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Risk of bowel obstruction in patients undergoing neoadjuvant chemotherapy for high-risk colon cancer: A nested case-control matched analysis of an international, multi-centre, randomised controlled trial (FOxTROT)

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Conflicts of interest: None

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Structured abstract

Objective: This study aimed to identify risk-criteria available before the point of treatment initiation that can be used to stratify risk of obstruction in patients undergoing neoadjuvant chemotherapy (NAC) for high-risk colon cancer.

Summary background data: Global implementation of neoadjuvant chemotherapy (NAC) for colon cancer, informed by the FOxTROT trial, may increase risk of bowel obstruction.

Methods: A case-control study, nested within an international randomised controlled trial (FOxTROT. ClinicalTrials.gov: NCT00647530). Patients with high-risk operable colon cancer (radiologically-staged T3-4 N0-2 M0) that were randomised to NAC and developed large bowel obstruction were identified. Firstly, clinical outcomes were compared between

patients receiving NAC in FOxTROT that did and did not develop obstruction. Secondly, obstructed patients (cases) were age- and sex-matched with patients that did not develop obstruction (controls) in a 1:3 ratio using random sampling. Bayesian conditional mixed-effects logistic regression modelling was used to explore clinical, radiological, and pathological features associated with obstruction. Absolute risk of obstruction based on the presence or absence of risk criteria was estimated for all patients receiving NAC.

Results: Of 1053 patients randomised in FOxTROT, 699 received NAC, of whom 30 (4.3%) developed obstruction. Patients underwent care in European hospitals including 88 UK, 7 Danish and 3 Swedish centres. There was more open surgery (65.4% versus 38.0%, p=0.01) and a higher pR1 rate in obstructed patients (12.0% versus 3.8%, p=0.004), but otherwise comparable postoperative outcomes. In the case-control matched Bayesian model, two independent risk criteria were identified: (1) obstructing disease on endoscopy and/or being unable to pass through the tumour (adjusted odds ratio: 9.09, 95% credible interval: 2.34-39.66) and stricturing disease on radiology or endoscopy (OR: 7.18, 95% C.I.: 1.84-32.34). Three risk groups were defined according to the presence or absence of these criteria: 63.4% (443/698) of patients were at very low risk (<1%), 30.7% (214/698) at low risk (<10%), and 5.9% (41/698) at high risk (>10%).

Conclusions: Safe selection for NAC for colon cancer can be informed by using two features that are available before treatment initiation and identify a small number of patients with high risk of preoperative obstruction.

Introduction

Bowel obstruction is a serious complication of colonic cancer and accounts for 50% of mortality within a year of diagnosis. It is the precipitant for the majority of emergency bowel cancer surgery, which incurs a three-fold higher risk of death compared with a planned operation[1-4]. Bowel obstruction also has a detrimental impact on longer term survival and oncological outcomes[5,6].

The Fluoropyrimidine, Oxaliplatin and Targeted-Receptor pre-Operative Therapy for patients with high-risk, operable colon cancer (FOxTROT) trial[7], has demonstrated the safety and efficacy of short-course neoadjuvant chemotherapy (NAC) in patients with high-risk operable colon cancer. A substantial and rapid response to NAC was observed at histopathological assessment of the resected tumour; up to 60% treated with a 6 week duration of NAC had tumour regression at surgery, which translated into a 25% reduction in recurrent or persistant disease at 2-years, compared with straight to surgery[8] and NAC can now be considered a therapeutic option in this patient group. However, for patients undergoing NAC, deferring surgery can put patients at risk of colonic obstruction. Oncologists need to be aware of this risk to their patients, as timely management is critical.

As more integrated treatment pathways are developed for high-risk colonic cancer, improved patient stratification for large bowel obstruction risk will be required. Recognising patients risk factors would inform the consent process, enrich multidisciplinary team (MDT) decision making, and enable targeted active monitoring.

This study aimed to identify clinical, pathological, radiological, and endoscopic features of colon cancer that can be used to stratify patients at risk of bowel obstruction. This sought to inform perioperative management of locally advanced colon cancer.

Methods

Study setting and design

The Fluoropyrimidine, Oxaliplatin and Targeted-Receptor pre-Operative Therapy for patients with high-risk, operable colon cancer (FOxTROT) trial (ISRCTN 87163246) was an international, multicentre, randomised controlled trial testing the feasibility, safety, and efficacy of preoperative chemotherapy for colon cancer. Patients with radiologically staged locally advanced tumours (cT3 and above) were randomly assigned in a 2:1 ratio to short course (three-cycles) NAC and standard adjuvant chemotherapy (AC) or standard AC alone[7,8]. Patients with emergency presentations of colon cancer such as obstruction or perforation were excluded. The full trial inclusion and exclusion criteria are available in the published FOxTROT trial protocol. Hospitals managing patients with colon cancer through a multidisciplinary team in the UK, Sweden or Denmark were eligible. This study was a pre-planned secondary analysis of FOxTROT data with a nested case-control study. National and institutional approvals were obtained for the FOxTROT trial protocol from the University of Birmingham, an NHS National Research Ethics Service, and all participating international institutions according to relevant local requirements. An Independent Data Monitoring Committee reviewed the database annually.

Definition of cases and controls

Cases were selected according to the following criteria: (1) Met inclusion criteria for the FOxTROT [7,8]; (2) Randomised to receive NAC and standard postoperative chemotherapy; (3) Developed proven or symptomatic colonic obstruction after randomisation; (4) Diagnosis of

obstruction was made before the planned date of surgery. Colonic obstruction was defined pragmatically as: (1) proven obstruction, with radiological and clinical evidence of complete obstruction and/or obstruction requiring radiological placement of a colonic stent or urgent surgery (within 48 hours of presentation); (2) symptomatic obstruction, where radiological evidence was inconclusive but with clinical symptoms consistent with obstruction and/or obstruction requiring expedited surgery (greater than 48 hours from presentation).

