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# Chapter 9

Colonic stenting versus emergency surgery for acute left-sided malignant colonic obstruction: a multicentre randomised trial (Stent-in 2 study)

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## Abstract

**Background:** Colonic stenting as bridge to elective surgery is becoming an increasingly popular alternative for emergency surgery as treatment of acute malignant colonic obstruction. We undertook a multi-centre randomised trial comparing colonic stenting with emergency surgery in patients with acute obstructive colorectal cancer.

**Methods:** Twenty-eight hospitals in the Netherlands participated. Patients were eligible if presented with obstructive symptoms existing less than one week and imaging compatible with a left-sided colorectal cancer. After informed consent patients were randomised to either endoscopic stent placement or emergency surgery. The primary outcome parameter was global health status during six months follow-up. Secondary outcome parameters were disease-specific and generic quality of life, morbidity, mortality and stoma rate. Group size was calculated based on the primary outcome parameter. Using a two-group t-test with a 0.05 two-sided significance level, 60 patients per arm were needed to detect an effect size of 0.5 on the EORTC QLQ-C30 global health scale with 80% power. Analysis was by intention-to-treat.

**Results:** Between March 2007 and September 2009, 98 patients with acute left-sided malignant colonic obstruction were randomly assigned to stent placement (n=47) or emergency surgery (n=51). Treatment was initiated within 24 hours after randomisation. The study was terminated early, following advice of the Data Safety Monitoring Committee (DSMC) because of an absolute risk increase of morbidity in the stent arm. At study termination 98 of the planned 120 patients had been randomised. No differences between emergency surgery and colonic stenting in response to treatment were observed regarding global health status (-4.7, p=0.36), 30 days mortality (Chi2=0.02, p=0.89), overall mortality (Chi2=0.04, p=0.84), morbidity (Chi2=0.64, p=0.43) and stoma rates at latest follow-up (Chi2=0.87, p=0.35). The only differences observed were a lower stoma rate directly after initial intervention (Chi2=5.8, p=0.016) and more frequently reported stoma-related problems (-12, p=0.046) in the colonic stenting group.

**Interpretation:** Colonic stenting as bridge to surgery has no decisive clinical advantages to emergency surgery in colorectal cancer patients with acute left-sided colonic obstruction. A persistent trend of increased 30 days morbidity in the colonic stenting group urged the DSMC to stop the trial prematurely. (ISRCTN46462267)

## Introduction

Colorectal cancer is the third most common cancer in men and the second most common cancer in women in Europe, with a total of 412.900 new cases and 207.400 deaths in 2006.<sup>1</sup> Between 7 and 29% of patients with colorectal cancer will present with a sub-total or total bowel obstruction.<sup>2;3</sup> Conventionally these patients are treated with emergency surgery to restore luminal patency. Emergency operations, involving an unprepared and obstructed bowel, are reported to have a mortality rate of 15-34% and a morbidity rate of 32-64% despite advances in perioperative care.<sup>3-7</sup> A variety of surgical techniques is applied to treat this condition. Mostly, an ostomy is fashioned. In many patients the ostomies will not be closed.<sup>2;5</sup> Patients with a permanent stoma do frequently report complications and lower health-related quality of life than comparable patients without colostomy; in addition they require costly stoma materials.<sup>8-12</sup>

Since the early 1990s colonic stenting has been introduced to restore luminal patency in patients with malignant obstruction of the left-sided colon. Stenting can be applied as a preoperative treatment to prepare patients for elective surgery as well as a definitive palliative procedure in patients with incurable disease or inoperable patients.<sup>13</sup> In uncontrolled studies stent placement before elective surgery (also known as "bridge to surgery") has been suggested to improve the patients' clinical condition and to decrease mortality, morbidity and number of colostomies.<sup>3-6;14;15</sup> Additionally this temporary procedure gives the opportunity to perform accurate tumour staging, leading to avoidance of surgery in patients with disseminated disease or unacceptable surgical risk. In these patients the colonic stent may serve as permanent palliation. A systematic review by Sebastian et al. of 54 uncontrolled trials and case reports on placement of self-expandable metal stents revealed a technical success rate of 68-97% and a clinical success rate of 71.7% when used as bridge to surgery.<sup>13</sup> Major complications related to stent placement included perforation (4%), stent migration (11.8%) and re-obstruction (7.3%), causing a cumulative mortality of 0.58%.<sup>13</sup> It has to be underlined that stent perforation is not only a severe acute complication but may also lead to peritoneal tumour spill, changing a potentially curable disease in an incurable one.

