse in outcome i.e.: better preoperative assessment and prehabilitation, less traumatic surgery and non-surgical organ preservation treatments, perioperative care focussing on nutritional, electrolyte and fluid balance, new anesthesiological techniques, early postoperative mobilization etc. The most important contribution solving this problem was the understanding that a multidisciplinary approach is necessary, and the recognition that actions may be needed to be taken before any invasive treatment.

Within this multidisciplinary setting, even more frail patients may undergo treatment. The development of special MDTs for seniors, who have to undergo major surgery, with a dedicated team encompassing not only a surgeon and anesthesiologist, but also a geriatrician has to be applauded.

Programs to deal with specific problems like acute obstruction, which still carries the highest risks for senior people, have to be developed further and implemented on a major scale.

If surgery is necessary for cure, surgery is a valid option for most senior citizens with colorectal cancer. Counselling and shared decision making should be based on modern insights in surgical outcomes rather than on outdated data.

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**Declaration of competing interest**

None.

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03

# Increased long-term mortality after emergency colon resections



Milad Fahim, Lea M. Dijkman, Paul B. van der Nat, Wouter J.M. Derksen, Douwe H. Biesma, Anke B. Smits

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## **ABSTRACT**

### **Aim**

Emergency surgery is a known predictor for 30-day mortality. However, the relationship with long-term mortality is still a matter of debate. The aim of this study was to analyse the effect of emergency surgery compared to elective surgery on long-term survival.

### **Method**

Data from the Dutch Colorectal Audit and the Dutch Cancer Centre registry of a large non-academic teaching hospital were used to analyse outcomes of patients who underwent surgery for colon cancer from 2009 until 2017. Univariable and multivariable Cox regression were used to assess the effect of emergency surgery on long-term mortality with adjustment for characteristics of patient, tumour and treatment.

### **Results**

A total of 1139 patients with a median follow up of 40 months (interquartile range 23-65) were included. Emergency surgery was performed in 158 patients (14%). The 5-year survival after emergency surgery was 46% versus 72% after elective surgery. After adjusting for baseline differences there was an independent and significant association between emergency surgery and increased long-term mortality (hazard ratio 1.79, 95% confidence interval: 1.28-2.51,  $p=0.001$ ).

### **Conclusion**

Emergency surgery for colon cancer seems to lead to a significantly increased risk of long-term mortality compared to elective surgery. Detection and treatment of early symptoms that can lead to emergency surgery might be the way forward.



## **What does this paper add to the literature?**

Emergency surgery for colon cancer, compared to elective surgery, not only leads to worse short-term outcomes, it can also lead to a significantly increased risk of long-term mortality. Detection and treatment of early symptoms that can lead to emergency surgery might be the way forward.

## **INTRODUCTION**

The relationship between emergency surgery and increased 30-day postoperative morbidity and mortality in colon cancer patients is well established (1–3). In the Netherlands, emergency surgery takes place in 19% of patients due to acute symptoms like colon obstruction, perforation or severe bleeding (4). The nationwide overall 30-day mortality for colon surgery in the emergency surgery setting is 9%, which is three times higher than the 3% mortality rate after elective surgery (4). Strategies to avoid emergency surgery are lacking. A nationwide population-based study in the Netherlands showed that in the emergency setting only 5% of colon patients received a diverting stoma or a stent as bridge to elective surgery, the remaining 95% of patients in the emergency setting received a resection (5).

Nevertheless, the evidence for the association between emergency surgery and increased long-term mortality is less convincing. Although several studies have demonstrated that overall long-term mortality after emergency surgery is increased compared to elective surgery, the patients undergoing emergency surgery have on average a higher ASA classification, higher stages of colon cancer and more comorbidity (6,7). These factors are known to influence long-term survival, but they have not been fully accounted for in these studies. However, recent studies using propensity score analysis to account for these differences found no association between emergency surgery and increased long-term mortality(8,9).

Given these conflicting results, more high quality research is needed. This study assessed the effect of emergency surgery, compared to elective surgery, on long-term mortality in colon cancer patients. Our hypothesis is that emergency surgery leads to increased long-term mortality.



## **METHODS**

### **Study design and data collection**

This was a retrospective analysis of a prospective database of a large Dutch non-academic teaching hospital. The catchment area of this hospital was the Utrecht province. A colorectal surgeon was available at all times, even during nights for emergency colorectal operations. As such, all the patients in this study were operated on by a specialized colorectal surgeon.

Data was acquired from the national Dutch ColoRectal Audit (DCRA) registry (10). The DCRA is a registry of patients who underwent surgery for colorectal cancer and contains data regarding patient characteristics, treatment and 30-day postoperative outcomes. Patients were registered in the DCRA after diagnosis of CRC by colonoscopy and biopsy, provided there were no contraindications for the procedure. Incomplete variables from the DCRA registry were supplemented by the primary researcher (MF) using pathology and operation reports. Long-term mortality data were derived from the Dutch Cancer Centre registry, which is based on the municipal registration of vital events (11). Incomplete variables from the DCRA database were supplemented by the primary researcher using pathology and operation reports. The study was approved by the medical ethical commission MEC-U in the Netherlands.

### **Patient population**

All patients receiving curative surgery for primary colon cancer (i.e. resection of primary tumour with curative intent) since the start of the DCRA registry in 2009 until 2017 were evaluated. Excluded from this study were patients who underwent HIPEC procedure as these patients had advanced disease and very often the treatment could even be seen as palliative treatment.

### **Definitions of exposure and outcomes**

Emergency surgery was defined as surgery within three days of an unplanned admission. Elective surgery was defined as no emergency surgery. For the purpose of this study we used emergency surgery as our primary exposure variable. Within the emergency surgery group we also compared those who underwent surgery within 24 hours (emergency) and those who underwent surgery after 24 hours but within 3 days (urgent). These definitions were well established and used since 2009 in the Dutch ColoRectal Audit registry (12).

Tumour symptoms consisted of: perforation (defined as preoperative perforation with clinical signs of faecal peritonitis), bowel obstruction (defined as preoperative [partial] mechanical bowel obstruction with signs of abdominal cramping) and bleeding (defined as preoperative

tumour-related blood loss requiring transfusion or emergency surgery). Adequate lymph node yield was defined as  $\geq 10$  lymph nodes according to the national colorectal cancer guideline formulated by the Dutch federation of medical specialist (13).

## Statistical analysis

Categorical data were presented as numbers and percentages and were compared using the chi-square test. Kaplan-Meier curves were used to display survival and the log rank test was used to compare the survival curves. Univariable and multivariable Cox regression were used to assess the effect of emergency surgery on all-cause long-term mortality while adjusting for potential confounders. These factors were: gender, age, BMI, ASA classification, preoperative tumour symptoms, conversion, additional resection, TNM-stage, adequate lymph node yield, positive resection margin and time period of surgery. Factors were chosen based on known risk factors from literature (4,14–16) and included the time period of operation, as a measure of hidden confounders (e.g. improved perioperative care in recent years). Patients who died within 30 days postoperatively were excluded from the survival curves and Cox regression analysis. The proportional hazards assumption of the Cox regression model was confirmed by eyeballing the Kaplan-Meier plot and the log minus log plot, both showed parallel curves with no crossing (17).

All P-values reported are two sided and a p-value of  $<0.05$  was considered significant. Data remaining missing after supplementing by the primary researcher were considered missing at random. Multiple imputation was used to impute five additional datasets, analyses were performed on the pooled datasets. Statistical analysis was performed using SPSS v.24.0 (IBM, Armonk, NY, USA).

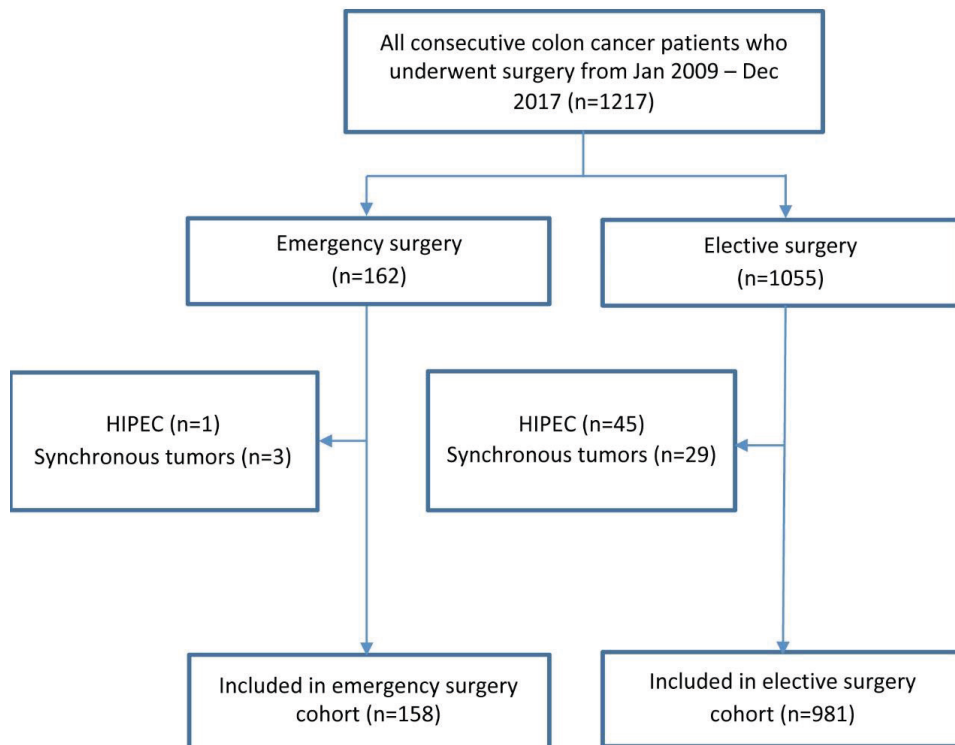
## RESULTS

### Patients

A total of 1139 patients who received surgery for primary colon cancer were included in this study (Fig 1). Median follow up was 41 months (IQR 65-23). In total 10 patients (0.9%) had missing data in one of the variables, this was significantly more in the emergency group ( $p<0.001$ ) than in the elective surgery group.

In this study, 158 out of 1139 patients (14%) were assigned to the emergency cohort: 104 patients underwent surgery within 24 hours and 54 patients underwent surgery within 3 days. This percentage gradually decreased from 18% in 2009 to 9% in 2017. Baseline data are shown in Table 1. The largest difference between patients who underwent emergency or elective surgery was seen in regards to the initial presentation: presentation with bowel obstruction

occurred in 98 (62%) in the emergency surgery group versus 38 (4%) in the elective surgery group. This is consistent with the finding that patients in the emergency surgery group had higher rates of advanced disease, defined as stage IV disease (27% vs 10%,  $p<0.001$ ). There were no differences in proportion of inadequate lymph node yield between both groups (11% vs 10%,  $p=0.65$ ). Positive resection margins were more common in the emergency group (3% vs 1%,  $p=0.007$ ).



**Figure 1.** Study flowchart (HIPEC, hyperthermic intraperitoneal chemotherapy).

**Table 1.** Baseline characteristics

	<b>Emergency surgery N=158</b>	<b>Elective surgery N=981</b>	<b>p-value</b>
<b>Patient</b>			
Missing data	5 (3)	5 (0.5)	0.001
Male	75 (48)	514 (52)	0.25
Age			0.34
<70	90 (57)	522 (53)	
70-80	43 (27)	323 (33)	
>80	25 (16)	136 (14)	
Body Mass Index			0.047
BMI 20-30	135 (89)	796 (81)	
BMI 30-40	15 (10)	172 (18)	
BMI 40+	1 (1)	13 (1)	
ASA classification			0.005
ASA I	31 (20)	154 (16)	
ASA II	79 (50)	583 (60)	
ASA III	40 (25)	229 (23)	
ASA IV	8 (5)	14 (1)	
Previous abdominal surgery	47 (30)	383 (39)	0.025
<b>TNM stage</b>			<0.001
Stage I	5 (3)	267 (27)	
Stage II	55 (35)	340 (35)	
Stage III	55 (35)	278 (28)	
Stage IV	43 (27)	96 (10)	
<b>Preoperative tumour symptoms</b>			
None	3 (2)	666 (68)	<0.001
Perforation	27 (17)	2 (0)	<0.001
Abscess	9 (6)	3 (0)	<0.001
Obstruction	98 (62)	38 (4)	<0.001
Bleeding	9 (6)	172 (18)	<0.001
Other	19 (12)	102 (10)	0.54
<b>Treatment</b>			
Open surgery	138 (87)	279 (28)	<0.001
Additional resection for locally advanced or metastatic disease	38 (24)	105 (11)	<0.001
Conversion	12 (8)	59 (6)	0.45

**Table 1.** Baseline characteristics

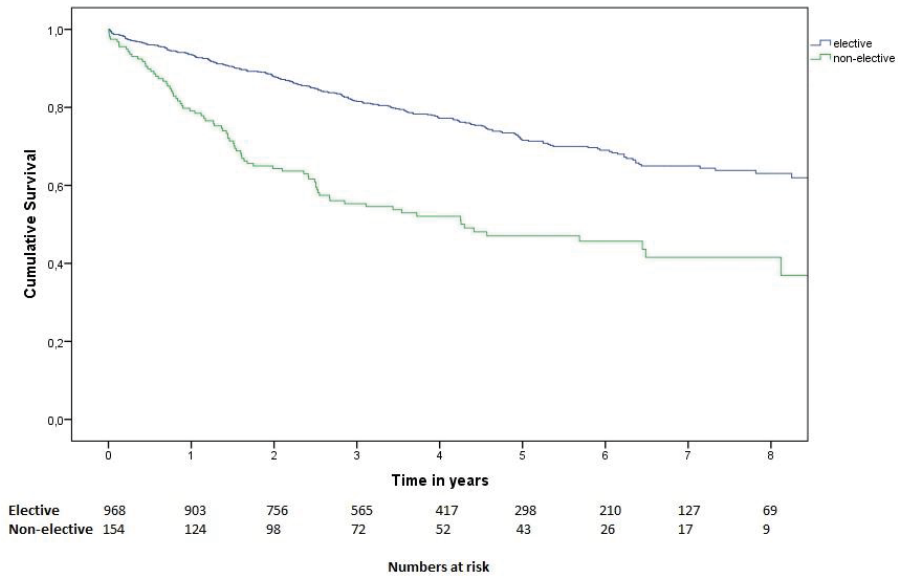
	<b>Emergency surgery N=158</b>	<b>Elective surgery N=981</b>	<b>p-value</b>
Positive resection margin	5 (3)	12 (1)	0.007
Inadequate lymph node yield (<10)	17 (11)	94 (10)	0.65
Adjuvant chemotherapy	69 (44)	274 (28)	<0.001
Period of surgery			<0.001
2009-2011	64 (41)	310 (32)	
2012-2014	62 (39)	340 (35)	
2015-2017	32 (20)	331 (34)	
<b>Postoperative complications</b>			
All complications	53 (34)	217 (22)	0.002
Serious complications (Clavien-Dindo $\geq$ 3)	17 (11)	108 (11)	0.92

*All variables are in n (%)*

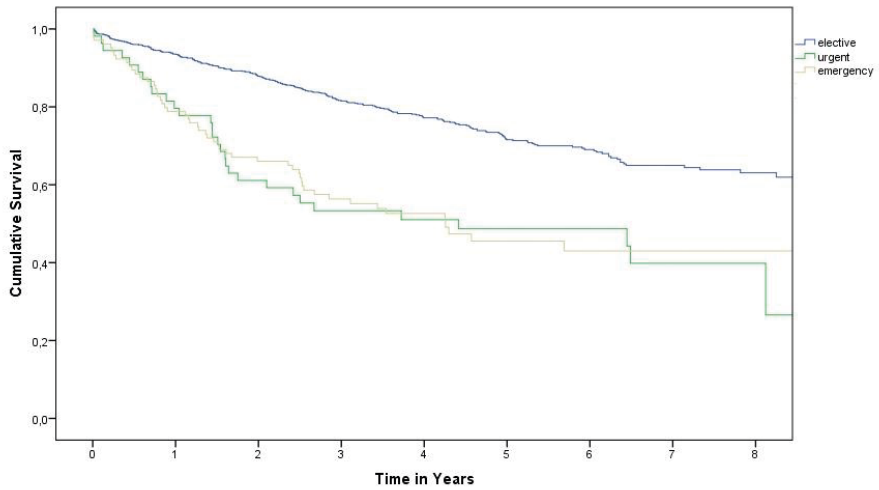
### Comparison of long-term mortality

Thirty-day mortality was 1.3% (13/981) in the elective group and 2.5% (4/158) in the emergency group; all these 17 patients died during their hospital admission. In our analysis of long-term mortality, we excluded these 17 patients because we wanted to assess survival after discharge. In our study cohort, long-term mortality in patients undergoing emergency surgery was higher than patients who underwent elective surgery. The five-year survival in the emergency group was 46% versus 72% in the elective group (Figure 2). The adverse effect of emergency surgery on long-term survival was confirmed by univariable and multivariable Cox regression analysis, as shown in Table 2. This showed a statistically significant difference (hazard ratio [HR] 1.79, 95% confidence interval [CI]: 1.28-2.51,  $p=0.001$ ) after adjusting for gender, age, ASA classification, BMI, conversion, additional resection, TNM-stage, adequate lymph node yield, positive resection margin and period of surgery. Within the emergency cohort there was no significant difference between patients who underwent surgery within 24 hours ( $n=100$ ) or patients who underwent surgery within 3 days ( $n=54$ ) (Figure 3, log rank test,  $p=0.87$ ).

One, three and five year HRs were also calculated in order to not compress possible relevant information into a single overall HR. After adjusting for the same variables as the primary analysis the one, three and five year HRs respectively were: 1.46 (95% CI: 1.04-2.06,  $p=0.029$ ), 1.70 (95% CI: 1.22-2.38,  $p=0.002$ ) and 1.81 (95% CI: 1.30-2.53,  $p<0.001$ ).



**Figure 2.** Kaplan Meijer survival curves (excluding 30-day mortality)



**Figure 3.** Kaplan Meijer survival curves for elective, urgent (<3 days) and emergency (<24 hours) surgery (excluding 30-day mortality)

**Table 2.** Cox proportional hazards model for crude and adjusted associations between risk factors and long-term mortality (excluding 30-day mortality)

	Univariable Cox regression		Multivariable Cox regression	
	Hazard ratio (95% CI)	p-value	Hazard ratio (95% CI)	p-value
<b>Gender</b>				
Female	1		1	
Male	1.05 (0.84-1.30)	0.68	1.17 (0.93-1.48)	0.17
<b>Age</b>				
<70	1		1	
70-80	1.61 (1.24-2.09)	<0.001	1.52 (1.15-2.01)	0.003
>80	3.91 (2.98-5.13)	<0.001	4.50 (3.25-6.23)	<0.001
<b>Body Mass Index</b>				
<30	1		1	
>30	0.98 (0.73-1.32)	0.91	1.14 (0.83-1.56)	0.41
<b>ASA score</b>				
I	1		1	
II	1.95 (1.28-2.97)	0.002	1.66 (1.07-2.58)	0.024
III	3.73 (2.42-5.75)	<0.001	2.45 (1.53-3.93)	<0.001
IV	8.83 (4.71-16.55)	<0.001	2.88 (1.42-5.86)	0.003
<b>Preoperative tumour symptoms</b>				
No	1		1	
Yes	1.75 (1.40-2.20)	<0.001	1.31 (0.94-1.83)	0.11
<b>Setting of surgery</b>				
Elective	1		1	
Emergency	2.50 (1.95-3.22)	<0.001	1.79 (1.28-2.51)	0.001
<b>Conversion</b>				
No	1		1	
Yes	1.44 (0.97-2.15)	0.074	1.41 (0.91-2.18)	0.12
<b>Additional resection for locally advanced or metastatic disease</b>				
No	1		1	
Yes	1.83 (1.39-2.41)	<0.001	1.11 (0.82-1.51)	0.48
<b>TNM stage</b>				
Stage I	1		1	
Stage II	1.50 (0.80-2.79)	0.21	1.07 (0.71-1.61)	0.74
Stage III	2.00 (1.14-3.52)	0.016	2.14 (1.44-3.17)	<0.001



**Table 2.** Cox proportional hazards model for crude and adjusted associations between risk factors and long-term mortality (excluding 30-day mortality)

	Univariable Cox regression		Multivariable Cox regression	
	Hazard ratio (95% CI)	p-value	Hazard ratio (95% CI)	p-value
Stage IV	4.66 (2.61-8.30)	<0.001	7.98 (5.19-12.26)	<0.001
<b>Adequate lymph node yield (<math>\geq 10</math>)</b>				
No	1		1	
Yes	1.47 (1.07-2.01)	0.019	1.29 (0.93-1.81)	0.13
<b>Resection margin</b>				
Negative	1		1	
Positive	2.82 (2.08-3.81)	<0.001	1.77 (1.29-2.44)	<0.001
<b>Period of surgery</b>				
2009-2011	1		1	
2012-2014	0.87 (0.68-1.11)	0.26	0.78 (0.67-1.07)	0.18
2015-2017	0.58 (0.41-0.83)	0.002	0.84 (0.58-1.21)	0.35

## DISCUSSION

In this retrospective cohort study, the effect of emergency surgery on long-term mortality was assessed in patients with colon cancer. After adjusting for confounders, long-term mortality in the emergency surgery cohort was significantly higher.

Our findings show that even when patients were healthy enough to be discharged from our hospital there was a significantly higher long-term mortality in the emergency group. We also found that the HR increases with longer follow up time. This indicates that emergency surgery increases cumulative risk of long-term mortality from the start of follow up and that this risk increases over longer periods.

This study shows similar results compared to other studies, which also have shown poorer long-term survival after emergency surgery. The findings of this study support those of Wong et al, who showed reduced long-term survival in 1923 colorectal cancer patients who underwent emergency surgery (6). The study results are also supported by studies of Xu et al and Wanis et al, who included 1180 and 214.174 colorectal cancer patients respectively and both showed worse long-term survival after emergency surgery (7,18).

The findings of this study are contrary to those of Weixler et al, who failed to show an independent association between emergency surgery and worse long-term survival (8). This might be caused by the long study duration of the Weixler study and the relative small number of included patients. The study by Weixler et al included patients over a period of 24 years (1989-2013) and still managed to include only 747 patients of which only 84 underwent emergency surgery. The surgical treatment of colorectal cancer patients has greatly improved in the last several decades due to several improvements in perioperative care, for example preoperative risk assessment, enhanced recovery programs and the increasing adoption of laparoscopic surgery (19).

There was no difference between patients who underwent surgery within 24 hours and patients who underwent surgery within 3 days in regards to long-term mortality. This was expected, because in practice the decision to operate within 24 hours or within 3 days often is often arbitrary and partially dependent on availability of operating rooms and medical staff. Therefore, we combined these patients together in one cohort.

The gradual decline of emergency surgery in 2009 to 2017 can be partly explained by the start of the national colorectal cancer-screening program in 2014 in the Netherlands and partly by implementing our new obstruction protocol in 2016 in our hospital (20). This obstruction protocol is used to prevent emergency surgery due to bowel obstruction and delays the operation which provides time for prehabilitation prior to elective surgery. A recent meta-analysis and systematic review of 15 RCTs regarding prehabilitation has shown that it is effective in reducing postoperative morbidity (21).

ASA score was slightly higher in the emergency cohort. This was expected as patients who undergo emergency surgery usually present in a later stage of their disease and often have symptoms such as bowel obstruction, borborygmi and loss of appetite. Pain and loss of appetite lead to chronic insufficient intake, loss of weight, fatigue and loss of energy. All these factors lead to a catabolic state and further deterioration of physical condition leading to higher surgical risk. This is supported by the higher rate of postoperative complication (and lower BMI) in the emergency surgery group. We would like to stress that this state should be avoided and patients should be prehabilitated whenever possible. Preoperative tumour symptoms were present in 98% of patients in the emergency cohort versus 32% in the elective cohort. Early detection and treatment of symptoms that can lead to emergency surgery can be an effective strategy as shown by a previous study in our hospital (20).

The strength of this study is the extensive dataset of the DCRA registry, which allowed us to perform detailed analysis. Case-ascertainment of the DCRA registry was 95% and external data verification with the Dutch Cancer Registry showed high concordance of data items (22).

This improves the generalizability of our results. Limitations of this study are the inherent risk of bias in a retrospective cohort study with no randomization. Secondly, rectal cancer was one of the exclusion criteria, however, the possibility exists that some patients with high rectal tumours have been wrongly classified as colon cancer patients and included in this study. Thirdly, all patients were operated on by a specialized colorectal surgeon, however case-load data per surgeon and timing of surgery (i.e. day/night) was not available. Fourthly, residual confounding stemming from comorbidity and selection bias caused by referral patterns might exist.

## **CONCLUSION**

Emergency surgery for colon cancer seems to lead to a significantly increased risk of long-term mortality compared to elective surgery. Detection and treatment of early symptoms that can lead to emergency surgery might be the way forward.

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04

# Increased long-term mortality after open colorectal cancer surgery; a multicenter population-based study



Milad Fahim, Lea M. Dijkman, Thijs A. Burghgraef, Paul B. van der Nat, Wouter J.M. Derksen, Hjalmar C. van Santvoort, Bareld B. Pultrum, Esther C.J. Consten, Douwe H. Biesma, Anke B. Smits

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## **ABSTRACT**

### **Aim**

Contrary to meta-analyses of RCTs, population-based studies have shown a significant association between open surgery and increased 30 and 90-day mortality, as compared with laparoscopic surgery, in colorectal cancer (CRC) patients. Long-term mortality, however, is scarcely reported. This retrospective population-based study aimed to compare long-term mortality after open and laparoscopic surgery for colorectal cancer (CRC).

### **Method**

The Dutch Colorectal Audit and the Dutch Cancer Centre registry were used to identify patients from three large non-academic teaching hospitals who underwent curative resection for CRC between 2009-2018. Patients with relative contra-indications for laparoscopic surgery (cT4 or pT4 tumours, distant metastasis requiring additional resection and emergency surgery) were excluded. Multivariable regression was used to assess the effect of laparoscopic surgery on long-term mortality with adjustment for gender, age, ASA score, TNM stage, chemoradiation therapy, and other confounders.

### **Results**

We included 4531 patients, of whom 1298 (29%) underwent open surgery. The median follow-up was 43 months (interquartile range 23-71). Open surgery was associated with an increased risk of long-term mortality (adjusted hazard ratio 1.26, 95% confidence interval: 1.10-1.45,  $p=0.001$ ). The mixed-effects Cox regression with year of surgery as random effect also showed an increased risk after open surgery (adjusted hazard ratio 1.33, 95% confidence interval: 1.11-1.52,  $p=0.004$ ).

