Colorectal Endoscopic Stenting Trial (CReST) for obstructing left-sided colorectal cancer

CReST Collaborative Group

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Self-Expanding Metal Stents versus emergency surgery for obstructing left sided colorectal cancer: Colorectal Endoscopic Stenting Trial. (CReST), a multicentre randomised controlled trial

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Summary

Background: Colorectal cancer often presents with obstruction needing urgent, potentially life-saving decompression. The comparative efficacy and safety of endoluminal stenting versus emergency surgery as initial treatment for such patients is uncertain.

Methods: Patients with left-sided colonic obstruction and radiological features of a carcinoma were randomized to endoluminal stenting using a combined endoscopic/fluoroscopic technique followed by elective surgery 1-4 weeks later, or surgical decompression with or without tumour resection. Treatment allocation was via a central randomisation service using a minimisation procedure stratified by curative intent, primary tumour site and severity (APACHE) score. Co-primary outcome measures were duration of hospital stay and 30-day mortality. Secondary outcomes were stoma formation, stenting completion and complication rates, perioperative morbidity, 6-month survival, 3-year recurrence, resource usage, adherence to chemotherapy, and quality of life. Log-rank and chi-square analyses were by intention to treat.

Results: 245 patients from 39 UK hospitals were randomized between 23-Apr-2009 and 22-Dec-2014. Stenting was attempted in 97% (119/123 patients allocated), achieving relief of obstruction in 82% (98/119). For the 89% treated with curative intent, there were no significant differences in 30-day post-operative mortality [3·6% (4/110) vs 5·6% (6/107), p=0·48], or duration of hospital stay [19 days (11-34) vs 18 days (IQR 10-28), p=0.94] between stenting followed by delayed elective surgery and emergency surgery. Stoma formation occurred less frequently in potentially curative patients allocated stenting than immediate surgery [47% (47/99) vs 68% (72/106), p=0·003]. There were no significant differences in perioperative morbidity, critical care utilization, quality-of-life, 3-year recurrence or mortality between treatment groups.

Conclusions: In patients undergoing attempted curative treatment for obstructing colorectal cancer, endoluminal stenting as a bridge to surgery reduces stoma formation without any detrimental effect on 30-day mortality or length of hospital stay, perioperative complications, quality of life and survival are similar with stenting and surgery.

The trial is registered (ISRCTN 13846816).

Funding: The CReST trial was funded by the Cancer Research UK (Ref C25359/A8975)

Introduction

Despite the introduction of national screening programmes and campaigns to raise awareness of early symptoms of colorectal cancer, a persistent one in six patients present with advanced, obstructing tumours that require a hazardous, but potentially life-saving emergency procedure.[1] Such patients are often elderly with significant co-morbidities and consequent increased risk of postoperative morbidity and mortality.[2,3,4] Historically, the standard approach has been emergency surgery with resection of the diseased segment usually requiring stoma formation, often permanent. On-table antegrade irrigation of the loaded colon[5] can allow primary resection and anastomosis, but is not performed widely, often because a specialist colorectal surgeon is not available or because the patient is physiologically unstable.

Insertion of a self-expanding metal stent (SEMS) to relieve obstruction may be a better initial treatment for left-sided carcinomas than surgery.[6-8] The theoretical advantages of stenting as a bridge to surgery include buying time to correct fluid and electrolyte imbalances, improve respiratory function, optimise medical co-morbidities, obtain more accurate staging and allow access to colorectal specialists, thereby enabling bowel continuity to be more safely restored. However, stenting is sometimes unsuccessful, can sometimes cause bowel perforation, and may thereby increase the risk of tumour dissemination.[9,10]

Indeed, two previous randomised trials comparing stenting versus emergency surgery for potentially curative colon cancer closed prematurely because of increased complications in the stenting arm and poor success rate of stenting, and increased 30-day morbidity following SEMS .[11,12] Consequently, European guidance did not recommend SEMS placement as a bridge to elective surgery for patients with potentially curative left-sided malignant colonic obstruction (strong recommendation, high quality evidence).[13]