It is important to realise that stenting so far has mainly been done by experts in tertiary centres and the published results are mostly retrospective and/or uncontrolled, subject to selection bias and not including learning curves. Notwithstanding a growing body of literature data, at the present a randomised prospective trial comparing the efficacy of treatment with colonic stenting before elective surgery against emergency surgery for malignant acute colorectal obstruction is lacking.<sup>14-18</sup> The objective of this multicentre randomised trial was to finally get grade A evidence and confirm the promising data of uncontrolled series. We compared both treatment strategies in a randomised fashion with respect to global health, disease-specific and generic quality of life, morbidity, mortality and stoma rate. The study was performed by the Dutch Stent-In study group

who previously reported a randomised study on colonic stenting in incurable malignant colonic obstruction.<sup>19</sup>

## Methods

### Patients

The study population consisted of patients presenting with an acute left-sided colorectal obstruction presumably caused by a colonic malignancy. Inclusion criteria were: clinical signs of severe colonic obstruction existing less than one week with dilation of the colon on either plain abdominal radiograph and typical abnormalities on a gastrografen enema study or contrast enhanced CT-scan. The imaging modalities had to be compatible with a (sub)total malignant colonic obstruction. The obstruction had to be located in the left side of the colon (descending colon, sigmoid or rectum); patients had to be 18 years of age or older and had to sign informed consent. Exclusion criteria were: signs of peritonitis, perforation, fever, sepsis or other serious complications demanding urgent surgery; American Society of Anesthesiologists (ASA) classification IV or V; obstruction caused by a non-colonic malignancy or a benign disease; distal tumour margin less than 10 cm from the anal verge; inability to complete self-report quality of life questionnaires. Recruitment started after approval of the study by the Medical Ethical Committee of the Academic Medical Centre (AMC) in Amsterdam and the local Medical Ethical Committees of every participating centre.

### Study design and randomisation

The study was designed as a multi-centred randomised clinical trial in 28 hospitals in the Netherlands comparing the effectiveness of colonic stenting as a bridge to elective surgery with emergency surgery (standard treatment) during a follow-up period of 6 months. The trial was notified to the Current Controlled Trials register under ISRCTN46462267.<sup>20</sup> Upon informed consent randomisation was performed centrally at the Academic Medical Centre using computer-generated lists prepared by the Department of Clinical Epidemiology and Biostatistics. Lists were constructed with randomly permuted blocks sized 4 or 6 per stratum, in which strata were defined by centre (participating hospital). Treatment was initiated within 24 hours of randomisation in both arms.

### Interventions

Colonic stenting was performed by experienced therapeutic endoscopists, having a track record of at least 20 enteral stents, 10 of which being colonic stents. Before colonic stenting was attempted the distal colon was prepared with an enema. In case a standard colonoscope or sigmoidoscope could traverse the lesion or the lesion appeared to be

benign, stent placement was considered not to be indicated. Because of our intention-to-treat principle these patients were neither crossed over, nor excluded. In case of a significant, probably malignant obstruction a guide wire was passed through the stricture into the proximal colon under fluoroscopic control. Thereafter an uncovered metallic self-expandable stent, 6 or 9 cm long, with a diameter of 22 mm (Enteral Wallstent™ (Boston Scientific, Natick, MA)) was advanced over the guide wire and released. Stents were selected to be approximately 3 cm longer than the lesion (1.5 cm at both sides). Dilation of the obstructive lesion prior to stent placement was not allowed in order to minimise the risk of perforation. If the stent did not cover the entire length of the tumour, a second overlapping stent was placed. Correct positioning of the stent was confirmed by fluoroscopy and endoscopy. If stent placement failed or symptoms of colonic obstruction did not resolve within 3 days, patients were treated surgically, but remained in the stent arm for intention-to-treat analysis. The self-expandable stent served as definitive palliative therapy if any of the following conditions appeared in the diagnostic work-up: patients at high surgical risk because of persistent co-morbidity, advanced local disease and/or incurable metastatic disease. Candidates for elective surgery were operated according to the protocol preferably between day 5 and 14 after inclusion. Type and extent of surgery was at the discretion of the treating surgeon.

In the emergency surgery arm of the study, patients were operated according to conventional standards. Whether a loop colostomy, resection with primary anastomosis with or without ostomy, Hartmann's procedure, (sub)total colectomy with ileostomy or ileorectal anastomosis was performed, was at the discretion of the treating surgeon. After emergency surgery further diagnostic work-up was performed. The colostomy served as a definitive solution if the patient refused re-operation, in case of incurable metastatic disease or when a re-operation was judged to carry an unacceptable risk (ASA class IV or V). In case of a primary colostomy, an attempt at restoration of bowel continuity was performed, preferably within 3-6 months after the initial intervention. After preoperative bowel preparation and administration of antibiotics, according to the individual hospital's protocol, stoma closure was performed in accordance with conventional surgical standards.