### **Conclusions**

Open surgery seems to be associated with increased long-term mortality in the elective setting for colorectal cancer patients. A minimally invasive approach might improve long-term outcomes.

## What does this paper add to the literature?

Open surgery for colorectal cancer, compared to laparoscopic surgery, not only leads to worse *short-term* outcomes, it can also lead to a significantly increased risk of *long-term* mortality. A minimally invasive approach is preferable whenever possible.

## INTRODUCTION

Several meta-analyses of randomized controlled trials (RCTs) have shown that laparoscopic surgery for colorectal cancer (CRC) leads to reduced surgical trauma and faster postoperative recovery, as compared with conventional open surgery, without jeopardizing oncological outcome (1–3). Other benefits of laparoscopic surgery are fewer incisional hernias due to maintained abdominal wall integrity, fewer adhesion-related bowel obstruction, and better aesthetics (4–6). Laparoscopic surgery also seems to be cost-effective due to reduced postoperative stay, despite the increased intraoperative costs of laparoscopic surgery (7). This effect is likely due to lower rates of readmission and re-interventions for incisional hernias and adhesion-related bowel obstruction in the long-term (4,7).

Several meta-analyses have, however, failed to show a significant difference in 30-day mortality between laparoscopic surgery and open surgery. The COLOR trial, which reported ten-year outcomes after laparoscopic and open surgery, also showed no mortality difference (8). This may be partially explained by the strict eligibility criteria of the RCTs. For example, the COLOR trial had several exclusion criteria such as BMI higher than 30, signs of bowel obstruction and previous ipsilateral surgery. On the other hand, several nationwide population-based studies demonstrated reduced 30-day and 90-day mortality after laparoscopic surgery, as compared to open surgery (9,10).

It is reasonable to assume that the adverse effects of open surgery extend beyond the 90-day postoperative period (4,6,11,12). Nonetheless, studies on the long-term effects of open surgery are scarce and the question whether open surgery increases long-term mortality in CRC patients remains unresolved. It seems population-based studies might be more suited to answer this question due to a larger number of patients, including high-risk patients with higher rates of events, reflecting daily clinical practice. This population-based study aimed to assess the effect of open surgery compared to laparoscopic surgery on long-term mortality in CRC patients.

## **MATERIALS & METHODS**

### **Study design and data collection**

This is a retrospective analysis of a prospective database of three large Dutch non-academic teaching hospitals. Data were derived from the nationwide mandatory Dutch ColoRectal Audit (DCRA) registry (11) in which all patients undergoing curative surgery for primary colorectal carcinoma are prospectively included. The registry contains data regarding patient characteristics, tumour characteristics, treatments received and 90-day postoperative outcomes. Patients were registered in the DCRA after diagnosis of CRC by colonoscopy and biopsy. Incomplete variables from the DCRA database were supplemented by the primary researcher using pathology and operation reports. The Dutch Cancer Centre database (12) was used to obtain long-term mortality data, based on the municipal registration of vital events.

### **Patient population**

All patients undergoing surgery with curative intent for primary CRC since the start of the DCRA registry in January 2009 until December 2018 were evaluated. Patients were excluded if they had multiple synchronous colorectal tumours, underwent transanal resection or underwent a HIPEC procedure. To reduce confounding by indication, we also excluded patients with characteristics for which either one of the surgical approaches was recommended. The choice for these characteristics was in line with other cohort studies who used the same exclusion criteria (9,10). These characteristics were: 1) T4 tumours (both clinical as pathological classification); 2) any distant metastasis for which an additional resection took place and; 3) an emergency setting.

### **Definitions of exposure and outcomes**

All the patients in this study were operated on by a specialized colorectal surgeon or surgical resident. There were 3 to 4 specialized colorectal surgeons per hospital with extensive open and laparoscopic surgery experience. Procedures were defined as laparoscopic surgery or open surgery based on the initial intent of the surgical approach (i.e., converted laparoscopic surgery was included in the laparoscopic group). There were no specific guidelines recommending either open or laparoscopic surgery. Situations in which one of the approaches was a common choice, like T4 tumours, distant metastasis requiring additional surgery, and emergency surgery, were excluded, as mentioned before. So for the elective T1-3 patients, it was up to the surgeon to decide the surgical approach.

Postoperative complications were classified using the Clavien-Dindo classification (13). Adequate lymph node yield was defined as  $\geq$  ten lymph nodes according to the national colorectal cancer guideline formulated by the Dutch federation of medical specialists (14). Mortality outcomes were 90-day mortality and one, three and five-year mortality.

## Statistical analysis

Categorical data were presented as numbers and percentages and were compared using the chi-square test or Fisher's Exact test. Univariable and multivariable Cox regression was used to assess the effect of open surgery on all-cause long-term mortality while adjusting for potential confounding factors. These factors were: gender, age, ASA classification, location of the tumour, TNM-stage, conversion to open surgery, additional intraoperative resection due to tumour growth, adequate lymph node yield, neoadjuvant and adjuvant treatment, time period of operation (namely 2009-2012, 2013-2015 and 2016-2018) and hospital in which surgery took place. Factors were chosen based on known risk factors from literature and included the time period of operation as a measure of hidden confounders (e.g., improved perioperative care in recent years) (9,10,15). As an additional check on the association between open surgery and all-cause long-term mortality, we used a mixed effects Cox regression model with time period of operation as random effect while adjusting for the same variables as the normal Cox regression model. We also performed a sensitivity analysis in which stage IV patients were excluded.

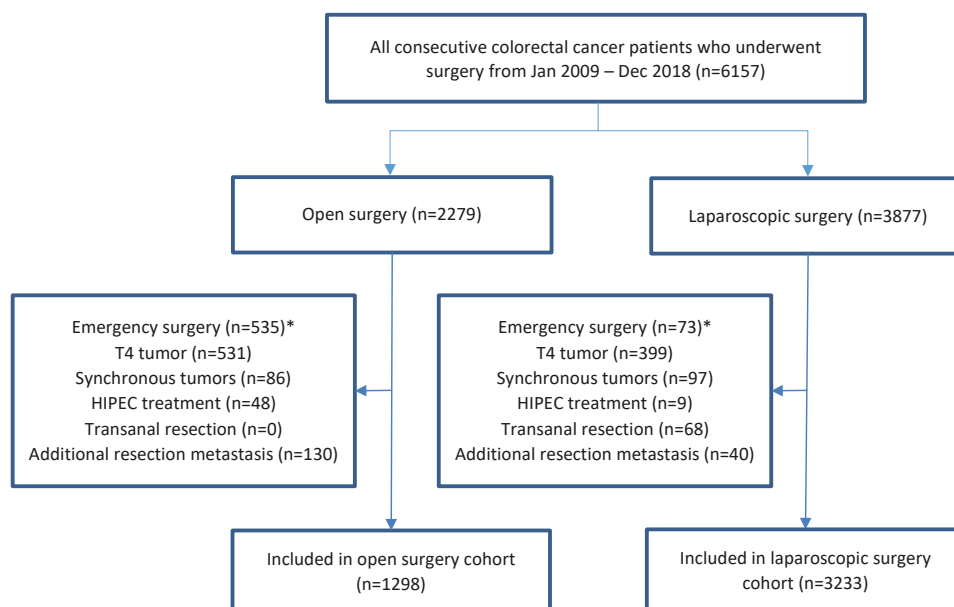
Results are presented as hazard ratios (HR) and odds ratios (OR) with corresponding 95%-confidence intervals (CIs). One, three and five-year HRs were calculated to prevent possible relevant information from being compressed into a single overall HR. All the P-values reported are two sided. A p-value of  $< 0.05$  was considered significant. Case-exclusion took place in cases with missing data after supplementing by the primary researcher. Missing data were not random and therefore multiple imputation was not possible. Patients who died within 90 days postoperatively were excluded from the survival analysis and the Cox regression models. The proportional hazards assumption of the Cox regression model was assessed by eyeballing the Kaplan-Meier plot and the log minus log plot (16). Statistical analysis was performed using SPSS v.24.0 (IBM, Armonk, NY, USA).

## RESULTS

### Patients

A total of 6157 CRC patients in three hospitals who received resection for primary CRC were evaluated for inclusion (figure 1). After excluding patients who met the exclusion criteria, 4531 patients remained (hospital A: n=1606, hospital B: n=1374, hospital C: n=1551). The median

follow-up was 43 months (interquartile range [IQR] 23-71) for the entire cohort, 37 months (IQR 20-63) for the laparoscopic cohort, and 54 months (IQR 32-82) for the open cohort. Case-exclusion took place in 2.7% of these cases due to missing data; this was not different between the open and laparoscopic groups (chi-square test,  $p=0.28$ ). In the participating hospitals 1298 out of 4531 patients (29%) underwent open surgery, the percentage of open surgery in these hospitals decreased from 51% (170 out of 334) in 2009 to 4% (22 out of 523) in 2018.



**Figure 1.** Study flowchart

*\* some patients had multiple exclusion criteria*

Baseline data are shown in Table 1. All the TNM stage 4 patients that were included had and pT1-3 tumour in combination with a metastasis for which no additional resection took place. There was no difference in BMI and previous abdominal surgery between the open and laparoscopic groups. These factors were therefore not included in the following Cox regression analyses.

Except for the surgical approach, the case-mix variables did not change significantly between the laparoscopic surgery and open surgery subgroups over the years (data not shown).

**Table 1.** Baseline characteristics

	Open surgery n=1298	Laparoscopic surgery n=3233	p-value
<b>Patient</b>			
Male	724/1298 (56%)	1897/3233 (59%)	0.08 <sup>a</sup>
Age			<0.01
<70	665/1298 (51%)	1827/3233 (57%)	
70-80	410/1298 (32%)	1073/3233 (33%)	
>80	223/1298 (17%)	333/3233 (10%)	
Body Mass Index			0.37
BMI <30	941/1167 (81%)	2516/3089 (82%)	
BMI 30-40	217/1167 (19%)	537/3089 (17%)	
BMI >40	9/1167 (1%)	36/3089 (1%)	
ASA classification			<0.01
ASA I	215/1282 (17%)	716/3169 (23%)	
ASA II	757/1282 (59%)	1873/3169 (59%)	
ASA III	284/1282 (22%)	556/3169 (18%)	
ASA IV	26/1282 (2%)	24/3169 (1%)	
Previous abdominal surgery	268/1298 (21%)	692/3233 (21%)	0.60 <sup>a</sup>
<b>Tumor</b>			
Primary location			0.73 <sup>a</sup>
Colon	860/1298 (66%)	2124/3233 (66%)	
Rectum	438/1298 (34%)	1109/3233 (34%)	
TNM stage			<0.01
Stage I	339/1284 (26%)	1234/3205 (39%)	
Stage II	527/1284 (41%)	1149/3205 (36%)	
Stage III	294/1284 (23%)	693/3205 (22%)	
Stage IV	124/1284 (10%)	129/3205 (4%)	
<b>Treatment</b>			
Additional resection due to primary tumor growth	90/1298 (7%)	87/3203 (3%)	<0.01 <sup>a</sup>
Adequate lymph node yield (≥10)	1135/1281 (89%)	2859/3162 (90%)	0.07 <sup>a</sup>
Neoadjuvant treatment	339/1298 (26%)	750/3233 (23%)	0.04
Adjuvant treatment	298/1298 (23%)	581/3233 (18%)	<0.01
Period of surgery			<0.01
2009-2012	690/1298 (53%)	776/3233 (24%)	
2013-2015	472/1298 (36%)	1011/3233 (31%)	
2016-2018	136/1298 (11%)	1446/3233 (45%)	

Data are n/total (%), unless otherwise stated p-values are calculated using the chi-square test.

<sup>a</sup> Fisher's Exact test.

Long-term mortality

Ninety-day mortality was 1.1% (37 out of 3233) in the laparoscopic cohort and 2.8% (36 out of 1298) in the open cohort. These 73 patients were excluded from the analysis of long-term mortality. As shown in figure 2 the 5-year mortality in the open surgery subgroup was 37% versus 22% in the laparoscopic surgery subgroup (log-rank test,  $p<0.001$ ).

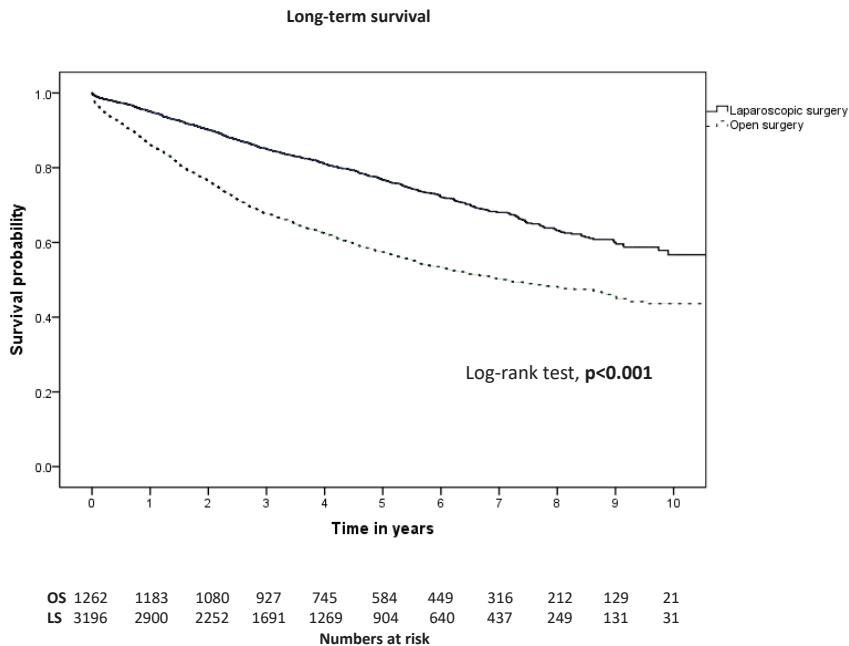


Figure 2. Kaplan-Meier survival curves of laparoscopic surgery versus open surgery

The increased risk of mortality in the open surgery subgroup was confirmed with univariable and multivariable Cox regression analysis, as shown in Table 2 (adjusted HR 1.26, 95% CI: 1.10-1.45,  $p=0.001$ ). The proportional hazards assumption of the Cox regression model was confirmed by eyeballing the Kaplan-Meier plot and the log minus log plot, both showed parallel curves with no crossing (16).

After adjusting for the same variables as before, the one, three and five-year HRs respectively were: 1.16 (95% CI: 1.01-1.34,  $p=0.04$ ), 1.21 (95% CI: 1.06-1.39,  $p=0.007$ ) and 1.26 (95% CI: 1.09-1.44,  $p=0.001$ ).



**Table 2.** Cox proportional hazards model for crude and adjusted associations between risk factors and long-term mortality (excluding 90-day mortality)

	Univariable Cox regression		Multivariable Cox regression	
	Hazard ratio (95% CI)	p-value	Hazard ratio (95% CI)	p-value
<b>Gender</b>				
Male	1		1	
Female	0.99 (0.87-1.12)	0.83	0.92 (0.81-1.06)	0.25
<b>Age</b>				
<70	1		1	
70-80	1.88 (1.63-2.20)	<0.001	1.78 (1.52-2.09)	<0.001
>80	4.09 (3.48-4.82)	<0.001	3.58 (2.97-4.33)	<0.001
<b>ASA score</b>				
I	1		1	
II	1.64 (1.34-2.01)	<0.001	1.36 (1.11-1.68)	0.004
III	3.57 (2.87-4.44)	<0.001	2.33 (1.84-2.95)	<0.001
IV	7.35 (4.73-11.41)	<0.001	3.31 (2.10-5.23)	<0.001
<b>Location tumor</b>				
Colon	1		1	
Rectum	1.01 (0.88-1.15)	0.95	1.05 (0.83-1.33)	0.67
<b>TNM stage</b>				
Stage I	1		1	
Stage II	1.41 (1.18-1.69)	<0.001	1.22 (1.01-1.47)	0.041
Stage III	2.20 (1.83-2.65)	<0.001	2.15 (1.74-2.65)	<0.001
Stage IV	6.91 (5.60-8.54)	<0.001	6.56 (5.23-8.23)	<0.001
<b>Surgical approach</b>				
Laparoscopic surgery	1		1	
Open surgery	1.52 (1.33-1.73)	<0.001	1.26 (1.10-1.45)	0.001
<b>Additional intraoperative resection due to primary tumor growth</b>				
No	1		1	
Yes	1.17 (0.85-1.61)	0.33	1.06 (0.76-1.46)	0.74
<b>Adequate lymph node yield (&lt;10)</b>				
No	1		1	
Yes	0.92 (0.76-1.11)	0.39	1.00 (0.81-1.22)	0.99
<b>Neoadjuvant treatment</b>				
No	1		1	

**Table 2.** Cox proportional hazards model for crude and adjusted associations between risk factors and long-term mortality (excluding 90-day mortality)

	Univariable Cox regression		Multivariable Cox regression	
	Hazard ratio (95% CI)	p-value	Hazard ratio (95% CI)	p-value
Yes	0.91 (0.79-1.04)	0.17	1.30 (1.01-1.67)	0.04
<b>Adjuvant treatment</b>				
No	1		1	
Yes	0.89 (0.77-1.04)	0.15	0.98 (0.81-1.19)	0.81
<b>Period of surgery</b>				
2009-2012	1		1	
2013-2015	0.93 (0.80-1.08)	0.35	1.03 (0.88-1.20)	0.74
2016-2018	0.61 (0.47-0.77)	<0.001	0.74 (0.57-0.95)	0.018

The mixed effects Cox regression model with time period of surgery (2009-2012, 2013-2015 and 2016-2018) as random effect confirmed the previous analyses and showed an HR of 1.33 (95% CI: 1.11-1.52,  $p=0.004$ ). The sensitivity analysis, excluding the stage IV patients, also showed a significant result (adjusted HR 1.11, 95% CI: 1.05-1.38,  $p=0.040$ ).

## DISCUSSION AND CONCLUSION

In this multicentre population-based study, the effect of open surgery on long-term mortality was assessed in patients with colorectal cancer in the elective setting. After adjusting for confounders, long-term mortality in the open surgery cohort was significantly higher.

Our results show that even after exclusion of 90-day mortality, there is a significantly higher long-term mortality in the open surgery group. We also found a slight increase in HR with longer follow-up time, indicating that open surgery increases the risk of long-term mortality from the start of follow-up. This risk increases over more extended periods. As an additional check to account for variability of care over time, we used a mixed effects Cox regression model with year of surgery as random effect. This model showed similar results and strengthened our conclusion. The findings agree with a recent population-based study which included 16,378 rectal cancer patients and showed reduced 5-year survival after open surgery (17).

Several factors might explain the association with open surgery and increased long-term mortality. Firstly, patients often do not fully recover to their previous level of health, most

notably the elderly CRC patient (18). Secondly, patients might need additional surgery for incisional hernia or adhesion-related bowel obstruction in the years following the initial open operation (4,6).

The shorter follow-up time in the laparoscopic cohort was expected because in the open cohort the majority of procedures were done in the early years of the study. In contrast, in the laparoscopic cohort, a significant proportion of the procedures were done in the last few years of the study. This caused a lower median follow-up time of the laparoscopic cohort.

An extensive body of literature exists regarding the effect of the surgical approach on short-term postoperative mortality and morbidity. Thus far, the meta-analyses of RCTs have shown trends favouring laparoscopic surgery, but they have failed to show a significant difference between the two methods of surgery and postoperative mortality (1–3). This might be due to the strict selection criteria of the studies, which lead to the study population being relatively healthier than the real-world population. Population-based studies seem to be more suitable to assess the effect of surgical approach on long-term mortality. Nonetheless, inherent bias remains as these studies are retrospective in nature and non-randomized. In the present study, we attempted to create relatively homogenous and comparable subgroups by excluding cases with relative contra-indications for the laparoscopic approach. To deal with an unequal distribution of baseline predictors of outcome in the groups of interest we adjusted for case-mix differences in a multivariable model. The exclusion of cases was necessary for the internal validity of our study, nonetheless, our inclusion criteria were broader than those of the RCTs (1–3). For example, the large CLASICC trial (19) excluded patients with cancer in the transverse colon and chronic cardiac or pulmonary disease. These subgroups who were excluded in the CLASICC trial were included in the present study.

A study using all the national data from the DCRA would have been preferable, even when missing data would have been difficult to correct. However, only aggregated national data was available from the DCRA and many analyses are not possible with aggregated data. Therefore, we chose the three hospital approach in which each hospital agreed to release their patient-level DCRA data for this study.

Since the implementation of the Dutch Colorectal Audit (DCRA), there has been a nationwide trend of steadily improving surgical outcomes in the Netherlands (20). In recent years, we also saw the rise of Value-Based Health Care, which is seen as a possible method to continuously improve quality of care and deal with rising healthcare costs (21). These developments might have influenced some outcomes in our study, however we believe that both the laparoscopic as well as the open cohort in our study are affected to the same extent.

Our cohort's baseline characteristics showed that patients in the open surgery group were older, had higher TNM stage and required more neoadjuvant and adjuvant treatment indicating more advanced or aggressive disease. We also observed that the overall rate of open surgery decreased dramatically from 51% in 2009 to 4% in 2018, while baseline characteristics of the study population did not change substantially over the course of those years. Therefore, the decision for either laparoscopic surgery or open surgery is probably mainly surgeon-driven. However, surgeon judgement as a factor in decision-making is extremely difficult to parse out in a retrospective manner and can lead to confounding by indication. We have tried to minimize this effect by excluding patients for which either one of the surgical approaches is recommended (such as T4 tumours or emergency surgery) and adjusted for other potential confounders. We also observed significant variation between open surgery rates across the three hospitals in this study and the decision for one of the approaches could partly be hospital-driven. The choice for the open approach seems to be a risk factor that can and should be influenced.

The DCRA database is currently the best source of population-based surgical colorectal cancer data in the Netherlands. Case-ascertainment was 95%, and external data verification with the Dutch Cancer Registry showed high concordance of data items (22). Furthermore, we included three large non-academic teaching hospitals. Therefore, the generalizability of our results to the Dutch surgical CRC population as a whole is considered strong. Limitations of this study are the inherent risk of bias in a nonrandomized retrospective comparison. Secondly, specialized colorectal surgeons operated all patients, however case-load data per surgeon and timing of surgery (i.e., day/night) were not available. Thirdly, as mentioned before, surgeon judgement as a factor in decision making can lead to confounding by indication and is extremely difficult to account for in a retrospective manner and is a limitation of the current study. Fourthly, residual confounding stemming from comorbidity and selection bias caused by referral patterns might exist.

## **Conclusion**

Open surgery seems to be associated with increased long-term mortality in the elective setting for colorectal cancer patients. A minimally invasive approach might improve long-term outcomes.

## **Acknowledgements**

The authors thank the registration team of the Netherlands Comprehensive Cancer Organization (IKNL) for the collection of data for the Netherlands Cancer Registry.

## **Ethics approval**

Medical Ethics Committees United (MEC-U), located in Nieuwegein at the St. Antonius Hospital and consisting of a partnerships between 7 large regional hospitals in the Netherlands, reviewed and approved this study.

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**05**



# Promising results of a new treatment in patients with bowel obstruction in colorectal surgery



Milad Fahim, Lea M. Dijkman, Charlotte S. van Kessel, Diederik P.J. Smeeing, Akje S. Braaksma, Wouter J.M. Derksen, Anke B. Smits

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## **ABSTRACT**

### **Introduction**

Bowel obstruction increases risk of emergency surgery and leads to suboptimal physical and nutritional condition. Preventing emergency surgery and prehabilitation might improve outcomes. This pilot study aimed to examine the effect of a multimodal obstruction protocol for bowel obstruction patients on the risk of emergency surgery and postoperative morbidity and mortality.

### **Materials and methods**

All bowel obstruction patients treated according to the obstruction protocol in the period 2013-2017 were included in this uncontrolled observational cohort study. Benign and malignant causes of bowel obstruction were included. The protocol consisted of: 1. specific dietary adjustments to reduce prestenotic dilatation, 2. oral laxatives and 3. prehabilitation. Emergency surgery and postoperative morbidity and mortality rates were compared to known rates from the literature.

### **Results**

Sixty-one patients were included: 44 (72%) were treated for colorectal cancer and 17 (28%) for Crohn's disease or diverticulitis. Four patients (7%) underwent emergency surgery. Primary anastomosis was constructed in 49 out of 57 elective patients (86%). Severe complications (Clavien-Dindo  $\geq$ III) occurred in four patients (7%). No bowel perforation, anastomotic leakages or 30-day mortality was observed. These rates were much lower than rates reported in the literature after surgery for colorectal cancer (3% bowel perforation, 8% anastomotic leakage, 4% 30-day mortality, 15% severe complications) and benign disease (30-day mortality 17%, severe complications 7%).

### **Conclusion**

Using the obstruction protocol in patients with bowel obstruction reduced emergency surgery and postoperative morbidity and mortality in this pilot study. This protocol seems to be a viable and efficient alternative to emergency surgery.

## INTRODUCTION

Bowel obstruction occurs frequently in patients with colorectal cancer (CRC) or benign bowel disease like diverticulitis or Crohn's disease. Incidence of bowel obstruction in CRC patients is 10% to 30% (1-3). Bowel obstruction leads to several consequences, which can lead to postoperative morbidity and mortality. Patients with bowel obstruction are at risk of undergoing emergency surgery, often resulting in a laparotomy with colon resection and the construction of a stoma by a surgeon who is not specialised in colorectal surgery (4). Emergency surgery is associated with higher 30-day morbidity (33% vs 20%) and 30-day mortality (9% vs 3%) than elective surgery (5-7). In the Netherlands, the national average of emergency surgery in colorectal cancer (CRC) patients is 18% with bowel obstruction being the most frequent indication for emergency surgery (7). In addition, the prestenotic distention of the bowel wall in combination with the stenosis causes pain and malabsorption leading to chronic insufficient intake and lethargy. This in turn causes suboptimal physical and nutritional condition which are known risk factors for postoperative morbidity (8-11).

In elective surgery there is time for prehabilitation of the patient prior to surgery. In our hospital we are used to prehabilitating our colorectal patients for 3 weeks prior to elective surgery if they are in poor physical condition. Prehabilitation consists of: daily physical exercise, smoking cessation, reducing alcohol consumption and nutritional support if needed. A recent meta-analysis and systematic review of 15 RCTs regarding prehabilitation has shown that it is effective in reducing postoperative morbidity (12).

In patients with bowel obstruction presenting with sepsis, a near blow-out or signs of perforation, there is no time for prehabilitation and emergency surgery is required. Luckily however, an important proportion of the patients with bowel obstruction present with less severe clinical signs of obstruction. These symptoms include abdominal pain, borborygmi, intermittent stool passage, anorexia and prestenotic bowel dilatation on imaging based on a large tumour or stenotic segment of chronic diverticulitis or Crohn's disease. In these patients, measures can be taken to prevent emergency surgery and prehabilitate the patient in order to make them fit for surgery.