To better evaluate the balance between benefits and risks of stenting, CReST (ColoRectal endoscopic Stenting Trial) was initiated to address two key questions: is there a worthwhile net benefit (in reduced operative mortality and morbidity, reduced stoma formation and better quality of life adjusted survival) from endoluminal stenting compared with immediate surgery for patients presenting with an obstructing colonic cancer and, if benefit exists, is this for patients undergoing attempted curative treatment, palliative treatment, or both? This report focuses on the patients with potentially curative tumours as, subsequent to the

commencement of the CReST trial, evidence for the benefit of SEMS in the palliative setting emerged[13] and, consequently, few patients requiring palliative treatment were randomised.

Methods

Study design and participants

This randomised controlled trial took place in 39 acute UK NHS hospitals. Eligible participants were aged over 18 years, presenting with left-sided colonic obstruction considered to be due to colonic malignancy, and fit enough to undergo emergency surgery. Patients with signs of peritonitis and/or perforation, incipient caecal perforation, or obstruction in the mid or lower rectum that might require neoadjuvant chemoradiotherapy were ineligible.

Participants were assigned (ratio 1:1) to either stenting or or to surgical decompression with or without tumour resection (Figure A1). Allocations were obtained by phone or internet from the Birmingham Clinical Trials Unit using a minimised randomisation procedure balancing for curative intent, primary tumour site (transverse colon, splenic flexure, descending colon, sigmoid, rectosigmoid, rectum), as diagnosed by CT scan and contrast enema, and Acute Physiology and Chronic Health Evaluation (APACHE) severity score. There was no blinding of participants, clinicians, or research staff. All participants provided written informed consent. For the duration of the study, interim analyses of morbidity data, hospital stay and 30-day mortality were reviewed, in strict confidence, by an independent Data Monitoring and Ethics Committee. The study was approved by the Oxford Research Ethics Committee (B 08/H0605/90).

Procedures

Prior to study commencement, 5 stenting workshops, attended by approximately 150 colleagues, were held for participating units; each unit was required to have performed 30 stents for obstructing colorectal cancer and any participating radiologist must have performed at least 10 stents previously and consider themselves confident with the techniques stipulated for the trial. This included a pre-procedure enema, SEMS insertion using a combined endoscopic and fluoroscopic technique, no pre- or post-dilatation, and a post-procedure plain radiograph. The type and brand of stent used was decided by the local radiologist, not mandated. A team comprising designated lead surgeons, radiologists and, where required, gastroenterologist, was formed in each centre, to establish a clear management pathway.

Patients were classified prior to randomisation as palliative or potentially curative disease. After resuscitation, patients allocated stenting had a SEMS deployed across the tumour and, where stenting was performed as a bridge to surgery, this was recommended between one and four weeks following stent insertion. For patients with unresectable local or metastatic disease, or who were unfit for major surgery, stenting was considered palliative and no further surgery was mandated. Patients in whom stenting failed underwent appropriate emergency surgical decompression along lines similar to those allocated to surgery. Patients allocated emergency surgery underwent tumour resection, bypass (loop stoma) or decompression (stoma), as dictated by surgeons' preference, disease stage, and clinical condition.