## Outcomes measures and assessments during follow-up

The primary outcome parameter was global health status according to the European Organisation for Research and Treatment of Cancer (EORTC) quality of life questionnaire (EORTC QLQ-C30).<sup>21</sup> Secondary outcomes included mortality, morbidity, quality of life other than global health and stoma rate. Stoma rate was added to the secondary outcome parameters after publication of the protocol as it had been omitted in the initial protocol but nevertheless considered important.<sup>20</sup> Mortality was assessed as procedure-related mortality within 30 days post-intervention and as overall mortality including

mortality during follow-up. For morbidity the definition of serious adverse event was used: any event leading to hospital admission or prolonging hospital stay. Complications were defined as all unwanted events, thus including morbidity and other adverse events that did not cause admission or prolonged hospital stay. Oncology-specific and colon cancer-specific quality of life aspects were assessed with respectively the EORTC QLQ-C30 and EORTC QLQ-CR38.<sup>22</sup> Higher scores on the global health and functional scales indicate higher quality of life; higher scores on the symptom scales indicate lower quality of life. In addition, the EQ-5D visual analogue scale was used to assess patients' self-evaluation of health status, with higher scores indicating a better health status.<sup>23</sup> Finally, the EQ-5D health status scoring profiles over time were used to derive estimates of quality-adjusted survival. To this end, published health utility scoring algorithms based on time trade-off elicitation techniques for health status preferences in the general population<sup>24</sup> were used to calculate the number of quality-adjusted life years (QALY). It was assumed that observed health states reflected the health states during the period in-between (the actual and preceding) measurements. Six months of follow-up in perfect health equalled 0.5 QALY. Stoma rates were assessed after completion of the initial treatment (emergency surgery or colonic stent placement followed by surgery), at 30 days and at latest follow-up. Quality of life, morbidity, mortality and stoma rates following the two interventions were assessed until latest follow-up, either death (for exceptions: see below), withdrawal of informed consent or 6 months follow-up, whichever came first. During follow-up patients completed the quality of life questionnaires on weeks 4, 12, and 24 after inclusion. The questionnaires were sent to the patients by post. Collection was done by a research nurse. The research nurse contacted the patients by telephone every two weeks to assess complications, re-interventions, re-admissions, visits to the outpatient clinic and missing items of the collected quality of life questionnaires.

## Sample size and statistical analysis

The sample size calculation was based on the EORTC QLQ-C30 global health status as the primary outcome parameter. Using a two-group t-test with a 0.05 two-sided significance level, 60 patients per arm (or a total of 120 patients) were needed to detect with 80% power an effect size of 0.5 on the EORTC QLQ-C30 global health scale.<sup>25;26</sup> An effect size of 0.5 was chosen because a recent systematic review, based on 38 studies, indicated a "remarkable universality" among estimates of clinical significance that centred around 0.5 effect size.<sup>27</sup> The authors recommend an effect size of 0.5 to serve as a default value for clinically significant change on quality of life measures used with chronic disease patients, when more specific information is missing, as is the case in patients with malignant colonic obstruction. Sloan et al. argue that a 0.5 effect size is even a conservative estimate that is likely to be clinically meaningful.<sup>28</sup> Based on these data an effect size of 0.5 in the present group of patients seemed realistic. Analyses

were undertaken on an intention-to-treat basis. Quality of life scores during follow-up were averaged per patient, weighted by the length of the preceding period in-between measurements. Missing follow-up data were considered to be missing at random. Deceased patients were assigned EQ-5D VAS and health utility scores with value of zero until 6 months post intervention. Unless otherwise stated, differences in (weighted) quality of life scores between the emergency surgery and colonic stenting groups were assessed for statistical significance by analysis of covariance to adjust for baseline scores. Difference in procedure-related (30 days) mortality, overall mortality and stoma rates were assessed by the chi-square test. Differences in survival were assessed by the Kaplan Meier log rank test. All reported p-values are two-sided and considered significant if below 0.05. Analyses were performed with SPSS version 18.0 (SPSS, Chicago, Illinois). A Data Safety Monitoring Committee (DSMC) safeguarded the patients in the trial regarding safety and effectiveness data. Every serious adverse event defined as an event leading to hospital admission or prolonging hospital stay (further addressed as morbidity) and mortality in the experimental arm (colonic stenting) was reported to the DSMC on short notice. An interim analysis was scheduled following the completion of 30 days of follow-up after treatment of the first 60 patients. No formal stopping rule was formulated beforehand.

## Results

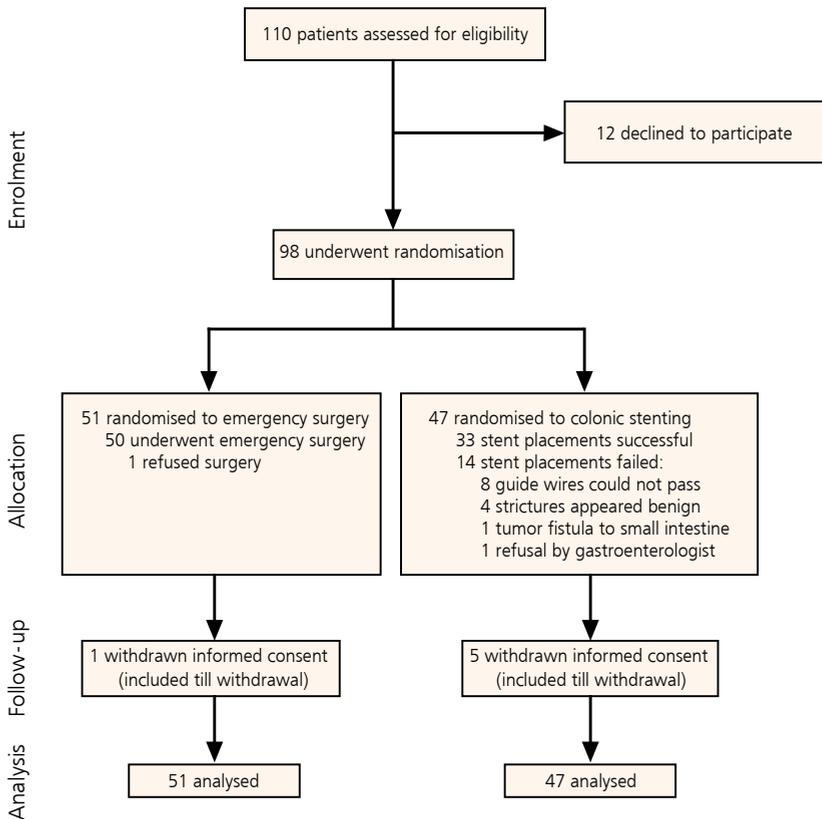
### Enrollment and termination of the trial