Therefore, we developed a multimodal obstruction protocol for patients with bowel obstruction, aimed at eliminating bowel wall distension and subsequently eliminating abdominal pain. In the absence of bowel distension and abdominal pain the need to perform emergency surgery disappears. Surgery can be postponed, planned electively and conducted laparoscopically (or robot assisted) by a specialized colorectal surgeon. It also provides time for proper prehabilitation of the patient.

While developing the obstruction protocol we hypothesised that when we reduce the amount of stool produced, this reduced volume of stool can more easily pass the obstructive bowel. This will reduce prestenotic bowel wall distension and consequently abdominal pain. The reduced volume of stool is achieved by a combination of laxatives and dietary measures. This varied from low-residue diet for mild obstruction, nutritional drinks for moderate obstruction and TPN for severe obstruction. The diets that the patients received covered all their nutritional needs and ensured caloric intake which resulted in the patients leaving the catabolic state. The primary goal of this exploratory pilot study was to examine the effect of this multimodal obstruction protocol for patients with bowel obstruction on the risk of emergency surgery and postoperative morbidity and mortality.

## **PATIENTS AND METHODS**

### **Patients**

Between February 2013 and March 2017 all patients presenting at the emergency room or outpatient department with signs and symptoms of bowel obstruction who were treated according to the obstruction protocol were prospectively evaluated. At least at least one of the following clinical symptoms had to be present: abdominal pain, rumbling sounds (borborygmic) or obstructive defecation (irregular, changed frequency, changed consistency). Secondly, obstruction had to be confirmed by a CT or MRI scan showing a stenotic tumour or bowel segment, with or without dilated bowel proximal from the stenotic segment or colonoscopy with a stenotic process which cannot be passed by the endoscope.

Both patients with a stenosis caused by a malignant tumour or a stenosis caused by bowel wall fibrosis or chronic infection (Crohn's disease, chronic diverticulitis) were included. Patients presenting with a bowel obstruction with signs of near blow out (cecum > 9cm), sepsis or perforation, thus requiring immediate surgery, were excluded.

### **Obstruction protocol**

According to the symptoms and radiological findings, four stages of obstruction were recognized:

- Stage 1: abdominal pain and borborygmi, no bowel distension.
- Stage 2: abdominal pain and severe borborygmi, distention of a segment of the bowel.
- Stage 3: abdominal pain, distention of the whole or large part of the bowel.
- Stage 4: signs of near blow out, sepsis or perforation. For patients in this stage emergency surgery should be considered.

The protocol was intended for patients in stage 1, 2 and 3 and consisted of a combination of laxatives, daily physical training and lifestyle changes for all the patients. Specific dietary adjustments were made according to stage:

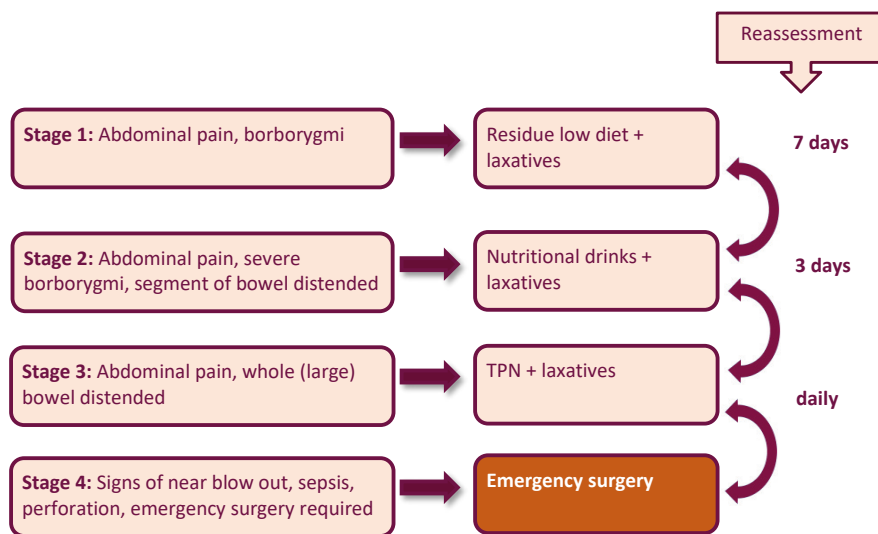
- Stage 1: Residue low diet (no large fibres, seeds and peels) depending on the required caloric intake as determined by the dietitian.
- Stage 2: Complete diet of nutritional drinks (orally or through nasoenteral tube).
- Stage 3: Total parenteral nutrition (TPN) and oral intake of clear fluids.

The surgeon determined which stage of obstruction was present in the patient based on the complaints and CT-scan and elective surgery was planned 7-10 days later for stage 3 patients and 3 weeks later for stage 1 and 2 patients (fig 1.).

Patients who could not drink the nutritional drinks orally, were hospitalized and received a nasoenteral tube. If enteral feeding through the tube developed well, patients were allowed to go on home leave in expectation of the operation. Patients who required TPN were hospitalized and stayed hospitalized until the operation. If they remained dependent on TPN, the surgery took place after 7 to 10 days due to the high costs of hospitalization. This was based on current surgical guidelines, which recommend a minimum of 7 days of nutritional support prior to surgery (13). All patients received oral laxatives in order to improve stool passage and prevent complete obstruction with either Movicolon powder and/or Magnesiumhydroxide tablets.

Prehabilitation and life style changes consisted of instructions to exercise daily, smoking cessation and reduction of alcohol consumption to <2 units per day before the operation. Patients were instructed to exercise twice a day for at least 30 minutes, exercises consisted of walking, cycling and training on the home trainer. Patients were also instructed to climb stairs as much as possible. Hospitalized patients had a home trainer next to their bed and daily exercise was stimulated by the physiotherapist.

To ensure that the obstruction protocol has a positive effect on the obstruction complaints, the patients were followed closely depending on the stage. If there was no relief of pain or distention of the abdomen, the stage of obstruction was increased and the patient was treated according to that stage. Stage 3 patients were hospitalized and observed twice a day. Stage 1 and 2 patients were seen at the outpatient department and were contacted at least once a week by the surgeon, physician assistant or the dietitian to evaluate obstruction complaints. Optimal duration of prehabilitation was deemed 3 weeks if the clinical condition of the patient allowed this duration. This was based on several RCTs that examined the effect of nutritional and physical prehabilitation and had a duration ranging from 2 weeks to 4 weeks (14-18).



**Figure 1.** Obstruction protocol flowchart

## Data analysis

Normally distributed continuous data were presented as means  $\pm$  standard deviation (SD), non-normally distributed continuous data as medians with interquartile range and dichotomous data as numbers with percentages. Mann-Whitney U test was used to compare median duration of treatment between patients with malign and benign bowel obstruction. Paired samples T-test was used to compare BMI at start of treatment with BMI at time of surgery. No further statistical analysis were performed as it was an uncontrolled observational cohort study.

## RESULTS

A total of 61 patients with bowel obstruction were included and we had no missing data. The most frequently observed symptoms were obstructive defecation, abdominal pain and weight loss (see table 1.) Median weight loss during the last 3 months was 5 kg (IQR 2-9) corresponding with a MUST score of 1 or more in 44 out of 61 patients (77%).

**Table 1.** Baseline table

	<b>n=61</b>
<b>Age in years</b>	63 (56-75)*
<b>Gender</b>	
Male	29 (48)
Female	32 (53)
<b>Disease origin</b>	
Malignant	44 (72)
Colon	30 (49)
Rectum	14 (23)
Benign	17 (28)
Cohn's disease	15 (25)
Chronic diverticulitis	2 (3)
<b>ASA classification</b>	
1	7 (12)
2	38 (62)
3	15 (26)
<b>BMI</b>	26 ± 4.6 a
<b>Symptoms</b>	
Changed defecation	57 (93)
Abdominal pain	57 (93)
Nausea	26 (43)
Vomiting	14 (23)
Weight loss	50 (82)
<b>Weight loss in last 3 months in kg</b>	5 (2-9) *
<b>MUST-score at presentation</b>	
0	14 (23)
1	27 (44)
2	17 (28)
3	1 (2)
4	2 (3)
<b>Albumine</b>	40 ± 4.5 a
<b>Pre-operative hemoglobine</b>	7.9 ± 1.2 a

All variables are in n (%) except marked

\* Median + interquartile range

a Mean ± Standard deviation

## Weight loss and diet

Median duration of the administered diet was 16 days (IQR 8-22). Separate analysis for patients with malignant disease (median 15 days, IQR 7-19) and patients with benign disease (median 24 days, IQR 16-39) showed that patients with benign disease were treated with the obstruction protocol for a longer period of time (Mann Whitney U test,  $p=0.002$ ). Median BMI at time of presentation was 25.5 (IQR 22.9-27.6) (table 1). Paired samples t-test showed a statistically significant increase in BMI after prehabilitation (mean increase of 0.33, 95% CI: 0.16-0.51,  $p<0.001$ ).

Out of the 14 patients who were allocated to a residue low diet (stage 1), eventually nine patients were relocated to a complete diet of nutritional drinks (stage 2). Although obstruction symptoms were resolved by the residue low diet in these nine patients, they were unable to eat enough to assure sufficient caloric intake resulting in further weight loss.

**Table 2.** Stages of disease

Type of nutrition	n=61
<b>Stage 1: Residue low diet</b>	5 (8)
<b>Stage 2: Nutritional drinks</b>	
Orally	18 (30)
Through nasoenteral tube	19 (31)
<b>Stage 3: Total parenteral nutrition (TPN)</b>	10 (16)
<b>Crossover during treatment*</b>	
Upstaging from stage 1 to stage 2: Residue low diet followed by nutritional drinks	9 (5)

*All variables are in n (%)*

*\* Upstaging in other stages or down staging did not occur*

## Surgical treatment

Out of 61 patients treated with the obstruction protocol, only 4 patients (7%) needed emergency surgery due to persisting or worsening of obstruction symptoms. This is much lower than the national average of 19% emergency surgery for colorectal cancer in the Netherlands (7). Of these 4 patients, 3 were treated with protein enriched drinks (stage 2) and 1 patient was treated with TPN (stage 3). This means that of the 10 patients in stage 3 who received TPN only 1 patient underwent emergency surgery.



**Table 3.** Surgical treatment

	<b>n=61</b>
<b>Emergency surgery</b>	4 (7)
<b>Laparoscopic surgery</b>	42 (69)
<b>Conversion during laparoscopy</b>	2/42 (5)
<b>Type of surgery</b>	
Right hemicolectomy	19 (31)
Left hemicolectomy	4 (7)
Sigmoid resection	18 (30)
Low anterior resection	13 (21)
Low anterior resection + left hemicolectomy	2 (3)
Rectum amputation	1 (2)
Subtotal colectomy	2 (3)
Partial small bowel resection	2 (3)
<b>Anastomosis</b>	51 (84)
<b>Blood loss in ml</b>	50 (20-100) *
<b>Duration of surgery in minutes</b>	110 (90-120) *

*All variables are in n (%), except marked*

*\* Median + interquartile range*

Two out of the 4 emergency surgery patients could be treated laparoscopically, 1 of these patients received a right hemicolectomy with primary anastomosis and the other patient received a right hemicolectomy with an ileostomy. The remaining 2 patients underwent an open Hartmann procedure.

The remaining 57 out of the 61 patients (93%) received elective surgery. In these patients, laparoscopic surgery was performed in 40 out of 57 patients (70%), conversion to open surgery was necessary in 2 out of 40 patients (5%) due to bowel distension in 1 patient and a congenital anatomic variation in another patient.

Primary anastomosis was performed in 49 out of 57 patients (86%), in the other 8 out of 57 patients (14%) a primary anastomosis was not possible or the risk of anastomotic leakage was considered too high, in these cases either an ileostomy or colostomy was performed. The reasons that a primary anastomosis was not performed were: locally advanced disease (4 patients), distended bowel (2 patients), APR procedure (1 patient) and subtotal colectomy (1 patient).

## Surgical outcomes

No bowel perforation, anastomotic leakages or 30-day mortality was observed. Overall, 34 complications occurred in a total of 23 patients (38%). Severe complications (Clavien-Dindo grade  $\geq 3$ ) occurred in only 4 patients (7%), mild complications (Clavien-Dindo  $<3$ ) occurred in 19 patients (31%). All of the patients with severe complications were stage 2 patients in the obstruction protocol and had received elective surgery.

Postoperative morbidity and mortality rates in our study cohort were much lower than the rates reported in the literature: after colorectal cancer surgery in the Netherlands the average nationwide bowel perforation rate is 3%, anastomotic leakage is 8% and 30-day mortality is 4% (7). Another study reported a severe complications (Clavien-Dindo  $\geq 3$ ) rate of 15% in a cohort of 2018 colorectal cancer patients (21). After surgery for benign causes of obstruction the rates of 30-day mortality and severe complications reported in the literature are 17% and 7% respectively (22,23).

**Table 4.** Postoperative outcomes

	<b>n=61</b>
<b>30-day mortality</b>	0 (0)
<b>All postoperative complications</b>	23 (38)
<b>Clavien Dindo classification</b>	
Grade I	10 (16)
Grade II	9 (15)
Grade IIIA	1 (2)
Grade IIIB	3 (5)
<b>Bowel perforation</b>	0 (0)
<b>Anastomotic leakage</b>	0 (0)
<b>Postoperative hospital stay in days</b>	9 (6-15) *

*All variables are in n (%)*

*\* Median + interquartile range*

## DISCUSSION

This observational uncontrolled cohort pilot study examined the effect of a multimodal obstruction protocol, which aimed to eliminate bowel wall distension to provide time for prehabilitation in patients with bowel obstruction. The rate of emergency surgery was reduced twofold, the rate of severe complications was more than halved and the rate of 30-day mortality

was eliminated completely in our study cohort compared to the rates reported in the literature after colorectal surgery for malignant disease (7,21). The literature regarding surgery for benign causes of obstruction is more limited, nonetheless, the rate of emergency surgery is comparable (7% vs 7%) and the rate of 30-day mortality in our study cohort is lower (0% vs 17%) than the rates reported in the few small studies that are available (22,23).

Patients with bowel obstruction are a vulnerable group at risk of emergency surgery. In our study cohort 77% of the patients had a MUST score of 1 or higher indicating malnutrition. In contrast, the large study by Hu et al, which used the American ACS-NSQIP database which included more than 42.000 colorectal cancer patients, reported a malnutrition rate of 28% (9). In regards to ASA classification, in our study cohort the proportion of patients with ASA  $\geq$ III was 26% which is comparable to the 25% ASA  $\geq$ III as reported by Bakker et al for colorectal cancer patients (7).

The obstruction protocol was successful in reducing the rate of emergency surgery. In the Netherlands, the nationwide incidence of emergency surgery for colorectal cancer patients is 19% (7). Bowel obstruction is by far the most frequent symptom in these patients with a prevalence of 61%. In our cohort of patients with bowel obstruction confirmed by MRI/CT scan or colonoscopy, one would expect a higher percentage of emergency surgery than the national average of 19%. However the incidence of emergency surgery was only 7% (4 out of 61 patients). Even if we only include the patients with prestenotic dilatation (stage 2 and 3), the rate of emergency surgery is still 7% (4 out of 57 patients). Lastly, the 10 patients in stage 3 had bowel distention through the whole large bowel, received TPN and were at real risk of emergency surgery. However, of these 10 patients only 1 patient underwent emergency surgery. Another beneficial effect of the obstruction protocol seems to be that most patients underwent elective laparoscopic surgery by an experienced colorectal surgeon (70%) and the percentage of intra-operative conversion to open surgery of 5% was lower than the national average of 14% in colorectal cancer surgery (24).

The surgical outcomes in this study were promising. Thirty-day mortality in our study cohort was 0%, which is a drastic reduction in mortality as compared to the large study by Bakker et al which included more than 30.000 colorectal cancer patients in the Netherlands and reported a 30-day mortality rate of 4% (7). The 0% mortality in our study is also drastically lower than the 30-day mortality rate of 17% in patients with benign causes of obstruction as reported by Oomen et al (22). Furthermore, severe complications in our study cohort occurred in 7% of patients and was less frequent than the 11% severe complication rate in colorectal cancer patients as reported by Bakker et al (7). The 7% severe complication rate of this study was comparable to the 7% rate reported by Goyer et al who reported postoperative outcomes in

patients with benign causes of obstruction (23). Although it should be noted that the numbers of the studies regarding benign causes of obstruction were low: 114 patients in the study by Oomen et al and 124 patients in the study by Goyer et al.

Our obstruction protocol also appeared to improve the nutritional status of the patients. Median duration of nutritional support in our study was 16 days (IQR 8-22), resulting in a statistically significant improvement in BMI prior to surgery (mean BMI increase of 0.33,  $p < 0.001$ ). Current surgical guidelines recommend a minimum of 7 days of preoperative nutritional support if malnutrition is present (13). However, we chose to extend this period of treatment to further increase nutritional status as well as to provide sufficient time for physical prehabilitation which has an optimal effect after 3 weeks of training (14-18).

This study showed that the obstruction protocol seems to be a viable and efficient alternative to emergency surgery and other approaches such as the stent as bridge to surgery. Furthermore, it is easy to apply and the burden on the patient is minimal. In a time of rising healthcare costs, this protocol might be a promising way forward in improving quality of care and preventing costly complications.

### **Strengths and limitations**

A strength of this study is that we provided tailor made exercise instructions which could be easily performed by the patients themselves at home. Previous studies have shown that home-based interventions (14) with moderate-intensity exercise may be the optimal approach in terms of effectivity and patient adherence in the elderly patient (26,27). A limitation of this study is that this was an uncontrolled observation study and as such we cannot claim statistical significance in our results.

### **CONCLUSION**

Using the obstruction protocol in patients with bowel obstruction reduced emergency surgery and postoperative morbidity and mortality in this pilot study. This protocol seems to be a viable and efficient alternative to emergency surgery. The promising results justify conducting a larger prospective multicentre study.

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06



# Prospective multicentre study of a new bowel obstruction treatment in colorectal surgery: reduced morbidity and mortality



Milad Fahim, Lea M. Dijkman, Wouter J.M. Derksen, Johanne G. Bloemen, Douwe H. Biesma, Anke B. Smits

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## **ABSTRACT**

### **Introduction**

Bowel obstruction patients are at increased risk of emergency surgery and have poor nutritional and physical conditions. These patients could benefit from prehabilitation and prevention of emergency surgery. This study assessed the effect of a multimodal obstruction treatment for bowel obstruction patients in colorectal surgery on the risk of emergency surgery and postoperative morbidity and mortality.

### **Materials and methods**

This multicenter observational cohort study included all consecutive bowel obstruction patients who received obstruction treatment (obstruction protocol) in the period 2019-2020 in two Dutch hospitals. Benign and malignant causes of bowel obstruction were included. Treatment consisted of 1. dietary adjustments, 2. postponing surgery for three weeks, 3. laxatives, and 4. prehabilitation. We compared emergency surgery and postoperative morbidity and mortality rates to known rates from the literature.

### **Results**

Eighty-nine patients were included: obstruction treatment was successful in 77 patients (87%) who underwent elective surgery and unsuccessful in 12 patients (13%) who underwent emergency surgery. Sixty-six (74%) had colorectal cancer, and 22 (25%) had benign disease. Thirty-day mortality of 0% in our study was significantly lower than the national average of 4% in colorectal cancer patients in the Netherlands ( $p = 0.049$ ). Anastomotic leakage rate was 3%, severe complications (Clavien-Dindo  $\geq$  III) 8%, and bowel perforation 0%. These rates did not differ significantly from rates reported in literature.

### **Conclusion**

The obstruction treatment prevented emergency surgery in most patients with bowel obstruction and reduced postoperative morbidity and mortality. The obstruction treatment seems to be a safe and efficient alternative to emergency surgery.

## INTRODUCTION

Bowel obstruction is a frequent occurrence in patients with colorectal cancer or benign bowel diseases like Crohn's disease or diverticulitis. The incidence of bowel obstruction in colorectal cancer patients is 8–29% (1–3). Bowel obstruction can lead to several complications, which in turn can lead to postoperative morbidity and mortality. Patients with bowel obstruction are at risk of undergoing emergency surgery, often resulting in a laparotomy with colon resection and the construction of a stoma. Also, emergency surgery is usually performed by a surgeon who is not specialised in colorectal surgery (4). Emergency surgery is associated with increased 30-day morbidity (33% vs. 20%) and 30-day mortality (9% vs. 3%) compared to elective surgery (5–7). In the Netherlands, 19% of all colon cancer patients undergo emergency surgery, with bowel obstruction being the most frequent indication for emergency surgery (7). In addition, the prestenotic distension of the bowel wall in combination with the stenosis itself causes pain and malabsorption leading to chronic insufficient intake and lethargy. This leads to suboptimal physical and nutritional conditions, which are known risk factors for postoperative complications (8–11).

Randomized controlled studies (RCTs) and systematic reviews have confirmed the effectiveness of prehabilitation in reducing postoperative morbidity in patients with poor physical and nutritional conditions (12–14). Prehabilitation is recommended for at least three weeks prior to surgery and is well within reach in the elective setting (13,15–18).

The emergency surgery patient presents with ileus, bowel distension, severe abdominal pain, borborygmi, intermittent stool passage, anorexia, and prestenotic bowel dilatation on imaging based on a tumour or stenotic segment due to chronic diverticulitis or Crohn's disease. Only patients with sepsis, a near blow-out, or signs of bowel perforation have to be operated on immediately; it would be too dangerous to start obstruction treatment in these patients. For the remaining emergency patients, measures can and should be taken to prevent emergency surgery which in turn provides time for prehabilitation to make patients fit for surgery.

The obstruction treatment (obstruction protocol) is a multimodal protocol to eliminate bowel wall distension and abdominal pain in patients with bowel obstruction. In the absence of abdominal pain and signs of sepsis, there is no need for emergency surgery. Surgery can be postponed, planned electively, and conducted laparoscopically (or robot-assisted) by a specialized colorectal surgeon. This also provides time for proper prehabilitation for the recommended duration of three weeks (13,15–18).

The premise of the obstruction treatment is that minimizing the stool production will allow for easier passage of the reduced volume of stool through the obstructive bowel. This will reduce

prestenotic bowel wall distension and consequently abdominal pain, nausea, and vomiting. The reduction in stool volume will be achieved by a combination of laxatives and dietary measures. These measures vary from a low-residue diet for mild obstruction, nutritional drinks for moderate obstruction, and total parenteral nutrition (TPN) for severe obstruction. These dietary measures also aim to ensure sufficient caloric intake so that the patient can exit the catabolic state.

The effects of the obstruction treatment were studied in a pilot study which showed reduced postoperative morbidity and mortality (19). Even though the patients were at increased risk of emergency surgery, the obstruction treatment helped achieve outcomes comparable to elective surgery. The primary goal of this prospective multicentre observational study was to examine the effect of the multimodal obstruction treatment for patients with bowel obstruction on the risk of emergency surgery and postoperative morbidity and mortality.

## **PATIENTS AND METHODS**

This was a prospective multicentre observational study in two large Dutch non-academic teaching hospitals. We obtained ethical approval from the Medical Research Ethics Committees United (reference number W19.041).

### **Patients**

Between May 2019 and August 2020, all consecutive patients presenting at the emergency room or outpatient department with bowel obstruction were included in this study. At least one of the following clinical symptoms of bowel obstruction had to be present: abdominal pain, rumbling sounds (borborygmi), or obstructive defecation (irregular, changed frequency, changed consistency) (3). In addition, obstruction had to be confirmed by a CT or MRI scan showing a stenotic tumour or bowel segment, with or without dilated bowel proximal from the stenotic segment or colonoscopy with a stenotic process that the endoscope could not pass. Ability to provide written informed consent was also an inclusion criterion.

Patients with a stenosis based on a malignant or benign cause were included (e.g., tumour, recurring diverticulitis, Crohn's disease). Patients presenting with a bowel obstruction with signs of near blow out (caecum > 9cm), sepsis, or perforation, thus requiring immediate surgery, were excluded.

## Obstruction treatment

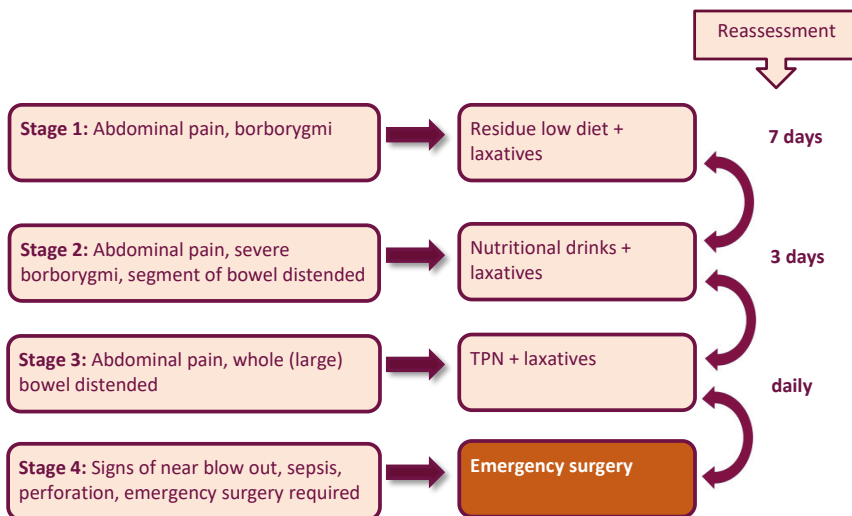
According to the symptoms and radiological findings, four stages of obstruction were recognized:

- Stage 1: abdominal pain and borborygmi, no bowel distension.
- Stage 2: abdominal pain and severe borborygmi, distention of a segment of the bowel.
- Stage 3: abdominal pain, distention of the whole or large part of the bowel.
- Stage 4: signs of near blow out, sepsis, or perforation. For patients in this stage, emergency surgery should be considered.

The treatment was intended for patients in stages 1, 2, and 3 and consisted of laxatives, daily physical training and lifestyle changes for all the patients. Specific dietary adjustments were made according to the stage:

- Stage 1: residue low diet (no large fibres, seeds, and peels) depending on the required caloric intake as determined by the dietitian.
- Stage 2: complete diet of nutritional drinks (orally or through a nasogastric tube).
- Stage 3: total parenteral nutrition (TPN) and oral intake of clear fluids.

The surgeon determined which stage of obstruction was present in the patient based on the complaints and CT-scan showing the extent of bowel dilatation.