Outcomes

Co-primary outcome measures were 30-day mortality and length of hospital stay during the first year following randomisation (including time in hospital for stenting, surgical resection and any subsequent stay under the care of a surgeon). This definition was intended to capture both the initial stay and subsequent hospitalisations for stoma closure. Secondary outcomes were stenting completion and complication rates, presence and duration of a stoma, anastomosis rates, Critical Care Unit stay, perioperative morbidity, 6-month survival, proportion disease-free at three years (potentially curative group only), resource usage, rate of adjuvant chemotherapy, adherence to chosen chemotherapy protocol, and quality of life. Cancer and tumour-specific quality of life were assessed using EORTC QLQ-C30 and EORTC QLQ-CR29, respectively. EuroQol EQ-5D-3L was administered to allow costs per quality-adjusted life-year to be calculated. Quality of life questionnaires were completed at baseline, 4, 12, and 24 months after randomisation. Stent-related complications included, but were not limited to, failure to deploy the stent, bowel perforation, stent displacement, and re-obstruction. Stent insertion was considered an adverse event if it resulted in further acute obstruction requiring a second stent insertion and/or emergency surgery. Morbidity was recorded at discharge and defined as any event leading to hospital admission or prolonging hospital stay and categorised according to the Clavien-Dindo system.[14] Stoma presence was recorded after the initial intervention was completed and stoma removal procedures recorded at subsequent follow-ups. Post-operative imaging was recommended every 12 months and mandated at 3 years. If patients were lost to hospital follow-up, their GP was contacted. Flagging via the NHS Information Centre monitored long-term survival

To investigate the representativeness of the randomised population, centres were asked to record a limited amount of anonymised data on patients with left-sided bowel obstruction presumed secondary to carcinoma who were potentially eligible for the trial but not entered.

Sample size and statistical analysis

Target recruitment was 400 patients (200 curative and 200 palliative), which would provide 90% power to detect differences in mortality similar to those reported in an earlier national audit of large bowel obstruction (16% following emergency surgery and 4% following elective surgery),[4] and 90% power to detect a 0·35sd reduction in days in hospital, equivalent to 1-2 days. With few palliative patients randomised, the Trial Management Group, blind to accumulating data, decided to close recruitment at a time when over 200 patients with potentially curative colorectal cancer had been randomised.

Analyses were undertaken on an intention-to-treat basis, ie using all available data irrespective of eligibility or treatment compliance, with stratification between potentially curative and palliative groups. We anticipated minimal loss to follow up and, originally, an equal number of palliative and potentially curative cases. We also anticipated that approximately 5% of patients would be found not to have cancer, but would be included in our intention-to-treat analyses.

Differences in survival, recurrence, and length of stay were compared using unadjusted log-rank analyses and displayed in Kaplan-Meier plots. Data on hospital stays from patients who died, withdrew, or had less than one year's follow-up were included in the primary analyses but sensitivity analyses were also undertaken excluding such patients. Differences in categorical variables were assessed using Mantel-Haenszel tests and differences in continuous variables were assessed using t-tests. All p-values are two-sided and considered significant if below 0·05. Analyses were performed with SAS version 9.4 (SAS Institute).

The trial is registered (ISRCTN 13846816).

Role of the funding source

The study funder had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between 23rd April 2009 and 22nd December 2014, 739 patients were assessed for eligibility, of whom 477 (65%) were considered eligible. Of these, 246 were randomised, one allocated surgery withdrew consent and is excluded from all analyses, leaving 245 participants who were randomly assigned to receive stenting (n=123) or emergency surgery (n=122): Figure 1. Baseline characteristics were balanced across treatment arms (Table 1). Median age was 71 years (IQR 61-79), 61% (149/245) were men, 17% (41) had severe, and 63% (154) mild systemic disease. 89% (217/245) of the randomised patients were classified as potentially (ie probably or possibly) curative (110 allocated stent, 107 allocated emergency surgery: Figure 1).

Stenting was attempted in 97% (119/123) of patients allocated stent (Table 2), achieving relief of obstruction in 82% (98/119), with similar success rates in potentially curative and palliative patients: 81% (86/106) vs 92% (12/13), p=0.32. Of the 25 in whom stenting was not attempted or failed, all then had surgery.

All but 3 (2%) of the 122 patients allocated emergency surgery underwent surgery: 1 potentially curative patient was found to have a non-cancer pseudo-obstruction, 2 palliative patients were stented. Fewer patients allocated stenting went on to have surgery: 11/110 (10%) vs 1/107 (1%) of potentially curative patients did not have surgery, all but one (who had cardiac arrest) because they were treated palliatively for unresectable or metastatic disease. Similarly, 9 of 13 (69%) palliative patients allocated stenting vs 2/15 (13%) allocated surgery did not have surgery (Figure 1).