Between March 2007 and February 2009, a total of 60 patients had been included. Before the planned interim analysis of these data had been completed, numerous morbidity and some mortality occurred in the colonic stenting arm in the next 30 patients leading to a request of the DSMC to finish the interim analysis of the first 60 patients promptly and prepare an additional analysis as soon as 90 patients had completed the first month of their follow-up. The 90th patient was included in July 2009. After finishing the interim reports, the study was put on hold at the suggestion of the DSMC in September 2009 when the first preliminary data suggested a higher morbidity in the colonic stenting arm. At the time of pausing the study a total of 98 patients had been included. An independent statistician together with the primary investigator analysed the data limited to 30 days of follow-up with regard to procedure-related and in-hospital mortality, complications (including morbidity), and overall morbidity. The causality of all events (mortality and complications) was graded definitely because they occurred within a follow-up of 30 days.

Neither the analysis after 60 patients nor the analysis after 90 patients revealed a significant difference with regard to in-hospital mortality nor 30 days mortality.

However, the number of patients with events graded as morbidity showed a persistent trend against the colonic stenting arm with an absolute risk increase of 0.19 (95% CI -0.06 to 0.4) in the first interim analysis of 60 patients (14/28 colonic stenting patients versus 10/32 emergency surgery patients) and 0.19 (95% CI -0.01 to 0.37) in the second interim analysis of 90 patients (23/47 colonic stenting patients versus 13/43 emergency surgery patients). In addition, when specifically looking at the subgroup of colonic stenting patients who underwent elective surgery a relatively high number of complications was observed. Fourteen out of 26 of these patients experienced one or more complications, 11 of them had at least one event graded as morbidity including 6 patients with anastomotic leakage.

Although the DSMC was well aware of the importance of a completed RCT, particularly because many consider colonic stenting as bridge to surgery the preferred therapy while high grade evidence is lacking, they felt obliged, after counselling an independent external expert, to advice stopping the trial definitely. The trial was officially terminated in March 2010; at that moment all 98 patients had reached an endpoint.



**Figure 1.** Trial profile.

**Table 1. Demographic and clinical characteristics of patients at baseline.**

Characteristic	Emergency surgery N=51	Colonic stenting N=47
Age (years, mean [SD])	71.4 (9.7)	70.4 (11.9)
Men/women	27/24	24/23
ASA classification		
unknown, no. (%)	1 (2)	1 (2.1)
1, no. (%)	17 (33.3)	16 (34)
2, no. (%)	27 (53)	24 (51.1)
3, no. (%)	6 (11.8)	6 (12.8)
Severity of obstruction		
Unknown, no. (%)	1 (2)	1 (2.1)
Incomplete*, no. (%)	14 (27.5)	13 (27.7)
Complete^, no. (%)	36 (70.6)	33 (70.2)

\*Demonstrated by clinical signs of ileus but able to pass flatus.  
^Demonstrated by inability to pass flatus during the last 24 hours before inclusion.

## Patient characteristics

Between March 2007 and September 2009 a total of 98 patients (median age  $\pm$  SD 71  $\pm$  10.8, 51 male) were included in 25 centres.

The flow chart of the study is presented in figure 1 with 51 patients randomised to emergency surgery and 47 to colonic stenting. Two protocol violations occurred, one patient refused emergency surgery and one endoscopist refused endoscopy because of uncertainty about the malignant nature of the stricture. The patient that refused emergency surgery was treated with a colonic stent followed by uneventful elective surgery. The other patient, though randomised to colonic stenting, underwent emergency surgery which was complicated by three events, two of which were graded as morbidity, the pathology report revealed a malignant obstruction. The characteristics of the 98 patients included in the intention-to-treat analysis are presented in table 1.