**Figure 1.** Obstruction protocol flowchart

For patients in stages 1 and 2, the operation was postponed for three weeks to allow prehabilitation (figure 1). Patients in stage 3, who required TPN, were hospitalized and stayed hospitalized until the operation 7-10 days later. This was based on current surgical guidelines, which recommend a minimum of seven days of nutritional support prior to surgery (20).

Patients in stage 2 could drink the nutritional drinks at home. In the rare case that patients were unable to drink the nutritional drinks orally, they were hospitalized and received a nasogastric tube. If enteral feeding through the tube developed well, patients were allowed to go on home leave in expectation of the operation.

All patients received oral laxatives to improve stool passage and prevent complete obstruction with either Macrogol powder and Magnesiumhydroxide tablets. Prehabilitation and lifestyle changes consisted of instructions to exercise daily, smoking cessation, and reduced alcohol consumption to less than two units per day before the operation. Patients were instructed to exercise twice a day for at least 30 minutes. Exercises consisted of walking, cycling, and training on the home trainer. Patients were also instructed to climb stairs as much as possible. Hospitalized patients had a home trainer next to their bed, and the physiotherapist stimulated daily exercise.

Stage 1 and 2 patients were seen at the outpatient department and were contacted at least once a week by the surgeon, physician assistant, or dietitian to evaluate obstruction complaints. If there was no relief of pain or distention of the abdomen, the obstruction stage was increased, and the patient was treated according to the higher stage. Of course, patients who reacted extremely well were treated according to a lower stage.

Stage 3 patients who were hospitalised to receive TPN because of ileus of large and small bowel were assessed twice daily. If they reacted exceptionally well to the obstruction treatment, they were treated according to a lower stage with drink feeding so that they could recover and prehabilitate at home. However, if the complaints persisted or worsened, the surgeon was consulted to assess whether emergency surgery was necessary.

Current surgical guidelines recommend a minimum of seven days of preoperative nutritional support if malnutrition is present (20). However, we chose to extend this period of treatment to 3 weeks to improve nutritional status further and provide sufficient time for physical prehabilitation. This was based on several RCTs that examined nutritional and physical prehabilitation and showed an optimal effect after three weeks of training (13,15–18).

## Definition of outcomes

Successful obstruction treatment was defined as elective surgery after prehabilitation, and unsuccessful obstruction treatment was defined as emergency surgery.

## Data analysis

Normally distributed continuous data were presented as means  $\pm$  standard deviation (SD), non-normally distributed continuous data as medians with interquartile range, and dichotomous data as numbers with percentages. Mann-Whitney U test was used to compare the duration of treatment between patients with malign and benign bowel obstruction. Paired samples T-test was used to compare BMI at the start of treatment with BMI at the time of surgery. A one-sided proportion binomial test was used to compare mortality, bowel perforation, anastomotic leakage, and serious postoperative complications with rates from literature.

## RESULTS

A total of 101 bowel obstruction patients in two hospitals were evaluated for inclusion. After excluding patients who met the exclusion criteria (signs of near blow out, sepsis or perforation), 89 patients who underwent obstruction treatment were included. During the clinical presentation, the most frequently observed symptoms were obstructive defecation, abdominal pain, and weight loss (table 1). Fifty-three out of 89 patients (60%) had a MUST score of one or higher, corresponding with medium to high risk of malnourishment (21). In 21 out of 89 patients (24%), the small bowel was also dilated. This is due to an incompetent valve of Bauhin, causing dilatation of the small bowel in case of colonic obstruction. This reduces the risk of dilatation and perforation of the caecum.

The median duration of obstruction treatment was 20 days (IQR 12-29). There was no significant difference ( $p = 0.481$ ) in the duration of treatment between patients with malignant disease (median 21 days, IQR 13-30) and benign disease (median 20 days, IQR 6-27). Mean BMI at time of presentation was 25.9 (SD 5.1), there was no significant difference in BMI after prehabilitation (mean increase of 0.12, 95% CI: -0.10-0.34,  $p$ -value 0.291). Stages of disease and the corresponding treatment can be seen in table 2.

Fifty-five out of 89 patients (62%) remained in the stage that they were initially assigned to. Downstaging occurred in six out of 89 patients (7%) who, after starting the treatment, had markedly improved obstruction symptoms and tolerated a lower stage of treatment. This benefited the duration of prehabilitation. Upstaging occurred in 28 out of 89 patients (31%) due to persisting or worsening obstruction symptoms. Downstaging and upstaging occurred in all stages.

**Table 1.** Baseline table

	<b>n = 89</b>
<b>Age in years</b>	69 (IQR 58-79)
<b>Male</b>	48 (54)
<b>Disease origin</b>	
Malignant	67 (75)
Colon	61 (67)
Rectum	6 (7)
Benign	22 (25)
Crohn's disease	7 (8)
Chronic diverticulitis	15 (17)
<b>ASA classification</b>	
1	5 (6)
2	41 (46)
3	40 (45)
4	3 (3)
<b>BMI</b>	24.7 ( $\pm$ SD 5.2)
<b>Symptoms</b>	
Abdominal pain	63 (71)
Nausea	36 (40)
Vomiting	34 (38)
Obstructive defecation	72 (81)
Weight loss	66 (74)
<b>Prestenotic dilatation of colon</b>	42 (47)
<b>Prestenotic dilatation of small bowel</b>	21 (24)
<b>Weight loss in last 3 months</b>	
No weight loss	23 (26)
0-5 %	34 (38)
5-10 %	25 (28)
>10 %	7 (8)
<b>MUST-score at presentation</b>	
0	36 (40)
1	26 (29)
2	18 (20)
3	5 (6)
$\geq 4$	4 (4)
<b>Pre-operative hemoglobine (mmol/L)</b>	7.6 ( $\pm$ SD 1.2)

*All variables are as number (%), SD = standard deviation, IQR = interquartile range*



**Table 2.** Stages of disease

Type of nutrition	n = 89
Stage 1: Residue low diet	35 (39)
Stage 2: Complete diet of nutritional drinks	30 (34)
Orally (home setting)	28 (31)
Through nasogastric tube	2 (2)
Stage 3: Total parenteral nutrition (TPN)	24 (27)

*All variables are as number (%)*

*Upstaging and downstaging occurred during treatment, table shows the highest stage that patients were treated in. Patients had no other nutritional intake besides the residue low diet, nutritional drink or TPN.*

**Table 3.** Surgical treatment

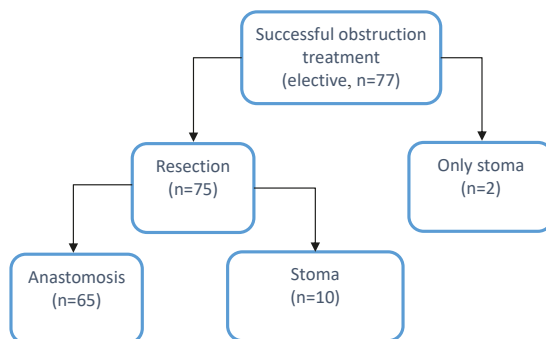
	Total (n = 89)	Successful obstruction treatment (elective, n=77)	Unsuccessful obstruction treatment (emergency, n=12)
<b>Type of surgery</b>			
Robotic	29 (33)	29 (38)	0 (0)
Laparoscopic	47 (53)	39 (51)	8 (67)
Open	13 (15)	9 (12)	4 (33)
<b>Conversion during laparoscopy<sup>a</sup></b>	6/76 (8)	4/68 (6)	2/8 (25)
<b>Procedure</b>			
Right hemicolectomy	27 (30%)	24 (31)	3 (25)
Transversectomy	1 (1)	1 (1)	0 (0)
Left hemicolectomy	12 (13)	12 (16)	0 (0)
Sigmoid resection	16 (18)	16 (21)	0 (0)
Low anterior resection	16 (18)	16 (21)	0 (0)
Abdominoperineal resection	2 (2)	2 (3)	0 (0)
Subtotal colectomy	1 (1)	0 (0)	1 (8)
Ileocecal resection	4 (4)	4 (5)	0 (0)
Hartmann	1 (1)	0 (0)	1 (8)
Diverting stoma	7 (8)	0 (0)	7 (58)
<b>Anastomosis</b>	65 (73)	65 (84)	0 (0)

*All variables are as number (%)*

*<sup>a</sup>Total of laparoscopic procedures for each cohort is shown*

## Elective surgical treatment

Obstruction treatment was successful in 77 out of 89 patients (87%) who reacted well to the treatment and could be prehabilitated and planned for elective surgery after three weeks of initial presentation (table 3). Elective laparoscopic or robotic surgery was performed in 68 out of 89 patients (76%). Conversion to open surgery took place in four out of 68 elective minimally invasive procedures (6%) due to locally advanced malignant disease.

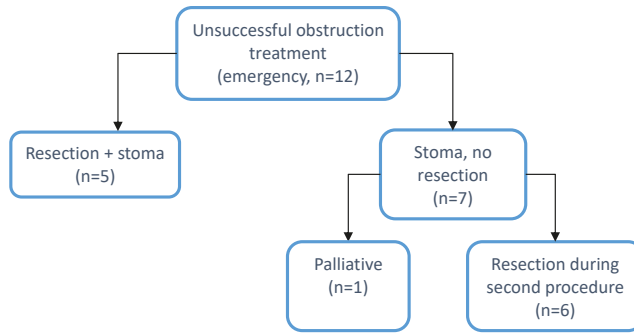


**Figure 2.** Successful obstruction treatment flowchart

In 75 out of 77 elective patients (97%), a resection of the primary tumor was performed (figure 2). In two out of 77 patients (3%), a palliative colostomy was constructed due to metastasized disease. A primary anastomosis was constructed in 65 out of 75 elective patients (87%). The remaining ten patients did not receive an anastomosis because two patients underwent an abdominoperineal resection, and in the eight other patients, the risk of anastomotic leakage was considered too high. In these eight patients, either an ileostomy or colostomy was constructed after resection of the primary tumor. The reasons that the risk of anastomotic leakage was considered too high were: extensive comorbidity (n=4), locally advanced disease (n=1), bowel distension (n=2), low rectal tumor in an elderly patient (n=1).

## Emergency surgical treatment

Obstruction treatment was unsuccessful in 12 out of 89 patients (13%) who underwent emergency surgery due to persisting or worsening bowel obstruction symptoms (table 3). Eight out of 89 patients (9%) underwent emergency laparoscopic surgery (of which two were converted to open surgery due to bowel distension). Only four out of 89 patients (4%) underwent open emergency surgery. Of these 12 emergency surgery patients, six patients had stage two obstruction, and the other six patients had stage three obstruction.



**Figure 3.** Unsuccessful obstruction treatment flowchart

Seven out of 12 emergency patients received a diverting colostomy during their emergency procedure (figure 3). As a result, the complaints decreased sufficiently to prehabilitate these patients for three weeks and perform an elective laparoscopic or robotic procedure afterward to remove the tumor (i.e., sigmoid resection, subtotal colectomy, right hemicolectomy, and low anterior resection). One out of these seven patients was in a palliative setting and did not undergo a second procedure. In five out of 12 emergency patients, a colostomy combined with a resection (i.e., three right hemicolectomies, a subtotal colectomy, and a Hartmann procedure) was performed without a second procedure. Of these five patients, two had their stoma removed in a later stadium. The stoma was not removed in the remaining three patients due to the palliative setting (n=1) and extensive comorbidity combined with old age (n=2). On closer examination in the emergency group, it turned out that these patients had no stool passage for five days or more before they presented themselves in the hospital.

## Surgical outcomes

Postoperative outcomes can be seen in table 4. We observed 30-day mortality and bowel perforation rates of 0%. Twenty-six out of 89 patients (29%) experienced complications. Of these 26 patients, only seven patients (8%) experienced a severe complication (Clavien-Dindo  $\geq 3$ ). These complications were: anastomotic leakage (n=2), abscess (n=3), bleeding (n=1) and fascia dehiscence (n=1). Of the patients with severe complications, three underwent emergency surgery.

Even though the patients in our study had bowel obstruction and therefore were at increased risk of emergency surgery, the obstruction treatment helped achieve outcomes better than or comparable to elective surgery. Observed 30-day mortality was 0% versus the national average of all colorectal cancer patients who underwent surgery in the Netherlands of 4%, this was a significant difference ( $p = 0.049$ ) (7). Bowel perforation in our study compared to the national

average for colorectal cancer patients was 0% versus 3% ( $p = 0.114$ ). This means that our high-risk patients had no significantly higher risk of bowel perforation than the general population. Anastomotic leakage in our study was 3% compared to the national average of 8% ( $p = 0.723$ ) and severe postoperative complications (Clavien-Dindo  $\geq 3$ ) was 8% versus 8% ( $p = 1.000$ ). When comparing to studies with benign causes of obstruction, the mortality rate in our study was 0% versus 4% ( $p = 0.049$ ), and the severe postoperative complication rate (Clavien-Dindo  $\geq 3$ ) was 8% versus 7% ( $p = 0.686$ ) (22–25).

**Table 4.** Postoperative outcomes

	Total (n=89)	Successful obstruction treatment (elective, n=77)	Unsuccessful obstruction treatment (emergency, n=12)
<b>30-day mortality</b>	0 (0)	0 (0)	0 (0)
<b>All 30-day complications</b>	27 (30)	24 (31)	3 (25)
<b>Clavien-Dindo classification</b>			
Grade I	9 (10)	9 (12)	0 (0)
Grade II	10 (11)	10 (13)	0 (0)
Grade $\geq$ III	7 (8)	4 (5)	3 (25)
<b>Bowel perforation</b>	0 (0)	0 (0)	0 (0)
<b>Anastomotic leakage</b>	2/65 (3)	2/65 (3)	0/0 (0)
<b>Postoperative hospital stay in days</b>	5 (IQR 4-7)	5 (IQR 4-7)	6.5 (IQR 5.3-7.8)

*SD = standard deviation, IQR = interquartile range*

*All variables are as number (%)*

*<sup>a</sup>Total of anastomoses for each cohort is shown*

Comparing our outcomes to outcomes after surgery in the general colorectal cancer population shows that the obstruction treatment improved outcomes. We see the same improved outcomes when comparing to outcomes after elective surgery for benign causes of obstruction. A comparison of outcomes after emergency surgery was not possible because the available studies in the literature included all emergency surgery patients (e.g., bowel perforation, sepsis, bleeding) and not only emergency surgery due to bowel obstruction. So in effect, we can say that a patient with a high risk of emergency surgery has become an elective patient after obstruction treatment.

## DISCUSSION

This multicenter observational study examined the effect of a novel multimodal obstruction treatment in patients with bowel obstruction. The treatment aimed to reduce bowel wall distension to avoid emergency surgery and postpone the operation providing time for prehabilitation.

In the past, bowel obstruction patients often underwent open emergency surgery. The obstruction treatment allowed surgeons to perform elective and minimally invasive surgery in the majority of patients. Furthermore, mortality in our study was significantly lower than what is reported in the literature (7). Other postoperative outcomes in our cohort of high-risk patients were comparable to elective patients (22–26).

In the Netherlands, bowel obstruction patients have a high risk of open emergency surgery (7). In the current study, we observed that many patients underwent elective laparoscopic or robotic surgery by using the obstruction treatment, and only 13% of patients underwent emergency surgery (12 out of 89). Stage 3 patients (bowel distension throughout the whole large bowel and receiving TPN) had the highest risk of emergency surgery. Nonetheless, of the 24 patients in stage 3, only six patients (25%) underwent emergency surgery. Another beneficial effect of preventing emergency surgery was that most patients underwent elective laparoscopic or robotic surgery by an experienced colorectal surgeon (68 patients out of 89, 75%) with the low intra-operative conversion rate of 6% compared to the national average of 14% in colorectal cancer surgery (27).

In our cohort of patients, who are specifically at risk of emergency surgery, the 30-day mortality was 0%. This is a statistically significant difference ( $p = 0.049$ ) compared to the extensive study by Bakker et al., which reported a 30-day mortality of 4% in the general colorectal cancer population in the Netherlands (7). The observed mortality in our study cohort is also lower than 30-day mortality rates ranging from 2% to 4% reported by several studies assessing surgery for benign causes of bowel obstruction (22–24). Severe postoperative complications in our study cohort occurred in 8% of patients. This is comparable or lower than the severe complication rates of 8% and 15% in colorectal cancer patients reported by Bakker et al. and Ketelaer et al., respectively (7,26). The 8% severe complication rate in our study was comparable to the 7% severe complication rate reported by Goyer et al., who reported surgical outcomes after surgery for benign causes of bowel obstruction (25).

The surgical treatment of bowel obstruction is mainly focused on the obstruction rather than on the patient's nutritional or physical condition. However, it is essential to realize that bowel obstruction patients are vulnerable and have poor nutritional and physical conditions due to

abdominal pain, malabsorption, and vomiting. In our study cohort, 60% of patients had a MUST score of 1 or higher, indicating malnutrition. This is a high malnutrition rate compared to the 28% malnutrition rate in the general colorectal cancer population, as reported by Hu et al., who included more than 42,000 colorectal cancer patients (9). Another factor illustrating the vulnerability of our study cohort is that 48% of the patients were classified as ASA  $\geq 3$ , compared to the 25% ASA  $\geq 3$  reported by Bakker et al. for colorectal cancer patients (7). This makes it even more remarkable that we observed such good results in such a vulnerable group. Increased awareness among surgeons regarding the vulnerability of bowel obstruction patients is desirable.

In our study cohort, the weight loss was successfully stopped during treatment, even though these patients had a chronic deficit in caloric intake and weight loss prior to presentation at the hospital.

BMI after a median obstruction treatment duration of 20 days (IQR 12-29) even showed a mean increase of 0.12 BMI points; however, this was not statistically significant ( $p=0.291$ ).

The obstruction treatment seems to be a safe and efficient alternative to emergency surgery and other approaches such as the stent as bridge to surgery. Even though the patients in our study had a high risk of emergency surgery, the obstruction treatment helped to achieve outcomes better than or comparable to elective surgery. It is possible to postpone surgery and prehabilitate for three weeks to achieve these results. Although the operation was postponed, there appears to be no increased risk for the patient. The obstruction treatment is non-invasive and has a low burden on the patients. Furthermore, it is easy to apply and involves low costs. In a time of rising healthcare costs, the obstruction treatment seems a promising way forward in improving the quality of care and preventing costly complications.

This study has several strengths; firstly, the obstruction treatment was implemented in two hospitals, which increases the generalizability of our results. Secondly, we provided tailor-made exercise instructions that the patients could easily perform at home or even during admission to the hospital. Studies have shown that home-based interventions (28) with moderate-intensity exercise may be the optimal approach in terms of effectivity and patient adherence in the elderly patients (29,30). Several limitations also exist. Data regarding adherence by patients to the obstruction treatment was not collected in this study. Furthermore, since the obstruction treatment was a multimodal, the individual effect of the physical exercise or the nutritional interventions cannot be evaluated.

## **CONCLUSION**

The obstruction protocol reduced emergency surgery and postoperative morbidity and mortality in patients with bowel obstruction. The protocol seems to be a safe and efficient alternative to emergency surgery.

## **ACKNOWLEDGEMENTS**

Study data, analytical methods, and study materials are available to other researchers on request. Preregistration of the study did not take place.

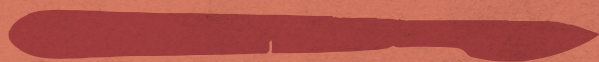
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## PART II



*Improving intraoperative  
surgical care*







**07**

# The effect of intraoperative hypothermia on postoperative morbidity in colorectal cancer patients



Milad Fahim, Lea M. Dijkman, Douwe H. Biesma, Peter G. Noordzij, Anke B. Smits

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## **ABSTRACT**

### **Background**

Current guidelines recommend maintaining intraoperative normothermia to avoid surgical site infections (SSI) after colorectal cancer surgery. The aim of this study was to assess whether compliance to normothermia as part of temperature management measures is an effective strategy to reduce postoperative SSI and complications.

### **Methods**

This was a cohort study of patients undergoing surgery for primary colorectal cancer in 2011-2017 in a large teaching hospital where temperature management using the Bair Hugger system was standard care. Data from the prospective Dutch Surgical Audit (DCRA) database was complemented by highly granular intraoperative central body temperature data. A multivariable logistic regression model was used.

### **Results**

A total of 1015 patients undergoing surgery for primary colorectal cancer were included. Temperature outcomes for the entire study cohort: mean temperature was 36.30 C (SD  $\pm 0.50$  C), median temperature nadir was 35.80 C (IQR 35.60 C - 36.10 C), median percentage of time at nadir was 2.0% (IQR 0.8%-10.7%) and median percentage of time  $< 36.00$  C was 1.0% (IQR 0.0%-33.3%). Thirty-day SSI rate was 10% (n=101). Logistic regression models adjusting for sex, Diabetes Mellitus, BMI, rectal cancer, duration of surgery, open surgery, emergency surgery and period of surgery showed no association between any of the four temperature outcomes and SSI. Multivariable analysis also failed to show an association between intraoperative hypothermia and 30-day complications, mortality or readmission.

### **Conclusion**

In a hospital where temperature management is standard care, intraoperative hypothermia and SSI rates in patients undergoing colorectal cancer surgery were low. Compliance to normothermia seems an effective strategy to reduce SSI.

## INTRODUCTION

In 2009, the World Health Organization published the Guidelines for Safe Surgery (1). One of several recommendations in these guidelines was the maintenance of normothermia during surgery aimed at reducing the incidence of postoperative surgical site infections (SSI). The WHO did not provide a clear definition of normothermia. The American Agency for Healthcare Research and Quality (AHRQ) has a similar recommendation of maintaining intraoperative normothermia to prevent SSI (2). The AHRQ defined normothermia as a temperature above 36°C, measured just before time of incision, before leaving the operating room and upon arrival at the recovery unit. Three randomized controlled trials were at the basis of these recommendations and showed increased incidence of SSIs, mortality and extended hospital stay after hypothermia (3–5). These RCTs were conducted in general and colorectal surgery populations.

Other studies have demonstrated that intraoperative hypothermia is associated with hypertension due to vasoconstriction (6), increased risk of blood transfusions (7,8) and longer duration of neuromuscular blockade due to medication (9). Hypothermia also contributes to the experience of discomfort of the patient. In order for patients to return to postoperative normothermia, an increased metabolism is required with an increased oxygen use. In addition, there is perioperative risk of arrhythmias, acidosis and coagulopathy (10). This has led to a variety of methods to reduce hypothermia (11).

Many hospitals have implemented temperature management measures such as warmed intravenous fluids and forced-air warming devices. However, several studies conducted in hospitals that already have implemented temperature management measures, have reported high rates of intraoperative hypothermia in orthopedic, gynecologic and colorectal surgery (12–15).

Core body temperature can vary greatly during the procedure and therefore it is important to continuously measure this variable. However, most of the previously mentioned studies have used nadir temperature, maximum temperature, temperature at the end of the procedure or postoperative temperature (12–14). This approach does not encapsulate the true nature of the continuous physiological core body temperature variable.

Postoperative complications are common in patients undergoing colorectal cancer (CRC) surgery (16). As resources are increasingly limited in healthcare, it is important to assess whether current temperature management measures are sufficient in preventing hypothermia

and related adverse postoperative outcomes. The current study aimed to assess whether compliance to normothermia as part of temperature management measures is an effective strategy to reduce SSI.

## **MATERIALS AND METHODS**

### **Study design and data collection**

This retrospective cohort study was conducted in a large teaching hospital where temperature management using the Bair Hugger system was standard care. Intraoperative core body temperature data was obtained from an anesthesia information management system (AIMS) used during surgery and postoperative stay on the recovery unit. Intraoperative core body temperature was measured continuously using a nasal temperature probe located in the nasopharynx at 1-minute intervals. A panel of a staff anesthesiologist and surgeon visually inspected all temperature graphs. Temperature values below 300 C, greater than 430 C or sudden fluctuations in temperature which could not be attributed to natural physiology were considered registration errors (i.e. temporary dislocation of the nasal probe outside the nasal cavity) and were removed from the dataset. Cases with incomplete AIMS temperature data (less than 100 temperature measurements) were also excluded. These cases were considered missing completely at random and therefore could be excluded without affecting the results of this study. The missing completely at random assumption was based on the fact that it was standard procedure to measure the temperature of every patient and failure to do so was caused entirely due to complete or partial dislocation of the nasal probe or other technical difficulties. These events would occur randomly. During transit to theater and during stay on the recovery unit, conventional ear thermometer was used; these temperatures were not included in the study, as they do not reflect core body temperature.

Preoperative antibiotics prophylaxis by administering a single dose of intravenous Metronidazol and Cefazoline 60 to 15 min prior to incision was standard care in our hospital. Compliance for antibiotic prophylaxis was assessed using AIMS data. The surgeons in our institution had a standardized procedure in regards to preoperative bowel preparation, preoperative skin preparation and anastomosis creation. Furthermore, they routinely inspect mesenteric vascularization by cutting the mesentery. They also routinely close the skin incision primarily.

Temperature management in our hospital consisted of the Bair hugger system (produced by 3M), which actively warms the patient using forced-air warming. The Bair hugger was used at the holding (full body) and during surgery (upper body). The Bair hugger did not warm at a fixed temperature, rather the temperature at which warming was performed was variable.



The most common target temperature was 36 °C, but this was raised up to 40 °C based on the patients observed core body temperature. Fluid warmers were not used perioperatively. Preheated blankets are used to keep the lower extremities warm during surgery.

The Dutch Colorectal Audit (DCRA) is a nationwide surgical registry (17). From the DCRA the following data was acquired: patient, tumor, treatment and 30-day postoperative outcome data. In our analysis we considered cases in which a laparoscopic procedure was converted to an open procedure as open procedures.

## **Patient population**

We evaluated all consecutive patients who underwent curative surgery for primary CRC in the period May 2011-January 2017. This period was chosen because a new AIMS was implemented in 2017. Patients who received hyperthermic intraperitoneal chemotherapy (HIPEC) treatment were excluded because the warmed fluid used during the procedure influences central body temperature. We also excluded patients for who no AIMS temperature data was available or who had fever (temperature  $\geq 38.50$  C) at the start of the operation.

## **Definitions of outcomes**

Primary outcome was the occurrence of SSI within 30-days of the operation. The SSI definition of the European Centre for Disease Prevention and Control (ECDC) was used which recognizes superficial, deep incision and organ space SSIs (18). Assessment of SSIs took place during daily ward rounds while the patient was still hospitalized and during a check-up appointment at the outpatient clinic two or three weeks after discharge. The assessment was conducted by a surgical resident or a colorectal surgeon. Secondary outcomes for this study were the occurrences of overall complications, serious complications (Clavien-Dindo  $\geq 3$ ) and cardiac complications and mortality within 30-days of the operation and readmission within 30 days of discharge as defined by the DCRA (17). A weighted composite endpoint consisting of 30-day readmission (weight 1), 30-day serious complications (weight 2) and 30-day mortality (weight 3) was also used.