Surgical procedures reflected the typical range performed in this group of patients (Table 3). Of those potentially curative patients undergoing surgery, 71% (70/99) allocated stenting and 57% (60/106) allocated surgery had anastomoses performed (p=0.04). In total, 47% (47/99) of curative patients in the stenting group compared with 68% (72/106) of the emergency surgery group had a stoma formed at the time of the index operation (p=0·003). Of these, 28 vs 44 (p=0.047) were stomas formed without anastomosis, and 5 vs 10 were loop stomas. Subsequent to the initial surgery, stoma reversal was reported for 1 allocated stent (1 loop stoma) and 2 allocated surgery (2 loop), and three stenting and one surgery patient had stomas formed. Hence, 45% (49/110) of stenting and 66% (71/107) of surgery patients had stomas at one year (p=0.001). Stoma formation was also less frequent in palliative patients allocated stenting than surgery: 23% (3/13) vs 67% (10/15), p=0.021.

There were four (3.3%) stenting-related perforations (Table 2): one was a guidewire perforation, managed by stent insertion with no further complication. Three resulted in urgent surgery, with one patient requiring post-operative mechanical ventilation. None died. Post stenting, no patients were admitted to HDU. Post-surgery, 35% (34/96) of the potentially curative group in the stenting arm and 40% (41/103) of the emergency surgery patients were admitted to Critical Care (p=0·52) with a median length of stay of 3 days in both groups (Table A2). Length of hospital stay in the first year after randomisation also did not differ significantly between the two curative surgery groups: median 19 days (IQR 11-34) for stenting vs 18 days (10-28) for surgery; [rate ratio (RR)=1·01 (95% CI 0·75 to 1·37), p=0·94, Figure 2a]. No difference was apparent either in sensitivity analyses excluding patients who did not contribute a full year of data due to death (32 allocated stent, 24 surgery), withdrawal (2 surgery), or lack of follow-up (3 stent, 2 surgery): Table A2.

For potentially curative patients, 30-day mortality rates were similar: 3·6% (4/110) for stenting and 5·6% (6/107) for emergency surgery: RR=0·63 (0·18, 2·25), p=0.48 figure 2b. Neither 6-month nor overall mortality differed by treatment group (Figure 2b), nor did 3-year recurrence: RR=1.24 (0·80 to 1·91), p=0·34 (Figure 2c). Of 28 patients considered at randomisation to require palliative treatment, all but 5 died within 24 months of randomisation.

Postoperative complications occurred in 40 (33%) patients in the stenting group and 46 (38%) patients in the emergency surgery group. Similar numbers of patients in the stenting and emergency surgery groups had complications graded at Clavien-Dindo grade 3 or worse: 22 (18%) versus 27 (22%). In potentially curative patients who had anastomoses, 7% (5/68) of the stent and 3% (2/57) of the surgery group had anastomotic leaks (p=0·35): table A4. There were no significant differences in complications requiring or prolonging hospitalisation, or any particular type of complication (table A1). Just under half of the patients received chemotherapy with similar proportions in the stent and emergency surgery groups (table A5). There were also no differences between the two groups at 3 or 12 months for any of the Quality of Life measures.

The proportion of patients who were found not to have colon cancer [9·4% (23/245)] was somewhat higher than the 5% predicted at study commencement. Of these, 16 had been allocated surgery and 7 stenting, and all were classified as potentially curative at randomisation. Most were found to have diverticular disease (Table A3). Three non-cancer patients died, one from multi-organ failure following failed stenting and post-operative

surgical complications (3 days post-randomisation), one from COPD (4 years post-randomisation), and one from stroke (5 years post-randomisation).