## Global health and disease-specific quality of life

Table 2 shows the cancer-specific quality of life results at baseline and follow-up for the emergency surgery and colonic stenting groups respectively. Overall global health and function scores at baseline were somewhat lower and symptoms scores were slightly higher in the colonic stenting group. Both groups however responded equally well to treatment without significant differences in follow-up scores after correction for baseline scores. Table 3 shows the colon cancer-specific results. Colonic stenting patients more

**Table 2. Differences between emergency surgery and colonic stenting for quality of life during follow-up, based on available data and corrected for differences at baseline.**

EORTC QLQ-C30 dimension	Emergency Surgery (ES)		Colonic Stenting (CS)	
	Baseline (SD) (N <sub>max</sub> *=42)	Follow-up (SD) (N=44)	Baseline (SD) (N <sub>max</sub> =40)	Follow-up (SD) (N <sub>max</sub> =39)
Global health	42.5 (28.0)	61.4 (21.9)	34.0 (23.2)	63.0 (23.8)
Functioning				
Physical (revised)	75.4 (28.8)	68.9 (24.1)	67.5 (31.3)	67.9 (28.7)
Role (revised)	55.6 (37.8)	57.6 (29.0)	39.6 (39.2)	55.5 (30.0)
Emotional	62.1 (23.3)	78.2 (21.6)	57.7 (26.8)	78.3 (23.5)
Cognitive	75.0 (22.2)	81.3 (17.8)	71.7 (27.0)	82.5 (23.9)
Social	68.7 (33.0)	70.8 (25.8)	62.1 (33.1)	76.3 (25.2)
Symptoms				
Fatigue	57.0 (30.9)	40.2 (22.9)	61.7 (33.9)	42.0 (26.4)
Nausea and vomiting	48.4 (36.2)	11.6 (16.0)	57.1 (34.8)	18.8 (25.7)
Pain	61.9 (32.6)	18.7 (22.7)	72.5 (30.6)	20.9 (24.7)
Dyspnea	20.6 (28.5)	16.9 (25.2)	25.0 (30.0)	17.5 (26.4)
Insomnia	44.4 (38.7)	25.4 (27.7)	60.8 (38.4)	23.6 (30.0)
Appetite loss	60.3 (39.8)	24.6 (26.2)	69.2 (31.5)	21.2 (30.5)
Constipation	84.1 (28.7)	6.6 (11.4)	86.3 (23.8)	12.3 (26.3)
Diarrhea	14.3 (25.7)	11.6 (18.5)	20.0 (32.7)	13.2 (18.7)
Financial difficulties	3.3 (12.5)	8.1 (19.6)	3.3 (10.1)	11.8 (23.8)

frequently reported stoma-related problems during follow-up compared to emergency surgery patients. No differences were noted for other colon cancer-specific dimensions after correction for baseline.

### Self-assessed health status, health utility and quality-adjusted life years

Table 4 shows that emergency surgery and colonic stenting patients rated their health equally high after the intervention and both interventions generated about 0.3 QALY of the maximum attainable 0.5 during the follow-up period. For 18 patients, EQ-5D VAS and health utility scores with a value of zero were imputed after their death.

Corrected follow-up difference	
Difference (95% LCL;UCL) <sup>^</sup> (N <sub>max</sub> =39 ES / 36 CS)	p-value
-4.7 (-14.8; 5.5)	0.36
0.2 (-11.5; 11.9)	0.98
1.0 (-13.3; 15.4)	0.88
-2.2 (-11.7; 7.2)	0.64
-2.0 (-11.6; 7.5)	0.67
-7.5 (-18.7; 3.7)	0.19
-1.6 (-13.1; 9.8)	0.78
7.6 (-9.9; 25.2) <sup>^^</sup>	0.39
-1.5 (-12.3; 9.4)	0.79
-0.9 (-12.6; 10.8)	0.88
-3.1 (-15.9; 9.7)	0.63
5.6 (-7.4; 18.7)	0.39
-3.9 (-12.2; 4.4)	0.36
-3.2 (-11.8; 5.4)	0.46
-2.1 (-11.5; 7.4)	0.67

\* Number of patients with available (i) baseline, (ii) follow-up and (iii) baseline and follow-up data ranges from 41 to 42, 44 to 44, and 38 to 39 in the emergency surgery group and from 39 to 40, 37 to 39, and 34 to 36 in the colonic stenting group, respectively.

<sup>^</sup> Difference ES follow-up minus CS follow-up based on estimated marginal means with baseline values as covariate; LCL: lower confidence limit; UCL: upper confidence limit.

<sup>^^</sup> Difference represents difference in change scores from baseline (ES follow-up – ES baseline) minus (CS follow-up – CS baseline) due to violation of the assumption of equality of error variances in covariance analysis.

## Mortality and morbidity

No differences in mortality and morbidity were observed between emergency surgery and colonic stenting. In each group, 5 patients died within 30 days of the intervention (Chi<sup>2</sup>=0.02, p=0.89) and 9 patients died during the full follow-up period (table 5). Patients in the emergency surgery and colonic stenting group on average survived at least 156 days (95% CI: 140–173) and 153 days (95% CI: 135–170) respectively, the difference being non-significant (log rank statistic=0.03, p=0.86).