## **Definitions of exposure variables**

To adequately capture periods of intraoperative hypothermia, we used several definitions of hypothermia as exposure variables. Based on expert opinion of the panel of staff anesthesiologist and surgeon and a review of the published literature on the subject of intraoperative hypothermia (12–15,19), we selected the following definitions of potential hypothermia: mean intraoperative temperature, temperature nadir (minimum measured temperature), percentage of time spent at temperature nadir and percentage of time spent at a temperature of  $< 36.00$  C.

## Data analysis

Dichotomous data were presented as number and percentage and analyzed using the chi-squared test. Continuous data were presented as medians with interquartile range and analyzed using the Mann-Whitney U test or as means with standard deviation and analyzed with the independent samples T-test. Incomplete variables from the DCRA database were supplemented by the primary researcher (MF) using pathology and operation reports. Data that remained missing after supplementation by the primary researchers was not at random and therefore case-wise exclusion took place. Multivariable logistic regression analysis was used to analyze the effect of mean intraoperative temperature on postoperative adverse events, while adjusting for potential confounding factors. These factors were: sex, Diabetes Mellitus, body mass index (BMI), rectal cancer, duration of surgery, open surgery, emergency surgery and period of surgery (2011-2013 vs 2014-2017) to account for possible changes in perioperative care over the years. Factors were chosen based on known risk factors from literature (20,21) and baseline differences observed in our study cohort. Ordinal logistic regression was used to analyze the effect of mean intraoperative temperature on the weighted composite endpoint. Cardiac complication as an adverse postoperative event was specifically included as this outcome is associated with hypothermia. All p-values reported are two sided. A p-value of  $<0.05$  was considered significant. Statistical analysis was performed using SPSS v.24.0 (IBM, Armonk, NY, USA).

## RESULTS

A total of 1270 CRC patients underwent surgery during the study period, and were evaluated for inclusion. After exclusion of 43 patients who underwent HIPEC treatment, 69 patients for whom no data was available and 143 patients who had less than 100 temperature measurements, the final study cohort consisted of 1015 patients. Mean age was 68 years (SD 10.2), 59% (601 out of 1015) was male, median duration of surgery was 159 minutes (IQR 133-198), open surgery was performed in 24% (246 out of 1015) of patients and emergency surgery was performed in 7% (66 out of 1015) of patients. Other baseline characteristics can be found in Table 1.

**Table 1.** Baseline table of 1015 patients

	All (n=1015)	SSI (n=101)	No SSI (n=914)	p-value
<b>Male</b>	601 (59)	71 (70)	530 (58)	0.019
<b>Age, mean (SD), year</b>	68.2 (10.2)	68.0 (9.8)	68.2 (10.3)	0.88 <sup>a</sup>
<b>American society of Anesthesiology (ASA) classification</b>				0.24
ASA I	173 (17)	11 (11)	162 (18)	
ASA II	626 (61)	68 (67)	558 (61)	
ASA III	203 (20)	20 (20)	183 (20)	
ASA IV	13 (1)	2 (2)	11 (1)	
<b>Body Mass Index, mean (SD)</b>	26.6 (4.4)	26.4 (4.2)	26.6 (4.4)	0.66 <sup>a</sup>
<b>Diabetes Mellitus</b>	154 (15)	22 (22)	132 (14)	0.057
<b>Primary tumor location</b>				0.003
Colon cancer	685 (67)	55 (54)	630 (69)	
Rectal cancer	330 (32)	46 (46)	284 (31)	
<b>TNM stage</b>				0.29
Stage I	256 (25)	20 (20)	236 (26)	
Stage II	267 (26)	25 (25)	242 (27)	
Stage III	396 (39)	48 (48)	348 (38)	
Stage IV	96 (10)	8 (8)	88 (10)	
<b>Single dose prophylactic antibiotics, 60 to 15 min prior to incision</b>	945 (93)	94 (94)	850 (93)	0.76
<b>Duration of surgery, median (IQR), min</b>	159 (133-198)	180 (146-220)	157 (132-197)	<0.001 <sup>b</sup>
<b>procedure</b>				-
Hemicolectomy right	276 (27)	14 (14)	262 (29)	
Transverse colon resection	9 (1)	2 (2)	7 (1)	
Hemicolectomy left	69 (7)	12 (12)	57 (6)	
Low anterior resection/sigmoid resection	448 (44)	43 (43)	405 (44)	
Abdominoperineal resection	176 (17)	27 (27)	149 (16)	
Subtotal colectomy	21 (2)	2 (2)	19 (2)	
Other	16 (1)	1 (1)	15 (1)	
<b>Emergency surgery</b>	66 (7)	9 (9)	57 (6)	0.29
<b>Open surgery</b>	246 (24)	52 (52)	264 (29)	<0.001
<b>conversion</b>	71 (7)	10 (10)	61 (7)	0.23
<b>Intraoperative blood transfusion</b>	41 (4)	3 (3)	38 (4)	0.42
<b>Time period of operation</b>				0.012
2011-2013	376 (37)	49 (49)	327 (36)	
2014-2016	639 (63)	52 (51)	587 (64)	

Values are presented in frequencies (percentage) unless stated otherwise. All p-values are calculated using the Chi square test, unless stated otherwise. <sup>a</sup> Independent samples t-test. <sup>b</sup> Mann-Whitney U test.

Overall 30-day SSI occurred in 10% of patients (101 out of 1015), superficial SSIs in 4% (41 out of 1015), deep incisional SSIs also in 4% (41 out of 1015) and organ space SSIs in 2% (19 out of 1015). Thirty day complications rate was 26% (266 out of 1015), serious complications (Clavien-Dindo 3-4) occurred in 11% of patients (114 out of 1015) and 30-day mortality was 1% (10 out of 1015). Intraoperative blood transfusion was rare and occurred in only 4% (44 out of 1015) of patients. A single dose of prophylactic antibiotics prior to surgery was standard care, however compliance in our study cohort was not 100% due to registration errors by physicians.

**Table 2.** Intraoperative temperature outcomes in SSI and non-SSI group

	SSI (n=101)	No SSI (n=914)	p-value
<b>Temperature mean (SD), 0 C</b>	36.3 (0.4)	36.3 (0.5)	0.99 <sup>a</sup>
<b>Temperature nadir, 0 C</b>	35.8 (35.5-36.2)	35.9 (35.6-36.1)	0.77
<b>Time at nadir, percentage</b>	2.0 (0.8-10.6)	2.0 (0.8-10.7)	0.35
<b>Time &lt;36.00 C, percentage</b>	1.7 (0.0-50.7)	1.0 (0.0-31.6)	0.41
<b>Absolute minutes under threshold temperature</b>			
37.5	160 (119-199)	136 (110-169)	<0.001
37.0	143 (106-190)	125 (97-157)	<0.001
36.5	98 (23-161)	88 (20-132)	0.10
36.0	2 (0-84)	1 (0-46)	0.15
35.5	0 (0-0)	0 (0-0)	0.40
35.0	0 (0-0)	0 (0-0)	0.36
<b>Percentage of time under threshold temperature</b>			
37.5	100.0 (100.0-100.0)	100.0 (100.0-100.0)	0.60
37.0	100.0 (83.8-100.0)	100.0 (97.8-100.0)	0.19
36.5	60.8 (15.3-100.0)	73.0 (16.0-100.0)	0.58
36.0	1.7 (0.0-50.7)	1.0 (0.0-31.6)	0.41
35.5	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.44
35.0	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.36

Values are presented in median (IQR) and p-values are calculated using the Mann-Whitney U test, unless stated otherwise.

<sup>a</sup> Independent samples t-test

Temperature outcomes for the entire study cohort were as follows: temperature mean was 36.30 C (SD 0.50 C), median temperature nadir was 35.80 C (IQR 35.60 C - 36.10 C), median percentage of time at nadir was 2.0% (IQR 0.8%-10.7%) and median percentage of time <36.00 C was 1.0% (IQR 0.0%-33.3%). Significant associations between SSI and the

following factors were found: male gender ( $p=0.019$ ), increased duration of surgery ( $p<0.001$ ), open surgery ( $p<0.001$ ) and rectal cancer ( $p=0.003$ ). We also conducted univariable analyses to examine if associations between the four intraoperative temperature variables and SSI could be found (Table 2.). None of the four variables (i.e. temperature mean, temperature nadir, percentage of time at nadir and percentage of time  $<36.00$  C) had a significant association with SSI.

When assessing the absolute and relative time that patients spent under different threshold temperatures the most notable finding is the strong significant association ( $p<0.001$ ) between SSI and the absolute number of minutes below the highest two temperature thresholds. This high cut-off value is correlated with the total procedure time, with SSI patients having a median duration of surgery of 180 minutes versus 157 minutes in non-SSI patients. In the multivariable analysis we showed that increased duration of surgery is significantly associated with increased risk of SSI.

As summarized in Table 3, a multivariable model was constructed for each of the four intraoperative temperature variables (i.e. temperature mean, temperature nadir, percentage of time at nadir and percentage of time  $<36.00$  C) and their possible associations with SSI. Each model included the same covariables: sex, Diabetes Mellitus, BMI, rectal cancer, duration of surgery, open surgery, emergency surgery and period of surgery (2011-2013 vs 2014-2017). All four models showed no significant association between the temperature variable and SSIs. All four models did show a significant association between open surgery, duration of surgery and rectal cancer in relation to SSIs.

**Table 3.** Overview of four multivariable logistic regression models, each with a different temperature variable. The outcome variable is SSI.

Temperature variable in the model	Variable	OR (95% CI)	p-value
<b>Mean intraoperative temperature</b>	Mean intraoperative temperature	1.00 (0.62-1.62)	0.97
	Male	1.59 (0.99-2.56)	0.054
	Diabetes Mellitus	1.69 (0.98-2.93)	0.060
	BMI	0.97 (0.92-1.03)	0.34
	Rectal cancer	1.69 (1.06-2.68)	0.027
	Duration of surgery (10 min increase)	1.06 (1.01-1.10)	0.007
	Open surgery	2.65 (1.68-4.17)	<0.001
	Emergency surgery	1.26 (0.55-2.87)	0.59
	Period of surgery (2011-2013 vs 2014-2017)	0.65 (0.42-1.01)	0.054
<b>Temperature nadir</b>	Temperature nadir	1.11 (0.68-1.82)	0.68
	Male	1.58 (0.99-2.53)	0.056
	Diabetes Mellitus	1.70 (0.98-2.93)	0.059
	BMI	0.97 (0.92-1.03)	0.30
	Rectal cancer	1.69 (1.06-2.69)	0.026
	Duration of surgery (10 min increase)	1.06 (1.02-1.10)	<0.001
	Open surgery	2.66 (1.69-4.19)	<0.001
	Emergency surgery	1.24 (0.55-2.80)	0.61
	Period of surgery (2011-2013 vs 2014-2017)	0.64 (0.41-0.99)	0.046
<b>Percentage of time spent at nadir</b>	Percentage of time spent at nadir	0.99 (0.97-1.01)	0.26
	Male	1.58 (0.99-2.53)	0.056
	Diabetes Mellitus	1.64 (0.95-2.85)	0.077
	BMI	0.97 (0.92-1.03)	0.32
	Rectal cancer	1.63 (1.02-2.60)	0.039
	Duration of surgery (10 min increase)	1.05 (1.01-1.10)	0.009
	Open surgery	2.70 (1.71-4.26)	<0.001
	Emergency surgery	1.21 (0.53-2.74)	0.65
	Period of surgery (2011-2013 vs 2014-2017)	0.64 (0.42-1.00)	0.047
<b>Percentage of time &gt; 36° C</b>	Percentage of time > 36° C	1.00 (1.00-1.01)	0.54

**Table 3.** Overview of four multivariable logistic regression models, each with a different temperature variable. The outcome variable is SSI.

Temperature variable in the model	Variable	OR (95% CI)	p-value
	Male	1.63 (1.01-2.62)	0.044
	Diabetes Mellitus	1.71 (0.99-2.96)	0.055
	BMI	0.98 (0.93-1.03)	0.39
	Rectal cancer	1.69 (1.06-2.68)	0.027
	Duration of surgery (10 min increase)	1.06 (1.01-1.10)	0.007
	Open surgery	2.62 (1.66-4.13)	<0.001
	Emergency surgery	1.30 (0.57-2.95)	0.53
	Period of surgery (2011-2013 vs 2014-2017)	0.66 (0.43-1.03)	0.068

**Table 4.** Adjusted associations between mean intraoperative temperature (per degree Celsius) and several 30-day adverse postoperative outcomes as outcome variables.

Outcome variable	n (%)	Odds ratio (95% CI)	p-value
All complications	248 (24)	1.26 (0.88-1.82)	0.21
Serious complications (Clavien-Dindo $\geq 3$ )	114 (11)	1.41 (0.86-2.31)	0.18
Anastomotic leakage	31 (3)	1.29 (0.54-3.05)	0.57
Cardiac complications	28 (3)	1.26 (0.50-3.15)	0.63
Readmission	74 (7)	1.25 (0.71-2.12)	0.45
Mortality <sup>a</sup>	10 (1)	-	-
Weighted composite endpoint <sup>b</sup>	160 (16)	0.24 (-0.18-0.67) <sup>c</sup>	0.25

Multivariable logistic regression adjusted for gender, age, ASA classification, BMI, emergency surgery, open surgery and period of surgery (2011-2013 vs 2014-2017). <sup>a</sup> Insufficient number of events for multivariable analysis. <sup>b</sup> Composite endpoint consists of serious complications, readmission and 30-day mortality.

<sup>c</sup> Ordinal regression with estimate (95% CI)

Several multivariable analyses were performed to examine possible associations between mean intraoperative temperature and 30-day postoperative complications, serious complications, anastomotic leakages, cardiac complications, readmission, mortality and a composite endpoint consisting of serious complications, readmission and 30-day mortality (Table 4.). In these models, adjustment took place for known risk factors of these adverse postoperative outcomes. There was no significant association between mean intraoperative temperature and any of the adverse postoperative outcomes.

Increased length of stay was defined as more than 7 days and occurred in 32% (234 out of 1015) of patients. There was no significant difference in mean intraoperative temperature between those with increased length of stay and those without (Mann-Whitney U test,  $p=0.62$ ).

## DISCUSSION

This study examined whether compliance to normothermia as part of temperature management measures is an effective strategy to reduce SSI in patients who underwent surgery for colorectal cancer in a hospital where temperature management was standard care. Intraoperative hypothermia and, subsequently, SSI rates were low and could not be associated with each other. Even when using four different definitions of hypothermia, this study failed to show a significant association between intraoperative hypothermia and SSI. Compliance to normothermia seems an effective strategy to reduce SSI.

This study is in agreement with other recent studies which have also shown low intraoperative hypothermia rates in hospital that use temperature management measures (i.e. forced-air warming and intravenous fluid warming). Under these conditions of active temperature management, no association could be found between the low intraoperative hypothermia rates and SSI (14,15,19).

The findings of this study are in contrast to those of the three initial RCTs, which we discussed in the introduction of this article (3–5). The most obvious explanation for this discrepancy might be that those studies were conducted late 1990s and early 2000s. Since that time, organizations such as the WHO and the American Agency for Healthcare Research and Quality have formulated guidelines which recommend maintenance of normothermia to prevent SSIs (1,2). In addition, hospitals have invested money, time and energy in implementing temperature management systems during the perioperative period. In the original three RCTs, patients who were randomized to the control group received standard of care at that time and were much more hypothermic than patients who receive a very different standard of care today. For example, the introduction of active warming systems like the Bair hugger had not occurred yet, nowadays it is standard practice in many hospitals. Another example of the differences in patient care was the use of perioperative antibiotic prophylaxis during four days, nowadays the standard practice is 24 hours. The introduction of the ERAS protocol in the early 2000s has also contributed to reducing hypothermia.

SSIs of any kind occurred in 10% of patients in this study, this is in accordance with rates reported in the literature ranging from 7% to 18% (15,19,22,23).



The incidence of intraoperative hypothermia in our study was low. Median temperature nadir was 35.80 C, however median time spent at this nadir was very low (2.0% of operating time). Even when using a cut-off value of 36.00 C, only 1.0% of median operating time was spent at that temperature.

Mean intraoperative temperature was also not associated with other adverse outcomes such as 30-day postoperative complications, readmissions or mortality. However, due to the aforementioned low incidence of intraoperative hypothermia, no definitive conclusions can be drawn.

Our study has several strengths and limitations. The first strength of our study is that core temperature was measured continuously with one-minute intervals during the perioperative period. This allowed us to conduct more detailed analysis without loss of data. The second strength is that a staff anesthesiologist and surgeon visually inspected all individual temperature graphs to identify erroneous measurements. This is time intensive but also the most reliable method to clean the dataset. Limitations of this study include the inherent bias of a retrospective nonrandomized comparison. Furthermore, no data regarding smoking or immunosuppression, which are associated with wound healing, were available to us.

## **CONCLUSION**

In a hospital where temperature management is the standard of care, intraoperative hypothermia and SSI rates in patients undergoing colorectal cancer surgery were low. Compliance to normothermia seems an effective strategy to reduce SSI.

## **Author disclosure statement**

The authors declare no conflict of interest or funding.

## **Ethics approval**

Medical Ethics Committees United (MEC-U), located in Nieuwegein at the St. Antonius Hospital and consisting of a partnerships between 7 large regional hospitals in the Netherlands, and the local medical ethical committee of the hospital reviewed and approved this study. Informed consent was deemed unnecessary according to the Dutch Medical Treatment Agreement Act.

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08

# The impact of endoractor™ SPONGE-assisted laparoscopic/ robotic surgery on short term outcomes in patients with colorectal cancer (SPONGE trial): a randomized controlled trial



Milad Fahim, Alice Couwenberg, Lea M. Dijkman, Helena M. Verkooijen, Anke B. Smits

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## **ABSTRACT**

### **Background**

In minimally invasive surgery of the sigmoid colon and rectum a retractor sponge, that allows for surgery in a horizontal position, has been introduced as an alternative to the Trendelenburg position. This study compared postoperative length of stay and perioperative outcomes in patients with sigmoid or rectal cancer undergoing sponge-assisted versus Trendelenburg position surgery.

### **Methods**

The SPONGE trial is a single-center RCT, nested within the Dutch nationwide prospective observational cohort of colorectal cancer patients (PLCRC), following the Trials within Cohorts (TwICs) design. Sigmoid or rectal cancer patients undergoing elective laparoscopic or robotic surgery were randomized to either sponge-assisted or Trendelenburg surgery. Length of postoperative stay (in days) was the primary outcome and was compared using the Mann Whitney U test and the proportion of complications, readmission, or mortality with the Chi-square test in an intention to treat analysis and an as-treated analysis.

### **Results**

Between November 2015 and June 2021, 163 patients were randomized to either sponge-assisted (n=82) or Trendelenburg surgery (n=81). After post-randomization exclusion, 150 patients remained for analyses (75 patients per arm). There was no statistically significant difference in terms of median length of hospital stay (5 days vs. 4 days respectively,  $p=0.06$ ), 30-day postoperative complications (30% vs 31%,  $p=1.00$ ), readmissions (8% vs 15%,  $p=0.30$ ), or mortality (0% vs 1%,  $p=1.00$ ). The as-treated analysis showed similar results.

### **Conclusion**

Sponge-assisted surgery, as compared to Trendelenburg surgery, in the elective setting using the laparoscopic or robotic approach, does not lead to a shorter postoperative length of stay or reduced postoperative morbidity and mortality.



## INTRODUCTION

Laparoscopic colorectal cancer surgery has progressively replaced open surgery and led to better short-term outcomes (1,2). Nowadays, over 80% of colorectal cancer resections in the Netherlands are performed laparoscopically (3). In recent years robotic surgery is increasingly being used. The most commonly used technique to acquire a clear field of view during laparoscopic and robotic surgery in the pelvic area is the Trendelenburg position, in which the patient is positioned at an angle of 15 to 40 degrees with the head down, using the effect of gravity to displace the small intestine cranially (4). The Trendelenburg position increases intrathoracic and intracranial pressure, leading to an increased risk of hemodynamic instability (5–7). This can complicate anesthesia, decrease postoperative lung function and cause postoperative laryngeal edema and airway obstruction (8–10). These factors can increase the postoperative length of stay and the risk of postoperative complications.

An alternative to the Trendelenburg position is the retractor sponge, which can be used to displace the small intestine to create a clear field of view during laparoscopic surgery of the distal colon, while the patient is in a horizontal position. A previous nonrandomized pilot study from The Netherlands compared the retractor sponge to the Trendelenburg position and included 45 patients in each group (11). The study showed that sponge-assisted surgery was associated with a reduced postoperative hospital stay (5.4 days versus 7 days in the Trendelenburg position) and decreased cardiac complications. Furthermore, the sponge was tested for potential adverse effects such as cytotoxicity and intracutaneous reactivity, and no tissue trauma or organ damage due to the sponge has been reported so far (12).

Based on these promising observational results, the randomized controlled SPONGE trial was initiated. This SPONGE trial compares sponge-assisted versus Trendelenburg laparoscopic surgery in terms of duration of postoperative hospital stay (primary outcome) and perioperative outcomes (secondary outcomes) in patients with sigmoid or rectal cancer.

## Methods

This paper was reported following the CONSORT-ROUTINE statement (13). The SPONGE trial was a single-center randomized controlled trial (RCT), nested within the Dutch nationwide observational prospective cohort of colorectal cancer patients: Prospectief Landelijk ColoRectaal carcinoom Cohort (PLCRC) (14). The PLCRC cohort was initiated in 2012 and includes colorectal cancer patients of all stages in 59 hospitals. The cohort follows the “Trials within Cohort” (TwICs) design (15,16). The SPONGE trial was registered with ClinicalTrials.gov, number NCT02574013. The Sponge trial was conducted in one of the centers participating in PLCRC, i.e. a large non-academic teaching hospital in the Utrecht region.

## **Cohort informed consent procedure**

Patients were enrolled in PLCRC after a diagnosis of colorectal cancer, using the staged-informed consent procedure (17). In the first stage, at cohort enrolment, participants had the option to provide broad consent for randomization into future trials. Here, participants were informed that they could be randomized to an intervention arm and offered an experimental intervention. Also, they were informed that when they were allocated to a control arm, they would serve as a control without further notice. In the second stage, after actual randomization of eligible patients, a second informed consent was sought only in those who were randomly selected for the sponge-assisted intervention. Patients who were eligible for the experimental intervention but were randomized to the control arm (i.e., Trendelenburg position) underwent standard care and were not informed about the Sponge trial.

## **Patient recruitment**

PLCRC Cohort participants were eligible for the Sponge trial when they met the following inclusion criteria: 1) histologically confirmed distal colon (sigmoid) or rectal cancer, 2) planned for elective laparoscopic/robotic surgery for sigmoid or rectal cancer, 3) performance status WHO 0 to 2 (18), and 4) broad consent for randomization. Exclusion criteria were: open surgery, emergency setting, and insufficient understanding of the Dutch language. Patients were included from December 2015 to May 2021. Inclusion was halted between January and December 2017 due to a change of primary researcher.

## **Random selection**

Eligible patients were randomized on a 1:1 basis to sponge-assisted surgery or standard treatment with varying block sizes ( $n=6-8$ ) (figure 1). Randomization was stratified for concurrent participation in the intervention arm of the RECTAL BOOST trial (19). In this trial, also embedded in the PLCRC cohort, patients in the intervention arm received dose-escalated chemoradiation for locally advanced rectal cancer (19). Stratified randomization, using dedicated software, took place at the Imaging Division University Medical Center Utrecht.

## **Blinding**

This trial was not blinded for patients in the intervention arm or physicians. Randomly selected patients were offered the sponge intervention, which they could accept or refuse. Patients in the control arm were not informed about the fact that they served as controls in the SPONGE trial. Physicians could not be blinded to sponge use because operation reports require an indication of the used devices for safety reasons. The analysis was performed by



the investigators while blinded for the assigned treatment of the patients. For this purpose, a researcher who was not involved in this study, assigned codes to the intervention and the control arms.

### **Intervention arm**

The Endoractor™ retractor sponge consists of compressed cellulose and can be inserted into the abdomen through a 12-mm port. The sponge is positioned while the patient is in the Trendelenburg position. After proper positioning of the sponge, saline solution is applied, which increases the sponge size approximately nine times. The expanding sponge displaces the small intestine, after which the patient can be repositioned into a horizontal position. After the procedure is finished, the sponge will be removed through the 12-mm port.

The retractor sponge is X-ray detectable in case it was left inside the abdomen. A strict safety checklist notes the use of all surgical products, including the sponge, and makes the chance of sponge non-removal negligibly small. Sponge-assisted surgery is performed by experienced colorectal surgeons who have all completed a learning curve of 10 sponge-assisted surgeries before participating in this trial.

### **Control arm**

Patients in the control arm received standard care, which is surgery in the Trendelenburg position. The angle of the Trendelenburg position was not specified in the study protocol and was decided by the surgeon during the procedure. Perioperative care in both arms, other than the positioning of the patient, was standardized and did not differ.

### **Primary outcome**

The primary endpoint was postoperative hospital stay, defined as days from surgery until discharge. Patients were only discharged by the attending physician when all criteria on the checklist were met. The checklist included the following items: absence of fever (temperature below 38.5 °C); adequate pain management (VAS score below 4); absence of leukocytosis; passing stool (anally or via stoma); resumption of normal food intake (no nausea or vomiting); absence of an active, unstable and untreated cardiac, pulmonary or surgical complication; and presence of a supportive person at home at the time of discharge (20,21).

### **Secondary outcomes**

Secondary endpoints included duration of surgery (minutes), blood-loss (mL), fluid balance (mL) which is monitored by anesthesia personnel, body temperature on arrival at the recovery room, oxygen therapy at discharge from the recovery room, and postoperative complications (until 30 days after primary surgery).

Pulmonary complications were defined as respiratory failure, requiring mechanical ventilation; atelectasis, pleural effusion, or pneumothorax, as diagnosed on chest radiographs; or pneumonia, based on clinical, laboratory, and imaging findings combined with initiation of antibiotic therapy. Cardiac complications were defined as myocardial ischemia and cardiac events, including acute myocardial infarction, congestive cardiac failure, new-onset or rapid atrial fibrillation, major arrhythmia, and cardiac arrest. Surgical complications were defined as surgical site infection, anastomotic leakage, postoperative bleeding, abscesses, ileus, or bowel perforation. Secondary outcomes were collected from patients' medical files, anesthesia and operation reports.