Discussion

CReST is, to our knowledge, the largest reported randomised trial of stenting in patients presenting with acute left-sided malignant colonic obstruction. Despite achieving high procedural success rates, which allowed meaningful comparison between stenting and surgery, we found that stenting as a bridge to surgery did not reduce the length of hospital stay under the surgical team in the year following surgery. Nor was there any significant reduction in 30-day mortality, the second primary outcome, although the number of such deaths was too few to preclude a moderate reduction. The main benefit from stenting was a significant reduction in long-term stoma formation, which is consistent with previous studies.[15,16] It is well recognised that stomas adversely affect Quality of Life but we did not demonstrate this, perhaps because our quality of life instruments were not sufficiently sensitive.

European guidelines currently recommend stenting for palliative patients,[13,17] and hence just 7% of patients randomised in CReST had palliative disease. By contrast, stenting as a bridge to surgery in potentially curative disease is recommended only as an option to consider,[17] but nevertheless remains commonly but sporadically practised.[18] The basis for not recommending stenting as a bridge to surgery is concern about procedural failure and consequent patient safety: two previous trials comparing stenting with surgery closed prematurely because of low stent insertion success rates, high stent-related complication rates, and increased 30-day morbidity following SEMS.[11,12] Stenting was more frequently successful in our study, relieving obstruction in 82% (98/119) of patients - a higher rate than the 71% (82/116) and 69% (80/116) technical and clinical success rates, respectively, reported in a meta-analysis of four small RCTs.[19] This was achieved across 39 hospitals, each providing an acute treatment pathway for SEMS insertion. We believe that the stenting workshops, protocol driven procedures, and shared experience through trial participation all contributed to these low failure rates. The clinical perforation rate in CReST was low, similar to that reported in the meta-analysis with no deaths from perforation.

In contrast to a recent meta-analysis showing reduced morbidity for SEMS as a bridge to surgery compared to immediate surgery,[20] post-operative complication rates were similar in

the stenting and surgery groups. One previous study closed prematurely because the emergency surgery group had a significantly increased anastomotic leak rate.[15] Few patients in CReST developed an anastomotic leak, with the overall rate comparable to the 3·5% reported in a large elective patient series,[21] and much lower than the 20% leak rate seen in the Dutch Stent-In trial.[11] We also found no difference in post-operative critical care or length of hospital stay.

There are concerns that stent insertion might lead to increased local and metastatic spread. Sloothaak et al reported an increased recurrence risk in a subgroup analysis of their patients who had stent related perforation,[10] and increased CK20 mRNA expression has been reported following stent insertion.[9] These concerns have persisted, with conflicting results from meta-analyses of randomised trials and large cohort studies.[22-25] In CReST, we found no significant difference in recurrence over three years following treatment, a timeframe within which seeding of tumour cells would be expected to become clinically apparent. This contrast with other studies may be explained by our lower perforation rate, but could also be due to lack of statistical power to detect moderate differences. While a meta-analysis of individual patient data from these trials might help clarify whether stenting increases the risk of recurrence, this study suggests that any increase in a patient population with predominantly advanced disease is unlikely to be of clinical significance.

In summary, stenting for patients with obstructing left-sided colorectal cancer can achieve high technical and clinical success rates across a large number of providing units. For patients with advanced or rapidly progressive disease, better treatment planning can be provided and unnecessary surgery and stoma formation can be avoided. For patients who proceed to surgery, stomas can be avoided in the majority of cases and anastomotic leak rates are low. This study provides no indication that stenting increases the risk of recurrent malignancy. Stenting as a bridge to surgery should therefore be considered as a standard option for patients with obstructing but potentially curable colon cancer, particularly when there are doubts about curability and patient desire to avoid stoma formation, or when there is no specialist colorectal surgeon available to perform urgent surgery.

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DECLARATION OF INTERESTS

We declare no competing interests.

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DATA SHARING

All data requests should be submitted to the corresponding author for consideration. Access to available anonymised data may be granted following review.

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