During the follow-up period 23 out of 51 emergency surgery patients experienced a prolonged hospital stay or additional hospital admission at least once against 25 out of 47 patients in the colonic stenting group (Chi<sup>2</sup>=0.64, p=0.43).

**Table 3. Differences between emergency surgery and colonic stenting for colon cancer-related quality of life during follow-up, based on available data and corrected for differences at baseline.**

EORTC QLQ-CR38 dimension	Emergency Surgery (ES)		Colonic Stenting (CS)	
	Baseline (SD) (Nmax*=40)	Follow-up (SD) (Nmax=44)	Baseline (SD) (Nmax=39)	Follow-up (SD) (Nmax=38)
Functional scales				
Bodily image	73.0 (30.8)	74.6 (24.8)	76.9 (23.8)	74.5 (23.6)
Future perspective	41.9 (34.8)	59.4 (27.9)	43.0 (35.4)	58.2 (29.4)
Sexual functioning	12.0 (20.8)	10.6 (15.8)	13.7 (20.7)	13.1 (18.6)
Sexual enjoyment*	36.7 (36.7)	28.8 (31.6)	35.7 (38.0)	41.6 (39.0)
Symptom scales				
Micturition problems	22.5 (20.8)	27.1 (14.0)	29.2 (19.1)	30.5 (13.0)
Chemotherapy side-effects	35.3 (20.8)	25.2 (19.4)	39.5 (28.2)	25.6 (22.7)
Gastrointestinal problems	40.9 (20.1)	15.7 (13.4)	49.9 (15.3)	15.3 (13.9)
Male sexual functioning	34.4 (42.5)	40.7 (36.3)	21.6 (28.1)	25.8 (30.6)
Female sexual functioning**				
Defaecation problems*	22.7 (15.6)	9.2 (6.4)	24.2 (15.9)	12.9 (10.3)
Stoma-related problems	-	28.6 (19.6)	-	40.5 (22.6)
Weight loss	37.6 (35.2)	25.0 (22.6)	45.0 (36.2)	30.8 (29.5)

## Stoma rates

After the initial intervention 38 patients (74.5%) in the emergency surgery group and 24 patients (51.1%) in the colonic stenting group had a stoma (Chi2 5.8, p=0.016). Of these stomas respectively 12 and 7 were definitive. Anastomotic leakage led to one additional stoma in the emergency surgery group (n=39) and 5 additional stomata in the colonic stenting group (n=29) within 30 days after the initial intervention. During the further follow-up restoration of bowel continuity was achieved in 4 patients in the emergency surgery group and in 1 patient in the colonic stenting group. At latest follow-up respectively 35 patients (68.6%) versus 28 (59.6%) had still a stoma (Chi2 0.87, p=0.35).

## Discussion

Over the years, a number of comparative non-randomised studies have reported that stoma rate, total hospital stay and stay on the intensive care unit were significantly shorter

Corrected follow-up difference		
Difference (95% LCL;UCL) <sup>^</sup> (Nmax=38 ES / 34 CS)		p-value
-1.4 (-10.8; 8.0)		0.77
-2.9 (-15.7; 10.0)		0.66
-1.5 (-10.7; 7.6)		0.74
-17.6 (-56.5; 21.3)		0.34
-4.5 (-10.8; 1.9)		0.17
0.9 (-9.4; 11.2)		0.87
1.2 (-5.2; 7.6)		0.71
5.0 (-13.3; 23.2)		0.59
-3.2 (-10.2; 3.7)		0.35
-12.0 (-23.7; -0.2) <sup>^^</sup>		0.046
-8.5 (-20.7; 3.8)		0.17

\* Number of patients with available (i) baseline, (ii) follow-up and (iii) baseline and follow-up data ranges from 10 to 40, 16 to 44, and 6 to 38 in the emergency surgery group and from 14 to 39, 17 to 38, and 7 to 34 in the colonic stenting group, respectively; lower numbers resulting from non-response to questionnaire items on sexual enjoyment or defaecation problems.

\*\* Too few baseline (ES 4; CS 4), follow-up (ES 3; CS 4), baseline and follow-up (ES 1; CS 1) data available from female patients.

<sup>^</sup> Difference ES follow-up minus CS follow-up based on estimated marginal means with baseline values as covariate; LCL: lower confidence limit; UCL: upper confidence limit.

<sup>^^</sup> Differences in stoma-related problems among 32 ES and 21 CS patients are reported for follow-up only.

in patients treated with a colonic stent as bridge to surgery.<sup>4,5;14;15</sup> In addition several non-comparative series on colonic stenting revealed high technical and clinical success rates as well as acceptable morbidity and very low mortality rates.<sup>13;29</sup> This was reason to perform this randomised clinical trial. Although we expected and even hoped to confirm these data, our results appeared to be different. Our study had to be terminated early because of patient safety concerns. The DSMC concluded that a persistent trend existed towards an increased morbidity in the group of patients randomised to colonic stenting in the 30 days follow-up after inclusion. This trend could however not be confirmed for the total follow-up period of 6 months of the 98 patients finally included. In the end our multi-centred trial revealed no benefits with regard to mortality, morbidity, quality of life and stoma rates for neither colonic stenting nor emergency surgery in patients with acute left-sided malignant colonic obstruction.