## **Data collection**

Data were captured from the patients' electronic medical files by the primary researcher and were collected in an electronic database (Redcap). Data included demographics, body mass index, tumor characteristics, neoadjuvant therapy, ASA classification, details of the surgical procedure, type of anesthesia, duration of surgery, blood loss, fluid balance, postoperative body temperature, and oxygen therapy. Patients were registered under a unique study number.

## **Sample size**

We assumed a difference in duration of hospital stay of 1 day to be clinically relevant (5 days in the intervention group versus 6 days in the control group). In the original sample size calculation we also assumed that 10% of patients randomized to the intervention arm would refuse to undergo the sponge intervention. With a two-sided type I error of 5 % and power of 80% the sample size was calculated to be 82 patients per arm. Because hospital stay generally does not have a Gaussian distribution, we decided to add 15% to adjust the sample size for analysis with nonparametric tests (22). The final sample size was calculated to be 98 patients per arm.

However, after enrolment of about 50% of the required number of patients, we observed that the refusal rate in the intervention arm was close to 0% (only 2 patients refused the sponge-assisted intervention). Therefore we recalculated the sample size, after removing the 10% refusal rate assumption. We assumed 5% for post-randomization withdrawal from the study. The newly calculated sample size was calculated to be 80 patients per arm.

## **Statistical analysis**

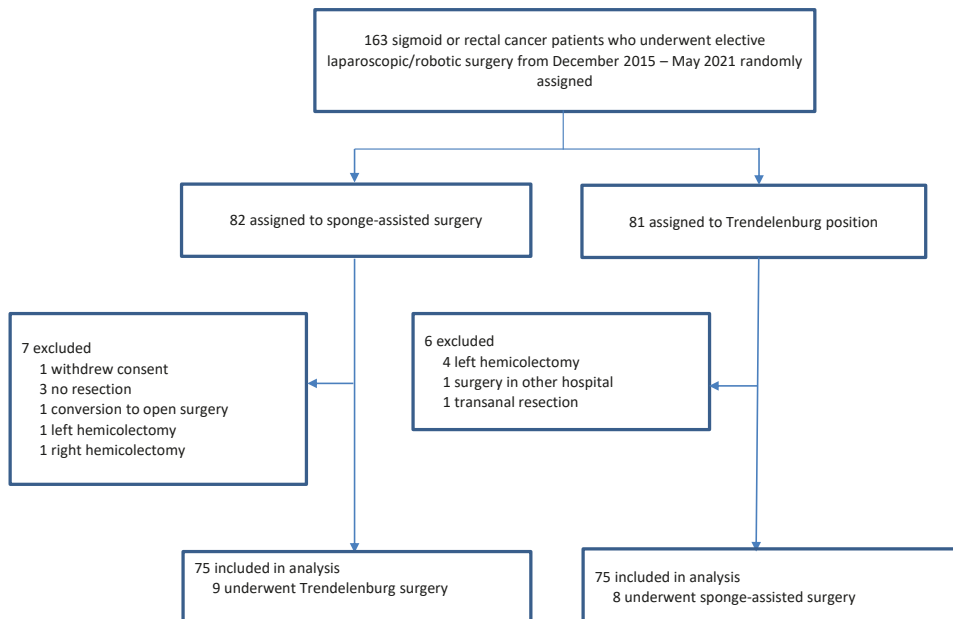
Intention-to-treat and as-treated analyses were performed. In the as-treated analysis, the patients were assigned to the control or intervention group based on the care that they received and not the group that they were randomized in. Continuous outcomes were analyzed using the independent samples t-test or the Mann-Whitney U test, depending on data distribution.

Categorical outcomes were analyzed using the chi-squared test or Fishers Exact test. All 30-day complications were combined in a composite endpoint to prevent multiple testing. A p-value of 0.05 was considered significant. Statistical analyses were performed using Statistical Package for Social Sciences (SPSS) software (IBM SPSS Statistics for Windows, Armonk, NY: IBM Corp.).

## Safety reporting

Serious adverse device events (SADEs) and study-specific serious adverse events (SAEs) were defined as an event in the first 30 postoperative days after sponge-assisted surgery leading to any serious surgical complication or death. SADEs leading to death or which are life-threatening, were reported within seven days after the responsible investigator was notified. Other SADEs and SAEs were reported within 15 days after notification. Reporting of SADEs and SAEs was done on a Dutch web portal ([www.toetsingonline.nl](http://www.toetsingonline.nl)).

## RESULTS



**Figure 1.** Study flowchart of randomized patients and the final intention-to-treat population after post-randomization exclusion

**Table 1.** Baseline characteristics in the intention-to-treat population

	<b>Sponge-assisted surgery, n=75</b>	<b>Trendelenburg surgery, n=75</b>
<b>Male</b>	53 (71)	49 (65)
<b>Age (years)</b>	66.6 ( $\pm$ 10.8)	64.6 ( $\pm$ 10.6)
<b>Body Mass Index (kg/m<sup>2</sup>)</b>	26.3 ( $\pm$ 4.0)	26.1 ( $\pm$ 4.3)
<b>ASA classification</b>		
ASA I	10 (14)	9 (12)
ASA II	48 (65)	56 (75)
ASA III	16 (22)	10 (13)
ASA IV	0 (0)	0 (0)
<b>TNM stage</b>		
Stage I	30 (40)	40 (53)
Stage II	24 (32)	22 (29)
Stage III	13 (18)	11 (15)
Stage IV	8 (11)	2 (3)
<b>Neoadjuvant chemoradiation</b>	23 (31)	27 (36)
<b>Procedures</b>		
Low anterior resection	29 (39)	24 (32)
Abdominoperineal resection	21 (28)	24 (32)
Sigmoid resection	24 (32)	27 (36)
<b>Concurrent participation in RECTAL BOOST trial</b>	3 (4)	1 (1)

*Data are n/total (%) or mean ( $\pm$  SD)*

Between November 2015 - December 2016 and January 2018 - May 2021, 163 patients with sigmoid or rectal cancer who underwent elective laparoscopic/robotic surgery were randomly assigned to either sponge-assisted or Trendelenburg surgery. Thirteen patients were excluded after randomization; reasons for exclusion included left hemicolectomy, withdrawal of consent, or cancellation of the surgical intervention (Figure 1). Of the remaining 150 patients, 75 were assigned to sponge-assisted surgery and 75 to Trendelenburg surgery. Nine patients in the intervention arm and 8 patients in the control arm crossed over between treatment arms. Crossover took place when the surgeon would decide that the field of view was not adequate using only the retractor sponge or Trendelenburg position, the surgeon would then use both the retractor sponge as well as the Trendelenburg position. These patients remained in their

allocated groups for the intention to treat analysis. All the patients in this study had WHO performance status  $\leq 2$  and were discharged only after they had met the discharge criteria of the standardized checklist.

In the intervention arm, a larger proportion was male, had higher ASA scores, and had higher TNM stages (Table 1). Other baseline characteristics were well balanced.

**Table 2.** Postoperative outcomes within 30 days

	Sponge-assisted surgery n=75	Trendelenburg surgery n=75	p-value
<b>Length of postoperative stay (days)</b>	5 (4-6)	4 (3-5)	0.06 <sup>a</sup>
<b>30-day complications</b>			
All complications	23 (30)	23 (31)	1.00 <sup>B</sup>
Surgical	12 (16)	14 (19)	
Anastomotic leakage	4 (5)	5 (7)	
Reintervention	8 (11)	8 (11)	
Pulmonary	0 (0)	3 (4)	
Cardiac	1 (1)	1 (1)	
Infectious	6 (8)	3 (4)	
Other	8 (11)	9 (12)	
<b>30-day readmission</b>	6 (8)	11 (15)	0.30 <sup>C</sup>
<b>30-day mortality</b>	0 (0)	1 (1)	1.00 <sup>C</sup>

Data are median (25-75 percentile) or n/total (%)

<sup>a</sup> Mann Whitney U test

<sup>B</sup> Chi-square test

<sup>C</sup> Fishers' exact test

There was no difference between the sponge-assisted and Trendelenburg groups in terms of length of hospital stay (median 5 days [first quartile 4, third quartile 6] vs. median 4 days [first quartile 3, third quartile 5],  $p=0.06$ ) or 30-day complications (only the composite endpoint including all 30-day complications was tested), readmissions, or mortality (Table 2). Anastomotic leaks in particular can significantly increase the length of stay and occurred 4 times (5%) in the intervention arm and 5 times (7%) in the control arm.

**Table 3.** Perioperative outcomes

	<b>Sponge-assisted surgery n=75</b>	<b>Trendelenburg surgery n=75</b>	<b>p-value</b>
<b>Duration of surgery (minutes)</b>	164 (143-202)	164 (131-205)	0.69 <sup>a</sup>
<b>Blood loss (mL)</b>	30 (3-75)	40 (3-100)	0.70 <sup>a</sup>
<b>Fluid balance (mL)</b>	+1605 (1045-2060)	+1702 (1050-2570)	0.19 <sup>a</sup>
<b>Body temperature on arrival recovery</b>	36.6 °C (±0.49)	36.5 °C (±0.49)	0.26 <sup>b</sup>
<b>Oxygen therapy at discharge recovery</b>			0.62 <sup>c</sup>
None	23 (31)	18 (24)	
Nasal tube	39 (53)	43 (57)	
Nasal canula	12 (16)	14 (19)	
<b>Maximum oxygen flow at recovery</b>	2 (0-3)	3 (1-3)	0.14 <sup>a</sup>
<b>Intraoperative complications</b>	0/0 (0)	0/0 (0)	-

Data are median (25-75 percentile), mean (±SD), or n/total (%)

<sup>a</sup> Mann Whitney U test

<sup>b</sup> Unpaired t-test

<sup>c</sup> Chi-square test

There were no significant differences in fluid balance, blood loss, need for oxygen therapy, and maximum oxygen flow (Table 3).

An as-treated analysis was also performed with 74 patients who underwent sponge-assisted surgery and 76 patients who underwent Trendelenburg surgery. There was no difference in length of stay between the groups (median 5 days [first quartile 4, third quartile 6] vs. median 4 days [first quartile 3, third quartile 5],  $p=0.11$ ). Secondary endpoints such as and 30-day complications, duration of surgery, blood loss, fluid balance, and oxygen therapy at discharge of the recovery room also showed no significant difference. Pulmonary and cardiac complications showed similar results as the intention to treat analysis: zero pulmonary complications in the Sponge group versus three pulmonary complications in the Trendelenburg group. Cardiac complications occurred in one patient in both the Sponge and the Trendelenburg groups.

No adverse device events occurred in this trial.

## DISCUSSION

Sponge-assisted rectal or sigmoid cancer surgery, as compared to surgery with the patient in Trendelenburg position, did not lead to a shorter hospital stay or reduced postoperative complications.

To the best of our knowledge, the SPONGE trial is the first RCT to assess short-term outcomes of sponge-assisted surgery as an alternative to traditional Trendelenburg position surgery. Contrary to the Dutch pilot study (11), which showed shorter hospital stay (5.4 and 7 days, respectively,  $p=0.041$ ), the SPONGE trial did not show a statistically significant difference in hospital stay nor in cardiac, pulmonary, or other postoperative complications. The as-treated analysis also showed no difference between the groups with regards to the length of stay.

Even though there was no significant difference in the primary endpoint between the groups, there might be some advantages to using the retractor sponge. The first is a more comfortable ergonomic position for the surgeon. The retractor sponge allows for horizontal positioning of the patient which makes the handling of the laparoscopic instruments easier and might reduce tension in the arms and neck. The second advantage of the retractor sponge might be the prevention of cephalad excursion (i.e., sliding) of the patient while angled downwards. This is especially an issue in obese patients or at steep angles. Sliding can cause dermal and neuropathic injuries and might disturb the surgical procedure (23,24). Sliding prevention devices, such as shoulder braces and headrests also increase the risk of neuromuscular injuries, most notably brachial plexus injury (24). The risk of sliding and the associated adverse events are not present in sponge-assisted surgery in the horizontal position. The third possible advantage to using the retractor sponge is the very rare but very serious lower limb compartment syndrome complication that has been associated with Trendelenburg position in some studies (25).

The trials within cohorts (TwICs) design was used for this study. This design was first described in 2010 in the BMJ and confers several advantages such as allowing for testing of multiple interventions in the same cohort (15). Firstly, enrolment in the trial was facilitated by embedding it in an existing cohort. Due to the staged informed consent, where patients consent to broad randomization at cohort enrolment, patients eligible for the Sponge trial could be systematically approached, which facilitated fast and efficient trial enrolment. This way, we were able to enroll the complete trial population of 163 individuals in a single-center within 41 months (Nov 2015 – Dec 2016 and Jan 2018 – May 2021). As such, a high proportion of eligible patients was actually recruited in the trial, improving the generalizability of the results. In addition, the patient-centered, staged informed consent procedure allowed that only patients allocated to the intervention arm needed to be informed about the Sponge intervention. As such, control patients did not receive information that was not relevant to



them. This approach is less time-consuming for doctors and researchers and eliminates the risk of disappointment (bias) that is sometimes seen in classic RCTs when patients, who are eager to get a new, experimental intervention, are allocated to the control arm. Downsides of the TwiCs design are the impossibility to blind patients in the intervention arm, as the staged informed consent procedure requires asking for second informed consent after patients have been randomized to the intervention arm. This may potentially influence their (health-related) behavior (Hawthorn effect). Since we saw no effect in hospital stay (the primary endpoint) in this trial, we think that it is very unlikely that the absence of blinding influenced the outcomes.

In this study, the Trendelenburg position was not standardized. It was not possible to set the operating table at exactly the same angle for the Trendelenburg position. Therefore it is possible that some patients underwent Trendelenburg surgery in a steeper incline than others. However, this was a pragmatic trial, in which we estimated the effect of the introduction of a retractor sponge in daily practice. Also, since ours was a single-center RCT, the generalizability of the study results may be somewhat limited due to differences in perioperative care or differences in demographic characteristics of the patients between different hospitals. Lastly, the lack of blinding of the physicians and possible different interpretations of the discharge criteria could have been a source of bias. A strength of the SPONGE trial is that patients in the Trendelenburg group were blinded to the fact they served as control group to the Sponge group, thereby minimizing disappointment bias or drop-out in the Trendelenburg group. The primary researcher was also blinded to treatment allocation while performing the analyses to reduce bias.

## CONCLUSION

Sponge-assisted surgery, as compared to Trendelenburg surgery, in the elective setting using the laparoscopic or robotic approach, does not lead to a shorter postoperative length of stay or reduced postoperative morbidity and mortality.

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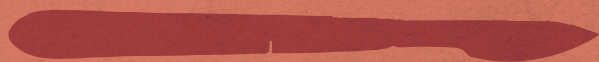
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## PART III



*Improving postoperative  
surgical care*







09

# Routine postoperative ICU admission after colorectal cancer surgery for the elderly patient reduces postoperative morbidity and mortality



Milad Fahim, Remco A. Visser, Lea M. Dijkman, Douwe H. Biesma, Peter G. Noordzij, Anke B. Smits

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## **ABSTRACT**

### **Aim**

Older colorectal cancer (CRC) patients are at increased risk of postoperative morbidity and mortality. Routine postoperative overnight ICU admission might reduce this risk. This study aimed to examine the effect of routine overnight ICU admission after CRC surgery on postoperative adverse outcomes and costs in patients aged 80 years or older.

### **Methods**

Patients aged 80 years or older who underwent CRC surgery in our centre were included in this observational cohort study. All patients in the period with routine overnight ICU admission (2014-2017) were assigned to the ICU cohort, all patients in the period 2009-2013 were assigned to the non-ICU cohort. Multivariable logistic regression was performed to compare the primary composite endpoint (30-day mortality, serious complications and readmission) between the groups. Cost data from literature were used to perform a cost-analysis.

### **Results**

A total of 242 patients were included, 125 in the ICU cohort and 117 in the non-ICU cohort. Routine overnight ICU admission was associated with a reduced risk of the composite endpoint (OR 0.44, 95% CI=0.22-0.87,  $p=0.02$ ) after adjusting for important confounders. In the ICU cohort 28% of patients experienced ICU events requiring intervention, this was not associated with postoperative morbidity or mortality. The 9% reduction in the incidence of serious complications in the ICU cohort is sufficient to offset the additional costs of routine overnight ICU admission.

### **Conclusion**

Routine overnight ICU admission after CRC surgery in patients aged 80 years and older is associated with reduced risk of postoperative mortality and morbidity and seems to be cost-effective.

## WHAT DOES THIS PAPER ADD TO THE LITERATURE

As ICU costs are high and ICU bed shortages are common, it is important to develop the body of scientific evidence in regards to routine ICU admission. The results of this study suggest that routine postoperative overnight ICU admission seems effective in improving surgical outcomes and also seems to be cost-effective.

## INTRODUCTION

Colorectal cancer (CRC) is increasingly becoming a disease of the elderly patient, with a median age at time of diagnosis in the Netherlands of 70 years (1). Due to population growth, ageing of the population and a national colorectal cancer screening program the incidence is expected to rise even further (1). These older CRC patients, in particular patients aged 80 years or older, are more prone to developing postoperative complications and are at increased risk of postoperative mortality (2-5).

It is unclear whether routine admission to an intensive care unit (ICU) immediately after colorectal surgery is beneficial for patients aged 80 years and older. A majority of complications after colorectal surgery, such as pneumonia, sepsis and anastomotic leakage, do not occur in the early postoperative period (6,7). However, It might be possible that routine ICU admission and close monitoring of vital signs prevents deterioration of the patient shortly after surgery and thereby reduce the incidence of postoperative complications in a later stage in these vulnerable elderly patients. Studies assessing the practice of routine ICU admission after thoracic surgery and neurosurgery have demonstrated that some patients benefit from routine ICU admission (8,9). No research has been done in the colorectal population of patients aged 80 years or older.

As ICU costs are high and ICU beds are scarce, it is important to determine whether patients may benefit from routine postoperative ICU admission (10). The main aim of this study was to examine the effect of routine ICU admission after colorectal surgery for patients aged 80 years or older with CRC on adverse outcomes and costs.

## METHODS

### Study design and data collection

CRC patients aged 80 years or older who underwent elective colorectal surgery were identified from the prospectively maintained Dutch Colorectal Audit (DICA) database (11). Starting in January 2014, all CRC patients aged 80 years or older who underwent surgery were routinely admitted to the ICU until the first postoperative day. All consecutive patients in the period

January 2014 to December 2017 were assigned to the ICU cohort and all consecutive patients in the period January 2009 to December 2013 were assigned to the non-ICU cohort (Fig. 1). Patients aged 80 years or older who undergo emergency surgery are always postoperatively admitted to the ICU and have nothing to gain with routine ICU admission, therefore we excluded these patients. Patients in the non-ICU cohort who underwent elective surgery and were immediately postoperatively admitted to the ICU were not excluded. During the perioperative process many factors determine whether a patient will be admitted to the ICU after surgery, selecting patients based on these factors would lead to selection bias.

The expected number of eligible patients undergoing surgery during the study period and the expected number of postoperative complications was insufficient to construct a multivariable model (3). Therefore we opted for a clinically relevant combined endpoint of 30-day mortality, serious complications (Clavien-Dindo 3-4) and readmission within 30 days(12).

Patient characteristics (age, gender, ASA classification, BMI, surgical history and comorbidity) and surgery characteristics (duration of surgery, type of surgery and elective/emergency surgery) were also collected from the DCRA database. For the patients in the ICU cohort we used an ICU data-management system, to manually assess the time spent on the ICU and to identify ICU events. Time between admission to the ICU and the occurrence of an ICU event was assessed. Data collection was performed by 2 researchers (MF and RV) and data was gathered in Redcap, a secure web application (13). Subsequently, all possible ICU events were reviewed by a panel of a staff anaesthesiologist-intensivist (PN) and surgeon (AS).

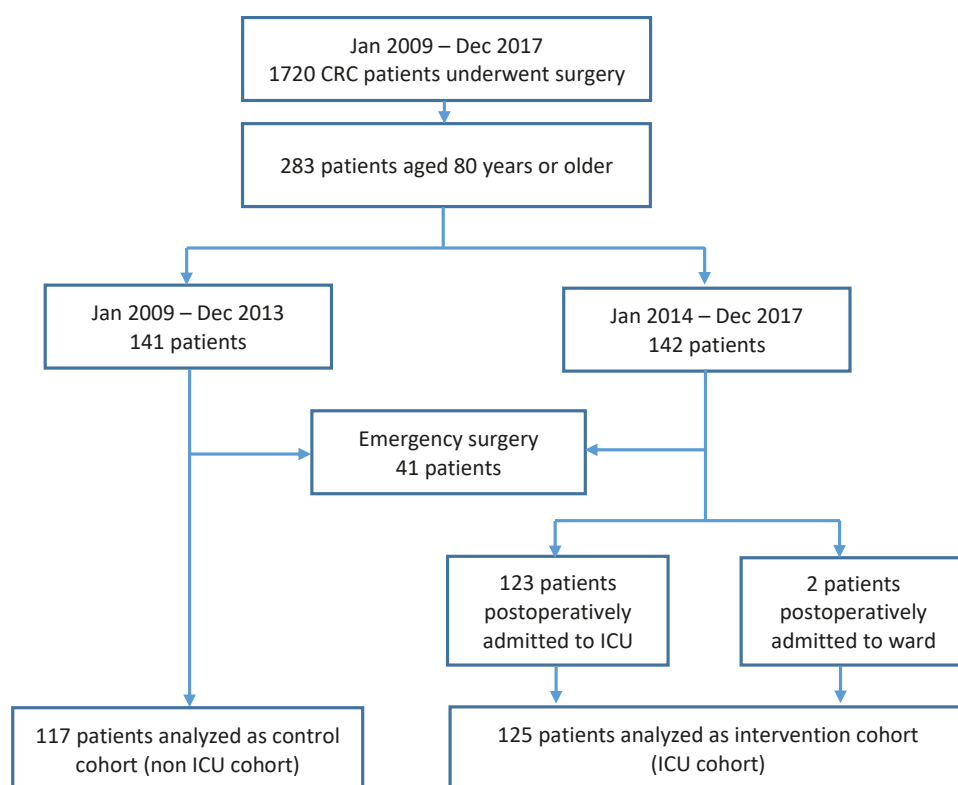
## **Definitions of outcomes**

The primary endpoint was a composite endpoint of 30-day mortality, serious complications and 30-day readmission. Thirty-day readmission was included in the endpoint because it is a proxy for wound healing and it is relevant for the patient. ICU events were classified as any of the following events requiring intervention occurring within 24 hours of ICU admission or until ICU discharge: hemodynamic instability requiring the use of vasopressors or inotropes, reintubation, invasive mechanical ventilation, CPAP, high-flow nasal oxygen therapy, bleeding requiring surgery or transfusion of blood, supraventricular arrhythmia, congestive heart-failure, myocardial infarction, severe pain needing continuous intravenous opioid treatment and re-intervention.

## **Statistical analysis**

Analysis was according to intention-to-treat. All eligible patients in the period 2014-2017 were included in the ICU cohort, even those who were not postoperatively admitted to the ICU for any reason. Continuous data were presented as medians with interquartile range (25%-75%) and analysed using the Mann-Whitney U test. Dichotomous data were presented as

numbers and percentages and analysed using the chi-squared test. Incomplete variables from the DCRA database were supplemented by the primary researcher (MF) using pathology and operation reports. We used multivariable logistic regression, with and without propensity score as a covariate (14), to analyse the primary composite endpoint. Propensity score was calculated as the probability of being routinely admitted to the ICU based on patient characteristics (gender, ASA classification, comorbidity and previous abdominal surgery) and treatment characteristics (surgical approach, conversion, additional resection, type of operation and year of surgery as proxy for changes in perioperative care). Within the ICU cohort, univariable logistic regression was used to identify risk factors for ICU events. All p-values reported are two sided. A p-value of  $<0.05$  was considered significant. Statistical analysis was performed using SPSS v.24.0 (IBM, Armonk, NY, USA).



**Figure 1.** Study flowchart

The cost-analysis was based on incidence rates seen in our study population and cost data from the literature. For the costs of surgical treatment for colorectal cancer and postoperative complications we used the study of Govaert et al which collected data from 29 Dutch hospitals using the advanced Time-Driven Activity-Based Costing (TDABC) methodology (15). The authors reported that total in-hospital costs for surgical treatment of colorectal cancer from the day of initial surgery till discharge were €9.226 in case of no postoperative complications, €11.648 in case of minor complications (i.e. no major complication) and €27.287 in case of major complications (i.e. leading to mortality, reintervention or prolonged hospital stay of at least 14 days). For the costs of ICU stay we used the study by Tan et al, a multicentre European study which reported that in-hospital costs of ICU stay per day ranged from €1.168 to €2.025 in ICU departments in Germany, Netherlands, Italy and the United Kingdom and average cost was €1.381 (16). The study by Goveaert et al reported cost data for 2012, the study by Tan et al reported cost data for 2007, to facilitate comparison between these two studies the cost data from the study of Tan et al were inflated to 2012 using Eurostat harmonized indices of consumer prices (17).

## RESULTS

A total of 283 patients aged 80 years or older who underwent colorectal surgery were evaluated for inclusion (Figure 1). After excluding patients with emergency surgery the final study cohort consisted of 242 patients. Of these, 117 patients were assigned to the non-ICU cohort and 125 patients were assigned to the ICU cohort. In the non-ICU cohort, 32 out of 117 patients (32%) were directly postoperatively admitted to the ICU. Two patients in the ICU cohort were not routinely admitted to the ICU, but were included in our analysis according to intention to treat. We had complete data for the statistical analysis in regards to the composite endpoint of this study. All the surgical procedures were performed by the same team of five GE-surgeons of the surgery department. In the ICU cohort, as compared to the non-ICU cohort (table 1), patients were significantly less ill in regards to ASA classification (p-value 0.011), open surgery was less frequent (p-value <0.001) and type of procedure performed was different (p=0.019). The rate of the APR procedure was higher in the ICU cohort and the rate of the LAR procedure was higher in the non-ICU cohort.