We might have selected a population at a higher risk for complications than the non-randomised studies published previously. In our series 70% of the patients presented

**Table 4. Differences between emergency surgery and colonic stenting for health status during follow-up, based on available data and corrected for differences at baseline.**

EQ-5D	Emergency Surgery (ES)		Colonic Stenting (CS)	
	Baseline (SD) (Nmax*=45)	Follow-up (SD) (N=50)	Baseline (SD) (Nmax=41)	Follow-up (SD) (Nmax=44)
Visual analogue scale	35.8 (24.8)	52.4 (27.7)	36.6 (21.2)	52.7 (30.5)
Health utility/quality adjusted life-years**				
UK preferences	0.41 (0.43)	0.30 (0.17)	0.18 (0.42)	0.28 (0.20)
NL preferences	0.48 (0.37)	0.32 (0.17)	0.31 (0.35)	0.29 (0.19)

**Table 5. Secondary outcome parameters.**

Outcome parameter	Emergency surgery N=51	Colonic stenting N=47	p-value
Mortality			
30 days mortality, no. (%)	5 (9.8)	5 (10.6)	0.89
Overall mortality, no. (%)	9 (17.6)	9 (19.1)	0.84
Morbidity, no. (%)	23 (45.1)	25 (53.2)	0.43
Stoma rates			
Directly after initial intervention, no. (%)	38 (74.5)	24 (51.1)	0.016
At latest follow-up, no. (%)	35 (68.6)	28 (59.6)	0.35

with a complete obstruction which is high in comparison to the existing literature.<sup>29</sup> Patients with a total obstruction are probably more difficult to stent, might be less easily decompressed and could still be in a marginal condition when going to surgery, resulting in a relatively high leak rate if resection without a stoma is attempted. In a recently published retrospective study from a renowned tertiary referral centre, complete obstruction was identified as a risk factor for complications.<sup>29</sup>

Our findings could in part also result from our meticulous survey of complications with telephone calls every 2 weeks during a 6 months period and a strict definition of morbidity. We included not only the complications of the initial intervention, colonic stenting combined with elective surgery or emergency surgery, but also the complications that occurred because of restoration of bowel continuity and all events that led to readmission within 6 months follow-up. The fact that most published studies

<b>Corrected follow-up difference</b>	
<b>Difference (95% LCL;UCL)<sup>^</sup> (Nmax=45 ES / 39 CS)</b>	<b>p-value</b>
-3.8 (-16.2; 8.6)	0.54
-0.03 (-0.11; 0.05)	0.41
-0.04 (-0.11; 0.04)	0.35

\* Number of patients with available (i) baseline, (ii) follow-up and (iii) baseline and follow-up data ranges from 43 to 45, 50 to 50, and 43 to 45 in the emergency surgery group and from 41 to 41, 44 to 44, and 39 to 39 in the colonic stenting group, respectively.

\*\* Baseline data represent health utility values at the time of measurement. Follow-up data represent the number of quality adjusted life-years during the first half-year post-intervention while assuming that a patient's health status at the time of measurement represents the health status in-between the actual measurement and the preceding one or baseline, whichever is appropriate. Applied scoring algorithms were available from the literature and were derived from time trade-off based elicitation techniques of health state preferences from the general public of the United Kingdom (UK) or, alternatively, the Netherlands (NL). See also Methods section.

<sup>^</sup> Difference ES follow-up minus CS follow-up based on estimated marginal means with baseline EQ-SD VAS or baseline health utility as covariate; LCL: lower confidence limit; UCL: upper confidence limit.

had a less strict follow-up will probably explain an underestimation of the morbidity in the previous studies.

Especially with regard to colonic stenting as bridge to surgery the existing data focus on technical success, clinical success, stent procedure-related (placement of the stent) and stent-related (presence of the stent in the colon) complications.<sup>5;13;14;29</sup> Our technical success rate of colonic stent placement was rather low (70%; 33 of 47) compared to the literature.<sup>13</sup> Though we did request a certain experience with regard to stent placement in 8 out of 47 patients (17%) a guide wire could not be passed along the colonic stricture. This while all these endoscopists were experienced in pancreaticobiliary endoscopy, who are according to the literature more proficient colonic stenters.<sup>29</sup>

Our relative high number of patients with a complete obstruction might have played a role: it is well recognized that stent placement in patients who present with a complete obstruction is a relatively difficult procedure.<sup>30</sup> One could plead for restriction of the numbers of centres or endoscopists executing this procedure but this might lead to challenging logistic consequences. None of the patients that did receive a colonic stent had to be operated because the symptoms of colonic obstruction did not resolve, leading to a clinical success of 70% which is in accordance with the literature.<sup>13</sup>

With regard to the stent procedure-related and stent-related complications the literature reveals a complication rate varying between 5% and 23.1%, of which on average 5% stent-related perforations.<sup>5;14;29</sup> In our population procedure-related or stent-related complications occurred in 6 patients (12.8%): in 2 patients a guide wire perforation was made in an attempt to traverse the stricture, in 4 patients (8.5%) the stent led to a

perforation after 1, 7, 14 and 17 days respectively. Three of these perforations must be considered stent-related rather than procedure-related as they occurred a week or more after the stent placement. In addition 3 out of 26 colonic specimens retrieved showed signs of silent colonic perforation by the prosthesis. This leads to a total percentage of perforations of almost 20% of our patients. The problem of silent perforations has recently been underlined in another study thus far only published as abstract. They found 2 stent perforations and 8 silent perforations in 30 patients randomised to colonic stent as bridge to surgery.<sup>31;32</sup> The oncological consequences of potential tumour dissemination caused by these silent perforations are unclear but the phenomenon is worrying and we feel strongly that these silent perforations cannot be disregarded.<sup>32</sup> A hint of the influence of dissemination could potentially be derived from survival data. These data are however inconsistent, ranging from no difference between the treatment modalities to a significantly lower 5 year survival rate for patients treated with colonic stenting before elective surgery, all in non-randomised studies.<sup>6;33</sup>

Another outcome parameter often used in the existing literature is the number of ostomies.<sup>4;5;14</sup> These studies revealed a significantly lower ostomy rate in the colonic stenting group.<sup>4;5;14</sup> Also our study revealed a significantly lower ostomy rate in the colonic stenting group after the primary intervention. However at the end of the six months follow-up the number of ostomies did not differ between the groups. Anastomotic leakage led to extra stoma creation in five patients from the colonic stenting group versus one in the emergency surgery group. Additionally a higher closure rate was achieved in the emergency group. Patients in the emergency surgery group did report significant less problems with their ostomies than the patients of the colonic stenting group. Disappointment of still having a stoma while being treated with a modality which was predicted to reduce the chance of stoma creation might explain this.

Our study obviously has some shortcomings; among these is the large number of participating hospitals, 25 hospitals out of the 28 hospitals actively included patients ranging from 1 to 17 patients. When designing the study we considered limited inclusion and endoscopic treatment to tertiary referral centres but this would introduce bias to the real life situation. This bias could be one of the reasons for the better results in the non-randomised studies. In addition patient accrual would be severely hampered and this kind of study can only be done with a large network of participating hospitals.

Next to the study design also the execution of the study had its shortcomings. In the emergency surgery group all but one of the patients received the allocated treatment. In the colonic stenting group however several patients appeared not to have an indication for stent placement (6 patients): figure 1 depicts the exact reasons. In 4 patients (9%) stent placement was not performed because of an endoscopically benign appearing stricture. While designing this study we were well aware of this possibility and its potential influence on our intention-to-treat analysis but we found it unethical to perform

a diagnostic endoscopy before inclusion and only after confirmation of malignancy randomise the patient to either study arm. Our study also had some methodological limitations which might have influenced our results. First, we included the coloncancer-specific EORTC QLQ-CR38 questionnaire validated for the Netherlands after consultation of the EORTC. At the time of analysis however, the alternative EORTC QLQ-CR29 version had become more popular for its superiority in comparing patients with and without stoma. Because the two questionnaires overlap only partially one should be cautious when comparing the results of table 3 with results from other studies based on the EORTC QLQ-CR29. Second, the study protocol foresaw the application of the extended Q-TWIST method to the quality of life data in order to estimate differences in quality-adjusted survival between groups.<sup>20</sup> However, with only 18 deceased patients, 10 of whom died before the first follow-up, insufficient data were available to perform the analysis as planned. Instead, an alternative method with similar information yield has been applied by deriving quality-adjusted life years after imputation of scores representing the state of death (i.e. health utility equals zero) in case patients died before the next measurement(s). Third, a cost-effectiveness analysis was planned alongside this randomised trial. Considering the advice by the DSMC however, we decided to refrain from judgement on the economic viability of colonic stenting when safety was possibly at stake. Fourth, though our trial was terminated early implying a loss of patients and hence, loss of statistical power, the very similar responses to treatment in both groups in terms of disease-specific and generic quality of life, mortality, morbidity and stoma rates suggest that the probability of colonic stenting becoming more effective than emergency surgery is negligible.

How should our outcomes be dealt with? As long as there are no other randomised trials either confirming or refuting our findings, we feel that colonic stenting as bridge to elective surgery should only be performed in randomised controlled settings with a stringent follow-up focussing on specific groups of patients who might benefit from either one of the treatment modalities, like recently initiated by Small et al.<sup>29</sup> In addition we should be very keen on acquiring more information on (micro-)perforations and their possible consequences on the prognosis of patients.

At the moment we can only state that this first randomised controlled trial did not reveal any advantage with regard to quality of life, mortality, morbidity or stoma rates of colonic stenting as bridge to surgery in patients with left-sided colonic obstruction and can therefore not replace emergency surgery as standard treatment. Oncologic concerns of overt and silent perforations of stenting cannot be disregarded, particularly since no clear benefits of stenting as bridge to surgery could be shown.

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