**Table 1.** Baseline characteristics

	ICU cohort (n=125)	Non-ICU cohort (n=117)	p-value
Age	83 (81-84)	83 (81-85)	0.98
Male gender	69 (55)	57 (49)	0.37
ASA classification			0.011
ASA I-II	75 (60)	51 (44)	
ASA III-IV	50 (40)	66 (56)	
Body mass index			0.13
<30	105 (84)	106 (91)	
>30	20 (16)	11 (9)	
Previous abdominal surgery	56 (45)	52 (44)	0.96
Comorbidity			0.75
Cardiac	52 (42)	57 (49)	
Pulmonary	24 (19)	21 (18)	
Vascular	67 (54)	70 (60)	
Neurologic	13 (10)	22 (19)	
Diabetes mellitus	26 (21)	18 (15)	
Gastro-enteral	18 (14)	21 (18)	
Urogenital	14 (15)	7 (24)	
Thrombotic	4 (3)	2 (2)	
Infectious	4 (3)	1 (1)	
Malignancy	19 (15)	18 (15)	
Open surgery	28 (22)	54 (46)	<0.001
Procedure			0.019
Hemicolectomy right	58 (46)	51 (44)	
Low anterior resection/sigmoid resection	32 (26)	48 (41)	
APR	20 (16)	8 (7)	
Transverse colon resection	3 (2)	3 (3)	
Hemicolectomy left	7 (6)	5 (4)	
Subtotal colectomy	3 (2)	0 (0)	
Local excision	2 (2)	1 (1)	

*All variables are in number (%) or median (IQR)*

## Comparison of outcomes

**Table 2.** Outcomes within 30 days after surgery

	ICU cohort (n=125), n (%)	Non-ICU cohort (n=117), n (%)	RRR (%)	p-value
Mild complications (Clavien-Dindo 1-2)	41 (33)	44 (38)	13	0.43
Serious complications (Clavien-Dindo 3-4)	12 (10)	22 (19)	48	0.040
Readmission	7 (6)	18 (15)	60	0.012
Mortality	3 (2)	5 (4)	50	0.42
Composite endpoint*	17 (14)	36 (31)	55	0.001

RRR=relative risk reduction, \* composite endpoint consists of serious complications, readmission and 30-day mortality. Some patients had more than one outcome.

The composite endpoint consisting of 30-day mortality, serious complications and readmissions occurred in 53 out of 242 patients (22%). Univariable analysis showed no significant difference in mild postoperative complications ( $p=0.43$ ) or 30-day mortality ( $p=0.42$ ) between the ICU and non-ICU cohorts (Table 2). However, the ICU cohort had significantly reduced percentage of serious complications (10% versus 19%, relative risk reduction [RRR] of 48%,  $p=0.040$ ), readmissions within 30 days (6% versus 15%, RRR of 60%,  $p=0.012$ ) and the composite endpoint (14% versus 31%, RRR of 55%,  $p<0.001$ ) in comparison to the non-ICU cohort. The multivariable analysis also showed an association between routine overnight ICU admission and reduced risk of the composite endpoint (adjusted odds ratio [OR] 0.44, 95% confidence interval [CI]: 0.22-0.87,  $p=0.018$ ) after adjusting for gender, ASA classification, BMI and surgical approach (Table 3).

As an additional check of the internal validity of our study we used propensity score as a covariate in our multivariable analysis. Due to the number of events the number of variables in the model was limited, therefore we replaced the least significant variable (i.e. gender) with propensity score. In accordance with our previous analysis routine ICU admission was significantly associated with a reduced risk of the composite endpoint (adjusted OR 0.41, 95% CI: 0.20-0.83,  $p$ -value 0.014).

### ICU events in ICU cohort

Two patients in the ICU cohort were not admitted to the ICU for the first postoperative night and 6 patients who were admitted to the ICU were not properly registered in Metavision. Therefore these 8 patients had missing data in regards to ICU events. A total of 117 patients were admitted to the ICU and had complete data, 33 of these patients (28%) experienced a total of 39 ICU events. The most common ICU event was hemodynamic instability requiring



the use of vasopressors or inotropes (31 events, 79% of all ICU events). Other events were: invasive ventilation (n=5), bleeding requiring intervention (n=2) and severe pain needing continuous intravenous opioid treatment (n=1). In regards to the missing data for the 8 patients, assuming that all of these 8 patients had ICU events, the incidence would be 41 events in 125 patients (33%). Likewise, assuming that none of these patients had ICU events, the incidence would be 33 events in 125 patients (26%).

Median time to first postoperative ICU event was 2 hours (IQR 1-8 hours). Median time to first 'hemodynamic instability requiring the use of vasopressors or inotropes' and 'invasive ventilation' ICU events were respectively 4 hours (IQR 1-10 hours) and 1 hour (IQR 1-1 hour).

**Table 3.** Univariable and multivariable analysis of risk factors for composite endpoint (30-day mortality, serious complications and readmission)

	Univariable		Multivariable	
	Odds ratio (95% CI)	p-value	Odds ratio (95% CI)	p-value
<b>Gender</b>				
Female	1		1	
Male	1.14 (0.62-2.11)	0.67	0.97 (0.51-1.87)	0.94
<b>ASA classification</b>				
ASA I-II	1		1	
ASA III-IV	2.34 (1.25-4.40)	0.008	1.84 (0.95-3.56)	0.07
<b>Body Mass Index</b>				
<30	1		1	
>30	1.62 (0.69-3.78)	0.27	1.48 (0.58-3.82)	0.41
<b>Surgical approach</b>				
Laparoscopic	1		1	
Open	0.36 (0.19-0.68)	0.001	0.49 (0.25-0.94)	0.033
<b>Routine ICU admission</b>				
No (non ICU cohort)	1		1	
Yes (ICU cohort)	0.36 (0.19-0.69)	0.002	0.44 (0.22-0.87)	0.018

Univariable analysis in the ICU cohort showed that patients who received ICU specific interventions due to an ICU event were more likely to have a BMI>30 (30% versus 11% of patients, p=0.010) and increased median duration of surgery (139 minutes versus 108 minutes, p=0.036), no other significant risk factors for ICU events could be identified. Hemodynamic

instability was the most frequently occurring ICU event. In most cases hemodynamic instability was not accompanied by any other event (28 out of 31 patients). Significant predictors of only hemodynamic instability were increased duration of surgery (139 minutes versus 106 minutes,  $p=0.008$ ) and the use of an epidural (93% versus 75% of patients,  $p=0.034$ ). There was no significant association between experiencing an ICU event and increased risk of mild complications ( $p=0.26$ ), serious complications ( $p=0.53$ ), readmission ( $p=0.77$ ), 30-day mortality ( $p=0.84$ ) or the combined endpoint ( $p=0.32$ ).

### Cost analysis

The additional cost of a major postoperative complication in 2012 was €18.961 (15), after adjusting the average daily ICU cost of €1.381 in 2007 for inflation the average daily ICU cost in 2012 was €1.567 (16). The average stay at the ICU in our ICU cohort was 1.1 days due to 8 out of the 125 patients being admitted longer than 1 day. Therefore we increased the cost of ICU stay by a factor 1.1 ( $€1.567 \times 1.1 = €1.723$ ). The additional cost of a major complication (€18.961) roughly equals the cost of routine ICU admission for the first postoperative night for 11 patients (€18.953). Therefore at least one major complication has to be prevented per 11 patients (i.e. incidence reduction of 9%) to offset the costs of routine ICU admission. Likewise, the additional costs of a minor complications (€2.422) roughly equals the costs of routine ICU admission for 1.4 patients (€2.412). Therefore at least one minor complications should be prevented per 1.4 patients (i.e. incidence reduction of 71%) to offset the costs of routine ICU admission. Based on the incidence rates in our study population, routine ICU admission seems cost-effective as the incidence of serious complications is reduced by 9% in favour of the ICU cohort.

## DISCUSSION

The effect of routine ICU admission for the first postoperative night after colorectal surgery in patients aged 80 years or older was assessed in this study. There was a significant beneficial effect on serious complications (10% in the ICU-cohort versus 19% in the non-ICU cohort,  $p=0.040$ ) and readmission rate (6% in the ICU cohort versus 15% in the non-ICU cohort,  $p=0.012$ ). After adjusting for confounding variables, the relative incidence of the composite endpoint was reduced with 56%.

It is interesting that patients who received routine ICU admission had less postoperative adverse events. This might be due to the close monitoring of the hemodynamic status of the elderly patient immediately postoperative which is beneficial for the rest of the hospital stay. It is possible that the basis of serious complications like pneumonia, sepsis and anastomotic

leakage lies in the hemodynamic status of the patients in the first 12-18 hours after operation. As the hemodynamic status of the elderly patients is less stable, better monitoring might be beneficial for this group as it leads to fast interventions before the patient deteriorates.

Some baseline differences exist between the ICU and non-ICU cohorts. The ICU cohort has lower ASA III-IV scores than the non-ICU cohort. We believe that this is due to random chance, which is supported by the yearly variation in ASA scores in the colorectal cancer population as a whole that we observe in our own hospital since the start of the Dutch Colorectal Audit in 2009 (ref). Another difference between the two groups is a higher rate of APR in the ICU cohort. Generally patients who undergo the APR procedure have more postoperative morbidity than other common colorectal cancer procedures (ref). Despite the higher APR rate, there was less postoperative morbidity in the ICU cohort. Suggesting that the actual effect of routine ICU admission might be even greater.

In patients who received routine ICU admission, 28% experienced an ICU event in the direct postoperative period requiring ICU specific intervention. This further illustrates the vulnerability of this population and their increased perioperative risk. If these patients would have been admitted to the surgical ward, there would probably have been a delay in recognizing their deterioration and ICU specific interventions would not have been administered. Reassessing and transferring these patients from the surgical ward to the ICU is time consuming and will also results in more ICU consultations on the ward, and thus higher workload, discontinuation in medical care by changing departments and can cause distress in patients and their families. These factors may explain the poorer outcome in the control group. Furthermore, experiencing an ICU event and intervention in the immediate postoperative period was not associated with increased risk of morbidity or mortality, suggesting that close hemodynamic monitoring and early intervention reduced the expected additional risk of ICU events later during the hospital stay. However, as this was not the primary endpoint of our study it is also possible that our study population is too small to measure these differences.

ICU costs are high and ICU bed shortages are common (10), therefore we attempted to identify predictors for efficient ICU use (i.e. experiencing an ICU event requiring ICU specific intervention). In our cohort only BMI>30 and increased median surgery time were predictors of ICU events. However, if we would use these 2 predictors we would miss 6 out of the 33 patients with ICU events because these 6 patients had a BMI<30 or surgery time below the median time for the entire ICU cohort (123 min). Based on these results it is not possible to optimize patient selection for routine ICU admission, but these predictors might be useful to prevent ICU interventions. Surgeons should strive to reduce operation time whenever possible and increased awareness for ICU events is appropriate in the presence of BMI>30 and increased surgery time.

Hemodynamic instability was by far the most frequent postoperative problem. Thirty-three patients scored a total of 38 events, of which 31 events consisted of hemodynamic. In 27 patients hemodynamic instability was the only scored event. The use of epidural anaesthesia was a significant predictor of hemodynamic instability, which is a well-known common side-effect of neuraxial anaesthesia (18). In accordance with the new ERAS guidelines, supplemental epidural anaesthesia in colorectal surgery should be limited to support fast recovery (19,20). In our ICU cohort, 75 out of 96 epidurals were performed for laparoscopic surgery. In laparoscopic surgery, a good alternative to an epidural is spinal anaesthesia, as this is shown to provide similar pain reduction and is associated with a faster recovery and hospital discharge when compared to epidural anaesthesia (21). The question whether the 28% incidence of hemodynamic instability will reduce in patients aged 80 years or older when epidural anaesthesia is replaced by spinal anaesthesia requires further research.

Most events occur directly post-operative or, in other words, are continued interventions from the intraoperative period (median time to first event was 1.5 hours, IQR 1-9). This is especially true for the respiratory complications as all events of respiratory nature represent patients who remained intubated postoperatively. There were no re-intubations or cases with use of high flow oxygen therapy in the first 24 hours after postoperative extubation, representing a low risk of postoperative respiratory complications. A lower level of care, e.g. high or medium care with the possibility to provide hemodynamic support appears to be a cost-saving alternative to ICU admissions for post-operative care in this population. We also considered the possibility of extended postoperative observation in the recovery room as an alternative to overnight ICU admission. However with a post-operative observational period of 6 hours we deemed the number of ICU events that will be missed to be unacceptable (n=6, 18% of patients with ICU events occurring after 6 hours).

From an economic perspective, routine overnight ICU admission seems to be cost-effective in our study population. The study by Goveart et al. showed that complications after colorectal cancer surgery are associated with substantial increase in costs (15). Due to the large number of participating hospitals in the study, the cost data can most likely be generalized to our hospital. The costs of ICU stay per day, as reported by the large multicentre European study of Tan et al (16), are substantially lower than the increased costs due to postoperative complications. Therefore a relatively small decrease in the incidence of postoperative complications is sufficient to justify routine ICU admission.

This study has several strengths. First, a staff anaesthesiologist-intensivist and a staff surgeon validated ICU events after reviewing all the possible ICU events. This ensured that only valid ICU events were included and errors due to wrong data registration were not. Second, conventional multivariable analysis and multivariable analysis with propensity score as a

covariate were used and the results were in agreement making the conclusions of this study more plausible. This study also has some limitations. First, the inherent risk of bias in a nonrandomized retrospective comparison. Second, no conclusions can be made on the basis of our data in regards to the mechanism by which routine ICU admission leads to reduced morbidity and mortality, this will require further research.

## **CONCLUSIONS**

This study shows that routine overnight ICU admission after CRC surgery is associated with reduced risk of postoperative adverse outcomes in patients aged 80 years or older. Patients who experienced an ICU event requiring intervention during their ICU stay, did not have an increased risk of adverse outcomes later during their hospital stay, suggesting that the additional risk of complications is reduced due to close monitoring and early intervention. And finally, routine overnight ICU admission seems to be cost-effective.

## **Ethics approval**

Medical Ethics Committees United (MEC-U) , located in Nieuwegein at the St. Antonius Hospital and consisting of a partnerships between 7 large regional hospitals in the Netherlands, reviewed and approved this study.

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# PART IV



*General discussion  
and appendicis*







10

## General discussion and summary





## GENERAL DISCUSSION AND SUMMARY

The only way to be completely cured of colorectal cancer is surgery in which a section of the intestine containing the tumor is removed. In recent decades, several important improvements have been made in colon cancer surgery. Some examples are the introduction of laparoscopic surgery instead of surgery with a large incision in the abdomen, fast track surgery (minimum waiting time), and the Enhanced Recovery After Surgery (ERAS) protocol that has improved care immediately after surgery (1). Despite these improvements, colon cancer surgery is thus far still an area with a relatively high rate of postoperative complications and death compared to surgery in other parts of the body (2). Another point to improve is the large differences in postoperative outcomes between hospitals. In 2018, postoperative complications and mortality between hospitals in the Netherlands ranged from 14% to 21% and from 1.2% to 3.1%, respectively (3). This means the quality of care is inconsistent and there are significant differences in quality of care between hospitals. Quality improvement is therefore necessary, whereby hospitals should learn from each other.

One of the factors influencing postoperative outcomes is the age of patients with colorectal cancer. Colorectal cancer is common in older patients who are often more vulnerable and more likely to have complications after surgery. Due to an aging population, the number of colorectal cancer patients will only increase in the future, which will increase healthcare costs and put pressure on the health system. Therefore, there still is much to be gained, both in terms of quality and efficiency of care, to achieve high-quality but also affordable surgical care for colorectal cancer. A possible solution is given by Michael Porter et al. in their article “The Strategy That Will Fix Health Care” (4). In this paper, they describe that improving the quality of care will also lead to lower costs. Quality is therefore defined by Porter as health outcomes divided by the costs of achieving those health outcomes. This is the basic principle of Value-Based Healthcare.

This thesis addresses quality improvements of surgical colorectal cancer care in the three stages of treatment; preoperative, perioperative, and postoperative. In the preoperative stage we evaluated the long-term implications of open surgery and surgery in the emergency setting. We also assessed treatments to improve preoperative nutritional and physical condition. In the intraoperative stage we investigated intraoperative hypothermia and a new medical device to improve patient positioning during surgery. Lastly, in the postoperative stage the effect of improved postoperative monitoring in a select patient population and its cost-effectiveness was evaluated. The results are summarized below.

## Part 1, preoperative: optimizing patients for surgery

In the past, studies reported that postoperative morbidity and mortality have approximately doubled in patients over 75 years of age compared to patients younger than 75 years (5,6). This led to a tendency to withhold curative surgery for elderly patients. As colorectal cancer is mainly a disease of the elderly patient, this would mean that a large proportion of patients would not receive the optimal curative treatment. In **chapter 2**, we provided an overview of more recent studies, which have shown impressive improvements in postoperative outcomes in elderly patients (7). The postoperative survival gap seen earlier between younger and older patients is fading (8). Colorectal surgery can be performed safely without increased postoperative morbidity, mortality, and excess one-year mortality. Several changes in the last few decades have led to this improvement in outcomes. For example, the rise of minimally invasive surgery, first in the form of laparoscopic surgery and now robotic-assisted surgery. Other factors contributing to better outcomes are new anesthesiological techniques, early postoperative mobilization, and perioperative care focusing on nutritional, electrolyte, and fluid balance. However, the most important contribution might be the understanding that a multidisciplinary approach is paramount and that actions may be needed to better prepare patients for surgery.

Emergency and open surgery are known risk factor for unfavorable short-term postoperative outcomes (9,10). The long-term effects of these risk factors has received less attention in the scientific literature and is more difficult to study in the setting of a randomized controlled trial. Furthermore, since short term benefits for elective and laparoscopic surgery already have been reported it is unethical to randomize patients to elective/emergency or laparoscopic/open cohorts. Other disadvantages of RCT's is that the follow-up time is often limited and the study population is usually a selected group of patients. Longitudinal observational studies (at the population level) seem better tools to investigate the long term effects of emergency and open surgery. These types of studies include patients at high risk and with a higher number of events, which reflects daily practice. **Chapters 3 and 4** are both longitudinal observational studies assessing the long term implications of emergency and open surgery. In chapter 3 the effect of emergency surgery on long-term outcomes in 1139 colorectal cancer patients is reported. The findings of this study show that emergency surgery not only leads to poorer outcomes in the short term but is also associated with a significantly increased risk of long-term mortality and that this risk increases over longer periods. In chapter 4 the effect of open surgery on long-term outcomes is reported in 4531 colorectal cancer patients in three centers. In this study, open surgery, was also shown to be associated with increased long-term mortality.

Another important indicator for a good recovery of the patient nowadays is the frailty of the patient. As only a minority of older colorectal cancer patients are frail, a quick frailty assessment is crucial to distinguish the fit from the frail in the decision-making process (11). In some



cases, patients can be optimized before surgery to reduce their frailty. The use of prehabilitation programs can lead to significant improvements in physical and nutritional conditions prior to surgery and therefore better outcomes after surgery (12,13).

As mentioned before, emergency surgery is associated with increased short-term and long-term mortality. It seemed that emergency surgery could not be prevented. But based on modern insights, emergency surgery can be prevented more often than previously thought. Provided individual attention and care is given before surgery. A clear example of changing an emergency patient into an elective patient is seen in patients with bowel obstruction.

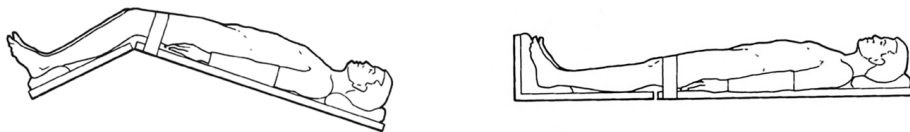
The incidence of bowel obstruction in colorectal cancer patients is 8-29% and still carries the highest risk for adverse outcomes (14,15). Usually these patients are in bad condition due to very little exercise and chronic insufficient nutritional intake leading to suboptimal physical and nutritional conditions. Therefore, these patients are at high risk of undergoing emergency surgery. All of these factors are known risk factors for postoperative morbidity and mortality (16–18). **Chapters 5 and 6** describe a pilot study and a subsequent multicenter study assessing the effect of a new multimodal obstruction treatment aiming to conservatively treat bowel obstruction and optimize preoperative physical and nutritional conditions. Thus reducing the risk of emergency surgery leading to lower postoperative morbidity and mortality. The results showed that the obstruction treatment protocol was successful in preventing emergency surgery in 87-93% of patients. The associated high risks of emergency surgery were subsequently avoided. These patients were treated with a median duration of 20 days. During this time their poor nutritional and physical condition was improved to prepare them for elective surgery. The 30-day mortality of 0% was significantly lower than the national average of 4% in the Netherlands. The percentages of other adverse postoperative outcomes in our study cohort were not significantly higher than in elective patients in the general colon cancer population. This means that despite the bowel obstruction, these patients did not have a higher risk of complications after the obstruction treatment than the average colon cancer patient without bowel obstruction.

## **Part 2, intraoperative: improving intraoperative surgical care**

The first area of interest in the intraoperative domain of this thesis was hypothermia. It has long been known that intraoperative hypothermia increases the risk of surgical site infections (SSI). Guidelines by the World Health Organization (WHO) have been formulated, and temperature management measures (e.g., Bair Hugger system) have been advised by the WHO to address this risk factor (19). Nonetheless, SSIs still occur in 7-18% of patients undergoing colorectal surgery (20–22). The question then remains, are these reported SSI rates the best we can do with current temperature management measures? Or is it a matter of non-compliance to recommendations in the guidelines? To answer these questions, intraoperative hypothermia

and SSI rates in colorectal cancer patients in a hospital in which the Bair hugger system was standard of care to maintain normothermia were assessed and described in **chapter 7**. As core body temperature is a fluctuating variable, it was measured continuously, and four different definitions of hypothermia were used. This allowed a more detailed analysis without loss of data. The findings showed that intraoperative hypothermia and SSI rates were low and could not be associated with each other. Compliance with normothermia seems an effective strategy to reduce SSIs.

Our final area of interest in the intraoperative domain was the Trendelenburg position, which is often used during laparoscopic colorectal surgery to obtain an adequate visual working field. This position is achieved by tilting the patient backward so that the small intestines move cranially due to gravity (figure 1). This position leads to hemodynamic changes that may increase the risk of cardiopulmonary complications and prolonged postoperative hospital stay (23,24). Until recent, there was no alternative to the Trendelenburg position. However, recently an intraoperative retractor sponge has been introduced as an alternative to the Trendelenburg position (25).



**Figure 1.** Trendelenburg position versus the horizontal position.

**Chapter 8** describes a randomized controlled study that randomized 163 patients to either surgery in the Trendelenburg position or surgery in a horizontal position using the retractor sponge to acquire a clear working field. The study was powered for the postoperative length of stay and did not find a significant difference between sponge-assisted surgery and Trendelenburg surgery. Sponge-assisted surgery was also not associated with reduced postoperative morbidity and mortality. Even though there was no significant difference in the primary endpoint between the groups, there might be some advantages to sponge-assisted surgery. It is a more comfortable ergonomic position for the surgeon due to the horizontal positioning of the patient which makes the handling of laparoscopic instruments easier. Another advantage might be the prevention of cephalad excursion (i.e. sliding) of the patient while angled downwards. This is especially an issue in obese patients or at steep angles. Sliding can cause dermal and

neuropathic injuries (26,27). Sliding prevention devices, similarly, have associated risks, such as neuromuscular injury (most notably brachial plexus) in the case of shoulder braces and headrests (27).

### **Part 3, postoperative: improving postoperative surgical care**

The standard ERAS guideline approach for postoperative management of patients has done much to improve postoperative surgical care. However, now that the population of colorectal cancer patients is increasing due to an aging population and new surgical and anesthesiological insights offer new possibilities for the treatment of this older population, a re-evaluation of postoperative surgical care seems necessary. Elderly colorectal cancer patients are at increased risk of postoperative morbidity and mortality, even in the current climate where ERAS guidelines have become the standard of care (28–30). As the hemodynamic status of the elderly patient is less stable, we hypothesized that increased monitoring in the first 24 hours after surgery might lead to faster interventions, preventing further deteriorating of the patient. Routine ICU admission of patients aged 80 years or older for the first postoperative night might be a valuable addition to the use of ERAS guidelines in daily practice. **Chapter 9** describes the study that tested this hypothesis. In 125 out of 242 patients who were admitted to the ICU for routine monitoring, a significant reduction ( $p = 0.02$ ) was found in the composite endpoint (30-day mortality, serious complications, and readmission). Given the high costs of an ICU admission, the cost-effectiveness of this intervention was also relevant. The study showed that the 9% reduction of serious complications in the ICU cohort is sufficient to offset the additional costs of routine overnight ICU admission for every patient aged 80 years or older. This intervention, therefore, seems to conform to the Value-Based Healthcare ideal of “higher quality of care, for equal or lower costs.”

### **Strengths**

A strength of the studies in chapters 3, 4, 7, and 9 is that the prospectively collected and high-quality national Dutch ColoRectal Audit (DCRA) database was used (3). The DCRA database is currently the best source of population-based surgical colorectal cancer data in the Netherlands and provides an accurate picture of the daily practice. Case-ascertainment was 95%, and external data verification with the Dutch Cancer Registry showed high concordance of data items (31).

**Table 1.** Main conclusions of this thesis

Chapter	Main conclusion
<b>Part 1: preoperative</b>	
2	This narrative review shows an overview of optimization methods for elderly colorectal cancer patients.
3	Emergency surgery for colon cancer is associated with a significantly increased risk of long-term mortality compared to elective surgery.
4	Open surgery in colorectal cancer patients is associated with a significantly increased long-term mortality compared to minimally invasive surgery.
5, 6	The obstruction protocol prevented emergency surgery in most patients with bowel obstruction and reduced postoperative morbidity and mortality.
<b>Part 2: intraoperative</b>	
7	In a hospital where temperature management is standard care, intraoperative hypothermia and surgical site infection rates in patients undergoing colorectal cancer surgery were low. Compliance with normothermia seems an effective strategy to reduce surgical site infections.
8	Preventing the Trendelenburg position by using sponge-assisted surgery in the elective setting using the laparoscopic or robotic approach is not associated with shorter postoperative length of stay or reduced postoperative morbidity and mortality.
<b>Part 3: postoperative</b>	
9	Routine overnight ICU is associated with reduced risk of postoperative mortality and morbidity and seems to be cost-effective.

*A summary of the main study questions of this thesis can be found in table 1 in the introduction.*

A strength of the studies in chapters 5 and 6 is that we provided tailor-made exercise instructions that could be easily performed by the patients themselves at home. Previous studies have shown that home-based interventions (32) with moderate-intensity exercise may be the optimal approach in terms of effectivity and patient adherence in the elderly patient (33,34).

A strength of the SPONGE trial (chapter 8) is the used TwiCs design. Firstly, enrolment in the trial was facilitated by embedding it in an existing cohort. Due to the staged informed consent, where patients consent to broad randomization at cohort enrolment, patients eligible for the Sponge trial could be systematically approached, which facilitated fast and efficient trial enrolment. This way, we were able to enroll the complete trial population of 163 individuals in a single center within 41 months (Nov 2015 – Dec 2016 and Jan 2018 – May 2021). As such, a high proportion of eligible patients was recruited in the trial, improving the generalizability of the results. In addition, the patient-centered staged informed consent procedure allowed that only patients allocated to the intervention arm needed to be informed about the Sponge

intervention. As such, control patients did not receive information that was not relevant to them. This eliminates the risk of disappointment (bias) that is sometimes seen in classic RCTs when patients, who are eager to get a new, experimental intervention, are allocated to the control arm.

## Limitations

Limitations of the studies in chapters 3 and 4 were the inherent risk of bias in a nonrandomized retrospective comparison. Secondly, specialized colorectal surgeons operated on all patients, however, case-load data per surgeon and timing of surgery (i.e., day/night) were not available. Thirdly, as mentioned before, surgeon judgment as a factor in decision making can lead to confounding by indication and is extremely difficult to account for in a retrospective manner.

A limitation of the studies in chapters 5 and 6 is that these were uncontrolled observational studies and as such, we cannot claim statistical significance in our results. Data regarding adherence by patients to the obstruction treatment was not collected in these studies. Furthermore, since the obstruction treatment was a multimodal protocol, the individual effect of the physical exercise or the nutritional interventions cannot be evaluated separately.

Downside of the TwiCs design in chapter 8 is the impossibility to blind patients in the intervention arm, as the staged informed consent procedure requires asking for second informed consent after patients have been randomized to the intervention arm. This may potentially influence their (health-related) behavior (Hawthorn effect) (35). Since we saw no effect in hospital stay (the primary endpoint) in this trial, we think that is it very unlikely that the absence of blinding influenced the outcomes. In this study, the Trendelenburg position was not standardized. It was not possible to set the operating table at exactly the same angle for the Trendelenburg position in all patients. Therefore it is possible that some patients underwent Trendelenburg surgery in a steeper incline than others. However, this was a pragmatic trial, in which we estimated the effect of the introduction of a retractor sponge in daily practice. Also, since ours was a single-center RCT, the generalizability of the study results may be somewhat limited due to differences in perioperative care or differences in demographic characteristics of the patients between different hospitals.

## Further research

### *Prehabilitation*

Colorectal cancer surgery is typically performed in elderly patients who are at higher risk of adverse surgical outcomes. Especially frail older patients with several comorbidities are at increased risk. The concept of improving pre-operative parameters of the patient to improve postoperative outcomes has proven successful in several surgical subspecialties and clinics around

the world. For example, treating iron deficiency anemia or improving physical condition using exercise programs (36). An example in this thesis is the obstruction treatment study in chapter 6, which was conducted in two centers and showed excellent results after prehabilitation of a vulnerable subgroup of colorectal cancer patients. Ongoing research is needed to further verify these results in a larger multicenter setting, preferably international. Future studies should also focus on exploring innovative and cost-effective prehabilitation approaches and their implementation strategies in daily practice. As multimodal prehabilitation finds more widespread adoption it will mean that more and more previously inoperable patients become operable by reducing frailty. Research is necessary to assess the outcomes in this newfound surgical population.

### *Continuous quality improvement cycle*

To improve the quality of care it is important to regularly analyze outcomes at the individual surgeon level. Immediate feedback is the most effective way of improving clinical skills, however, due to practical limitations, it is more pragmatic for some hospitals to have a meeting every few months in which data is reviewed by the surgeons. Several world-renowned clinics such as the Martini Klinik in Germany, the Cleveland and Mayo clinics in the United States and the Santeon Consortium of hospitals in the Netherlands have achieved their success in great part due to continuous quality improvement programs (37–39). For example, the Martini Klinik has six-monthly meetings in which outcomes at the individual surgeon level are analyzed, both for junior and senior faculty members. Surgeons received individual counseling by the department chair. Those with higher than expected complication rates were asked to assist in operations with more experienced surgeons, while surgeons with excellent results were asked to observe those colleagues with less strong results during their next operations. Another example is the Dutch Santeon consortium, which consists of seven teachings hospitals who deliver 11% of the nation's hospital care (40). These seven hospitals work together to measure and compare outcomes, costs and relevant process indicators across several patient disease groups. In doing so Santeon created a learning community of hospitals in which clinician level data could be shared transparently and value-based improvements are possible.

These continuous quality improvement programs will improve surgical outcomes and disseminating this knowledge of improved surgical treatments through high-quality studies will lift the quality of healthcare as a whole.

### *Value-Based Healthcare*

This thesis used Value-Based Healthcare concepts such as measuring outcomes and costs for every patient and assessing quality over the full cycle of care. Several quality improvement initiatives described in this thesis have been implemented in other Santeon hospitals participating in the Santeon Value-Based Healthcare initiative for colorectal cancer (38). However, several aspects

of Value-Based Healthcare have not been addressed in this thesis. To realize the full potential of Value-Based Healthcare, healthcare providers should also implement other components as formulated by Porter et al (4). For colorectal cancer in the Netherlands we believe the following items are most relevant:

*Organize into integrated practice units (IPUs):* Care should be organized around the patient, not the other way around. Traditionally, the patient would see the gastroenterologist for a colonoscopy, then go to the radiology department for a CT scan, then go to the surgeon to discuss surgical treatment or the oncologist to discuss chemoradiation treatment. All these different specialists have weekly multidisciplinary meetings with each other, but they are still members of separate departments. Porter et al suggest integrating all these services and specialists in a single practice unit (39). This would mean that the colorectal cancer patient would only need to go to the colorectal cancer IPU where specialists are aligned around the care of a single diagnosis. This will provide valuable insights to the physicians will be able to see beyond their own subdomain they are responsible for. For example, surgeons will be better informed or even feel accountable for stoma-related complications that they normally would not see. This includes non-surgical stoma-related complications that the stoma care nurse would otherwise see (e.g. superficial wound infection) or the internal medicine physician (e.g. dehydration). Shared accountability might also enable more direct feedback and relevant discussions between different specialists. Centers like the Martini Klinik in Germany and the Karolinska University Hospital in Sweden that have an IPU organizational structure have seen improved patient and physician satisfaction. The Martini Klinik exclusively focuses on prostate cancer care and has, compared to the German average, incontinence rates that are 11 times lower, severe erectile dysfunction that is 55% lower, complication rates that are 15 times lower for urethral injury and 62 times lower for sepsis (41).

*Integrate care delivery across separate facilities:* The complexity of treatment should be appropriate for the facility in which it is performed. Very complex procedures should be performed in academic centers that have high resource facilities. And less complex treatment like postoperative stoma care or physiotherapy should be performed in low resource facilities and preferably closer to home. The infrastructure and protocols between these facilities should be integrated across the different locations. The IPU should be responsible for the full cycle of care across these different facilities.

*Build an enabling information technology platform:* To implement the different Value-Based Healthcare components it is vital to have a supporting information technology platform. Unfortunately, the IT systems used in hospitals in the Netherlands vary greatly, with Chipsoft (HiX) and EPIC having the greatest market share followed by a few smaller companies. Just like the organizational structure of an IPU, the IT system should be centered around the



patient and not siloed by department, location, or type of data. Ideally, the IT system follows the patient across the full cycle of care, starting from the referring general physician and continuing through the hospitalization, outpatient visits, and postoperative revalidation. It uses common data definitions facilitating easy data transfer across the whole system and enables easy data extraction for audits like the Dutch Colorectal Audit (DCRA). Unfortunately, data extraction and data validation for audits like the DCRA is currently still being done manually which is a time-consuming process. As of this writing, the ideal IT system still does not exist in the marketplace.

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**AP**

# Appendices



Dutch summary (nederlandse samenvatting)

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## NEDERLANDSE SAMENVATTING

Wereldwijd, en in Nederland, is darmkanker de derde meest voorkomende vorm van kanker (1,2). In Nederland is het de op een na meest voorkomende doodsoorzaak als gevolg van kanker (2). De enige manier om volledig te genezen van deze ziekte is een operatie waarbij een stuk darm met daarin de tumor wordt weggesneden. In de afgelopen decennia zijn er een aantal belangrijke verbeteringen doorgevoerd bij darmkankerchirurgie. Een aantal voorbeelden zijn de invoering van kijkoperaties in plaats van een operatie met een grote incisie in de buik, fast track chirurgie (zo weinig mogelijk wachttijd) en het Enhanced Recovery After Surgery (ERAS) protocol die de zorg direct na de operatie heeft verbeterd (3). Ondanks deze verbeteringen is darmkankerchirurgie tot op heden nog steeds een gebied met een relatief hoog percentage van postoperatieve complicaties en sterfte in vergelijking met chirurgie in andere delen van het lichaam (4). Verder zien we ook grote verschillen tussen ziekenhuizen. In 2018 varieerden postoperatieve complicaties en sterfte tussen ziekenhuizen in Nederland respectievelijk van 14% tot 21% en van 1,2% tot 3,1% (5). Dit betekent dat de kwaliteit van zorg niet consistent is en dat er aanzienlijke verschillen zijn tussen ziekenhuizen. Kwaliteitsverbetering is daarom noodzakelijk, waarbij ziekenhuizen van elkaar zouden moeten leren.

Daarnaast komt darmkanker ook vaak voor bij oudere patiënten die vaak kwetsbaarder zijn en sneller complicaties hebben na de operatie. Vanwege de vergrijzing zal het aantal darmkankerpatiënten alleen maar toenemen in de toekomst waardoor de zorgkosten en de druk op het gezondheidssysteem zullen stijgen. Er valt dan ook nog veel winst te behalen, zowel qua kwaliteit als efficiëntie van zorg, om te komen tot kwalitatief hoogwaardige maar ook betaalbare chirurgische zorg voor darmkanker. Een mogelijke oplossing hiervoor wordt gegeven door Michael Porter et al. in hun artikel “The Strategy That Will Fix Health Care” (6). Hierin beschrijven ze dat het verbeteren van de kwaliteit van zorg ook zal leiden tot minder kosten. Kwaliteit wordt door Porter dan ook gedefinieerd als gezondheidsuitkomsten gedeeld door de kosten om die gezondheidsuitkomsten te behalen; dit noemen ze Value Based Health Care.

Dit proefschrift richt zich op kwaliteitsverbetering van de chirurgische zorg van patiënten met darmkanker in de drie stadia van behandeling: preoperatief, intra-operatief en postoperatief. In de preoperatieve fase evalueerden we de lange termijn effecten van open chirurgie en spoed chirurgie. We hebben ook behandelingen geëvalueerd die de voedingstoestand en de fysieke conditie verbeteren in de preoperatieve fase. In de intra-operatieve fase hebben we onderzoek gedaan naar hypothermie tijdens de operatie en een nieuw medisch hulpmiddel om de positionering van de patiënt tijdens de operatie te verbeteren. Tot slot werd in de postoperatieve fase het effect van verbeterde monitoring van de patiënt en de kosteneffectiviteit daarvan geëvalueerd. De resultaten zijn hieronder samengevat.

## Deel 1, preoperatief: patiënten optimaal voorbereiden op de operatie

In het verleden rapporteerden studies dat bij darmkankerpatiënten die ouder zijn dan 75 jaar, het risico op postoperatieve complicaties en sterfte ongeveer verdubbelde vergeleken met patiënten jonger dan 75 jaar (7,8). Dit leidt tot een tendens om curatieve chirurgie voor de oudere patiënt achterwege te laten. Aangezien darmkanker een ziekte is die vooral bij oudere patiënten voorkomt, zou dit betekenen dat een groot gedeelte van alle darmkankerpatiënten niet de behandeling krijgt om volledig te genezen. In **hoofdstuk 2** staat een overzicht van meer recente studies, die indrukwekkende verbeteringen hebben laten zien in de postoperatieve uitkomsten bij deze patiënten (9). Het eerder geconstateerde verschil in postoperatieve overleving tussen jongere en oudere darmkankerpatiënten is aan het verdwijnen (10). Darmkanker chirurgie kan veilig worden uitgevoerd zonder een toegenomen risico op postoperatieve complicaties en sterfte. Verschillende veranderingen in de afgelopen decennia hebben geleid tot deze verbetering van de resultaten. Bijvoorbeeld de opkomst van minimaal invasieve chirurgie, eerst in de vorm van laparoscopische chirurgie en nu robot geassisteerde chirurgie. Andere factoren die bijdragen aan betere resultaten zijn nieuwe anesthesiologische technieken, vroege postoperatieve mobilisatie en perioperatieve zorg gericht op voeding, elektrolyten en vochtbalans. De belangrijkste bijdrage zou echter het inzicht kunnen zijn dat een multidisciplinaire aanpak van het grootste belang is en dat er mogelijk acties nodig zijn om patiënten beter voor te bereiden op een operatie.

Spoedchirurgie en open chirurgie zijn beide bekende risicofactoren voor ongunstige postoperatieve korte termijn uitkomsten (11,12). De langetermijneffecten van deze risicofactoren hebben minder aandacht gekregen in de wetenschappelijke literatuur en zijn moeilijker te bestuderen in de setting van een gerandomiseerde gecontroleerde studie (RCT). Daarnaast zijn de voordelen van electieve en laparoscopische chirurgie al aangetoond en is het daarom onethisch om patiënten te randomiseren naar een electief/spoed cohort of laparoscopisch/open cohort. Andere nadelen van RCT's zijn dat de follow-upduur vaak beperkt is en de studiepopulatie meestal een heel specifieke groep is. Longitudinale observationele studies (op populatieniveau) lijken daarom beter geschikt om de lange termijn effecten van spoedchirurgie en open chirurgie te onderzoeken. Dit soort studies includeren namelijk ook hoog-risico patiënten met een hoger aantal events, gebeurtenis waar we in geïnteresseerd zijn, en geven daarom een beter beeld van de dagelijkse praktijk. **Hoofdstuk 3 en 4** zijn beide longitudinale observationele studies die de lange termijn implicaties van spoedchirurgie en open chirurgie onderzoeken. In hoofdstuk 3 wordt het effect van een spoedoperatie op de lange termijn uitkomsten gerapporteerd bij 1139 darmkankerpatiënten. De bevindingen van deze studie laten zien dat een spoedoperatie niet alleen leidt tot slechtere uitkomsten op de korte termijn, maar ook geassocieerd is met een significant verhoogd risico op mortaliteit op de lange termijn en dat dit risico toeneemt over langere perioden. In hoofdstuk 4 wordt het effect

van open chirurgie op de uitkomsten op de lange termijn gerapporteerd bij 4531 patiënten met darmkanker in drie centra. In deze studie werd aangetoond dat open chirurgie, net als spoedoperaties, geassocieerd is met verhoogde mortaliteit op de lange termijn.

Een andere belangrijke indicator voor een goed herstel van de patiënt is tegenwoordig niet de leeftijd, maar de kwetsbaarheid van de patiënt. Aangezien slechts een minderheid van de oudere darmkankerpatiënten kwetsbaar is, is een snelle kwetsbaarheidsbeoordeling van cruciaal belang om in het besluitvormingsproces de fitte van de kwetsbare patiënten te onderscheiden (13). Het blijkt ook in sommige gevallen mogelijk te zijn om een kwetsbare patiënt minder kwetsbaar te maken. Het gebruik van prehabilitatieprogramma's kan dan ook leiden tot significante verbeteringen in de fysieke en voedingstoestand voorafgaand aan de operatie en dus ook een betere uitkomst na de operatie (14,15).

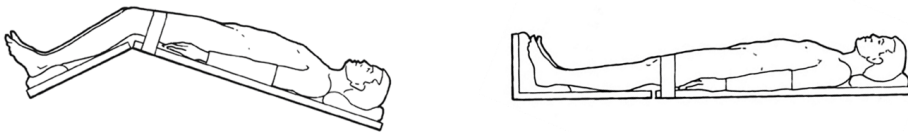
Zoals eerder vermeld is spoedchirurgie een risicofactor voor toegenomen mortaliteit op zowel de korte termijn als de lange termijn. Het leek hierbij dat een spoedoperatie niet te voorkomen was, maar op basis van moderne inzichten blijkt een spoedoperatie vaker voorkomen te kunnen worden dan vroeger werd gedacht. Mits er voorafgaande aan de operatie individuele aandacht en zorg wordt gegeven. Een duidelijk voorbeeld van het veranderen van een spoed patiënt in een electieve patiënt zien we bij patiënten met een darmobstructie.

Darmobstructie komt voor bij 8-29% van de patiënten met darmkanker (16,17). Deze patiënten lopen een verhoogd risico om een spoedoperatie te ondergaan. Ze hebben vaak een slechte fysieke conditie omdat ze weinig bewegen en door de darmobstructie wordt de voeding minder goed opgenomen waardoor ze vaak ook ondervoed zijn. Al deze factoren zijn bekende risicofactoren voor postoperatieve complicaties en sterfte (18–20). **Hoofdstuk 5 en 6** bevatten een pilotstudie en een daaropvolgende multicenter studie waarin is gekeken of een nieuwe behandeling voor darmobstructie spoedoperaties kan voorkomen en daardoor het risico op postoperatieve complicaties en sterfte kan verminderen. Deze studies toonden aan dat bij 87-93% van de patiënten een spoedoperatie kon worden voorkomen en dat patiënten voorafgaand aan een geplande operatie konden worden geprehabiliteerd. Op die manier konden de hoge risico's van een spoedoperatie worden vermeden. De 30-dagen sterfte van 0% was significant lager dan het landelijk gemiddelde van 4% in Nederland. De percentages van andere ongunstige postoperatieve uitkomsten in ons studiecohort waren niet significant hoger dan bij electieve patiënten in de algemene darmkankerpopulatie. Dit betekent dat ondanks de darmobstructie, deze patiënten na de behandeling geen hogere risico op complicaties hadden dan de gemiddelde darmkankerpatiënt.

## Deel 2, intra-operatief: verbetering van de intra-operatieve chirurgische zorg

Het eerste gebied van interesse in het intra-operatieve domein van dit proefschrift was hypothermie. Het is al geruime tijd bekend dat intra-operatieve hypothermie het risico op wondinfecties verhoogd. De Wereldgezondheidsorganisatie heeft richtlijnen opgesteld voor het voorkomen van hypothermie en maatregelen geadviseerd voor temperatuurbeheersing, zoals het Bair-Hugger-systeem (21). Niettemin komen wondinfecties nog steeds voor bij 7-18% van de patiënten die darmkankerchirurgie ondergaan (22–24). De vraag is dan ook of we deze wondinfectiepercentages, met de huidige uitgebreide temperatuurbeheersmaatregelen, nog kunnen verbeteren. Of is dit relatieve hoge percentage wondinfecties een kwestie van het niet naleven van de aanbevelingen in de richtlijnen? Om deze vragen te beantwoorden werd intra-operatieve hypothermie en het aantal wondinfecties bij patiënten met darmkanker onderzocht in een ziekenhuis waar het Bair-Hugger systeem de standaardzorg was om normothermie te handhaven. Deze studie wordt beschreven in **hoofdstuk 7**. Omdat de kerntemperatuur een fluctuerende variabele is, werd de kerntemperatuur continu gemeten tijdens de operatie en werden vier verschillende definities van hypothermie gebruikt. De bevindingen van deze studie toonden aan dat intra-operatieve hypothermie en wondinfectie zeer weinig voorkomen en niet met elkaar in verband konden worden gebracht. Naleving van normothermie lijkt een effectieve strategie om wondinfecties te verminderen.

Het laatste aandachtsgebied in het intra-operatieve domein in dit proefschrift is de Trendelenburg positie. Deze positie wordt vaak gebruikt tijdens darmkankerchirurgie en zorgt ervoor dat de dunne darm naar het hoofdeinde van de patiënt verplaatst wordt door de patiënt naar achteren te kantelen (figuur 1). De Trendelenburg positie kan leiden tot hemodynamische veranderingen die het risico van cardiopulmonaire complicaties en een verlengd postoperatief verblijf in het ziekenhuis kunnen verhogen (25,26). Tot voor kort was er geen alternatief voor de Trendelenburg positie. Recent is echter een intra-operatieve retractorspons geïntroduceerd als alternatief voor de Trendelenburg positie (27).



**Figuur 1.** Trendelenburg positie versus de horizontale positie.

In **hoofdstuk 8** wordt een gerandomiseerde gecontroleerde studie beschreven waarbij patiënten werden gerandomiseerd naar ofwel chirurgie in de Trendelenburg positie of chirurgie in een horizontale positie met behulp van de retractorspons om een vrij werkveld te verkrijgen. De studie was gericht op de postoperatieve verblijfsduur en er werd geen significant verschil gevonden tussen de twee groepen. Er werd ook geen verschil gezien tussen de groepen met betrekking tot postoperatieve morbiditeit en mortaliteit. Ook al werd er geen significant verschil gezien tussen de groepen, kunnen er toch voordelen zijn bij het gebruik van de retractorspons. De eerste is een meer comfortabele en ergonomische positie voor de chirurg vanwege de horizontale positionering van de patiënt, waardoor het hanteren van laparoscopische instrumenten makkelijker wordt. Het tweede voordeel zou kunnen zijn het voorkomen van het glijden van de patiënt terwijl deze naar beneden gekanteld is. Dit is vooral een probleem bij obese patiënten of bij steile hoeken. Glijden kan huid- en neuropathische verwondingen veroorzaken (28,29). Hulpmiddelen voor het voorkomen van glijden brengen eveneens risico's met zich mee, zoals neuromusculair letsel (met name de plexus brachialis) in het geval van schouderbraces en hoofdsteen (29).

### **Deel 3, postoperatief: verbetering van de postoperatieve chirurgische zorg**

De Enhanced Recovery After Surgery (ERAS) onderzoeksgroep heeft sinds 2001 meerdere ERAS richtlijnen opgesteld die veel hebben bijgedragen aan de verbetering van de postoperatieve chirurgische zorg. Echter, nu de populatie darmkankerpatiënten vanwege de vergrijzing steeds groter wordt en nieuwe chirurgische en anesthesiologische inzichten nieuwe mogelijkheden bieden voor de behandeling van deze oudere populatie, lijkt het opnieuw evalueren van de postoperatieve chirurgische zorg noodzakelijk. Oudere patiënten met darmkanker hebben meer kans op postoperatieve complicaties en mortaliteit, zelfs in het huidige klimaat waarin ERAS richtlijnen de zorgstandaard zijn geworden (30–32). De hemodynamische status van de oudere patiënt is minder stabiel dan die van een jongere patiënt. De hypothese hierbij is dat intensievere monitoring in de eerste 24 uur na de operatie zou kunnen leiden tot snellere interventies, waardoor een verdere verslechtering van de toestand van de patiënt zou kunnen worden voorkomen. Routinematige IC opname van patiënten van 80 jaar of ouder voor de eerste postoperatieve nacht zou daarom een waardevolle aanvulling kunnen zijn op het gebruik van ERAS richtlijnen in de dagelijkse praktijk. **Hoofdstuk 9** beschrijft de studie waarbij deze hypothese getest is. Bij 125 van de 242 patiënten die voor intensieve monitoring op de IC werden opgenomen, werd een significante reductie ( $p = 0,02$ ) gevonden in het samengestelde eindpunt (30-dagen mortaliteit, ernstige complicaties en heropname). Gezien de hoge kosten van een IC-opname was de kosteneffectiviteit van deze interventie ook relevant. De studie toonde aan dat de geobserveerde vermindering van ernstige complicaties met 9% in het IC-cohort voldoende is om de extra kosten van routinematige overnachting op de IC

te compenseren voor elke patiënt van 80 jaar of ouder. Deze interventie lijkt dus te voldoen aan het Value-Based Health Care ideaal van “hogere kwaliteit van zorg, voor gelijke of lagere kosten.”

Conclusie

Tabel 1. Belangrijkste conclusies van deze thesis

Hoofdstuk	Belangrijkste conclusie
Deel 1: preoperatief	
2	Deze narrative review toonde een overzicht van optimalisatie voor darmkankerchirurgie bij de oudere patiënt.
3	Spoedchirurgie voor dikkedarmkanker wordt geassocieerd met een significant verhoogde lange termijn mortaliteit in vergelijking met electieve chirurgie.
4	Open chirurgie bij patiënten met darmkanker is geassocieerd met een significant verhoogde lange termijn mortaliteit in vergelijking met minimaal invasieve chirurgie.
5, 6	Het obstructieprotocol kon bij de grote meerderheid van de patiënten met darmobstructie een spoedoperatie voorkomen en daarmee de postoperatieve morbiditeit en mortaliteit verminderen. Het obstructieprotocol lijkt een veilige en efficiënte alternatief te zijn voor spoedchirurgie.
Deel 2: intra-operatief	
7	In een ziekenhuis waar temperatuurbeheersing standaardzorg is, waren de percentages intra-operatieve hypothermie en wondinfecties bij patiënten die darmkankerchirurgie ondergingen laag. Handhaving van normothermie lijkt een effectieve strategie om wondinfecties te verminderen.
8	Het voorkomen van de Trendelenburg positie door de toepassing van sponsgeassisteerde chirurgie in de electieve setting met de laparoscopische of robotische benadering, is niet geassocieerd met een kortere postoperatieve opnameduur of verminderde postoperatieve morbiditeit en mortaliteit.
Deel 3: postoperatief	
9	Routinematige IC-opname is geassocieerd met een verminderd risico van postoperatieve mortaliteit en morbiditeit en lijkt kosteneffectief te zijn.

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## CURRICULUM VITAE

Milad Fahim was born in Kabul, Afghanistan in 1991 and is the eldest of three children. Due to the civil war, he moved with his family to the Netherlands at the age of three. Milad spent most of his youth in Arnhem, where he graduated from the Olympus College. He started with Medical School at the Radboud University in Nijmegen in 2010.

After having obtained his bachelor's degree, Milad took a gap year in which he interned at the Red Cross War Memorial Children's Hospital in Cape Town, South Africa. In the same year, he was also one of the cofounders of Synergy Apps, a company that developed and sold medical apps in the Apple store. During his master's studies, Milad joined the research group of prof H. Van Goor at the Surgery Department, University Medical Center Nijmegen, to conduct research on medical innovations in surgical care. He also worked at the Refugee Health Center as a triage assistant for refugees in the Netherlands requiring healthcare. After obtaining his medical degree in 2017, he started his PhD research on the quality of care in colorectal cancer surgery at the St. Antonius Hospital, supervised by prof. D. Biesma, dr. Smits, and dr. Dijkman. He was also the project leader for the colorectal cancer quality improvement team of the hospital, which implemented several quality improvement projects, some of which gained national attention and were implemented in other hospitals in The Netherlands. During this time, he was also a board member of the St. Antonius PhD students association.

In 2020 he participated in professor Porter's Value Based Health Care course at Harvard Business School, Boston, USA. In the same year, he also obtained his second master's degree at the University of Amsterdam, where he took the Evidence Based Practice in Healthcare study, which allowed him to register as a clinical epidemiologist. He finished his PhD in 2022 and currently is working as a physician at the Surgery Department at the St. Antonius hospital.



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