Controls were defined as patients randomised to the FOxTROT trial to receive NAC and AC but did not develop proven or symptomatic colonic obstruction before their planned date of surgery. Each case was matched with three controls (1:3 ratio) based on gender (male or female) and age group (<50, 50–59, 60–69, or ≥70 years). Controls were sampled at random from other (unobstructed) patients receiving NAC using a random number matching algorithm within SAS® Software (SAS Institute Inc., Cary, NC, USA)[9].

Identification of cases

Cases were identified from Serious Adverse Events (SAE) reported by site investigators in the FOxTROT trial and corroborated by data from the NAC Case Report Form. Where further detail was required, sites retrieved source data (clinical notes or Electronic Health Records) in order to confirm or refute the diagnosis of obstruction. Identification of cases from SAE data was performed independently by two investigators (JG, KH), and any differences were resolved by the trial Chief Investigator (DM).

Outcome measures

The primary outcome measure was colonic obstruction, defined as proven or symptomatic obstruction (see *Definition of cases*), after randomisation and before the planned date of

surgery. Secondary outcome measures were grouped into three categories: (1) surgical decision making (operative approach [laparoscopic versus open]; stoma formation); (2) pathological outcomes (resection plane [intramesocolic versus mesocolic versus muscularis propria]; other bowel perforation (away from the tumour site); resection margin status [pR0 versus pR1 versus pR2]); (3) clinical outcomes, defined within 30 days of surgery with day of surgery as day 0 (death; length of stay [days]; re-operation; anastomotic leak [in patients for whom an anastomosis was performed]).

Covariates and data sources

Covariates related to clinical and radiographic features at the time of randomisation were extracted from the FOxTROT study database including age, sex, tumour location, and baseline radiological TNM stage. All radiologists were provided with face-to-face training in the assessment of colonic primary tumours within the FOxTROT trial to standardise reporting. Stricturing disease was defined as annular tumours, with evidence of luminal narrowing (in the absence of upstream dilatation of the colon). Stricturing disease either on radiological examination or endoluminal evaluation (or both) was coded as 'stricturing' for the purposes of the risk model. Endoscopic data (annular versus other tumour type, ability to pass endoscope past the tumour site) were not collected routinely in the FOxTROT trial, so were extracted for both cases and controls in source data from collaborating sites. Data extraction was performed from source data by two independent investigators (JG, YS), with any differences resolved by the senior investigator (DM). Pathological data on tumour regression grade (no/mild regression, moderate/marked/complete regression) was extracted from postoperative histological data, confirmed with central analysis of all specimens. As biopsy data was not collected routinely within FOxTROT, tumour differentiation and subtype

derived from postoperative pathological analysis were used as a surrogate for likely biopsy findings.

Statistical analysis

The study was conducted according to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) extension for case-control studies (Appendix B, Supplemental Digital Content 1, http://links.lww.com/SLA/E942) and reported according to SAMPL (Statistical Analyses and Methods in the Published Literature). Missing data were described and included in summary tables where applicable. Full statistical methodology is reported in *Appendix A*, Supplemental Digital Content 1, http://links.lww.com/SLA/E942.

Clinical, radiological, endoscopic and pathological characteristics of patients and tumours, and clinical and pathological outcomes were compared between: (Analysis 1) cases versus all other (unobstructed) patients randomised to receive NAC; (Analysis 2) cases versus matched controls. Timing of obstruction was examined using a continuous variable of time (in days) from randomisation to diagnosis of proven or symptomatic obstruction. To explore the effect of treatment response on timing of obstruction, patients were grouped by their histopathological assessment of treatment response (no or minimal response versus moderate or marked regression).

Adjustment for confounding

We assessed the association between covariates and subsequent bowel obstruction in matched patients using Bayesian hierarchical unconditional (unmatched) logistic regression analysis[10], with the diagnosis of bowel obstruction as the primary dependent variable. In this mixed-effects model, both proven and symptomatic obstruction were coded into a single obstruction

outcome variable. Models were adjusted using clinically plausible covariables listed above, including the matching variables[10]. Model coefficients are presented as adjusted odds ratio (OR) and 95% credible intervals (CI); these can be interpreted similarly to 95% confidence intervals but are philosophically distinct[11]. A sensitivity analysis for the primary model was conducted using proven obstruction only as the dependent variable. Analyses were conducted using R Foundation Statistical Program version 3.1.1 and C-STAN (packages: *finalfit, tidyverse, BRMS*). Model diagnostics were explored using *shinystan*.

Calculation of absolute risk of obstruction in the presence of risk characteristics

The prevalence of clinical, radiological, endoscopic, and pathological characteristics independently associated with risk of obstruction in the Bayesian mixed-effects model (named 'risk criteria') in cases and controls were summarised as percentages. The absolute risk of obstruction in the patients receiving NAC in FOxTROT in the presence or absence of each high-risk feature alone or in combination were estimated for tumours across different locations by assuming consistency in prevalence of risk criteria in the controls sample and patients randomised to NAC. 95% confidence intervals (C.I.) for proportions are provided for all percentage estimates. Cut-offs for very low, low- and high-risk groups were defined pragmatically through consensus amongst the international writing group, based on clinically important thresholds to influence clinical practice.

Results

Of 1053 patients randomised in the FOxTROT trial between, 699 (66.4%) were randomised to receive NAC between May 2008 and December 2016. Patients were included from at 85 centres (79 in the UK, 3 in Denmark, and 3 in Sweden). One patient withdrew their data from the study and was subsequently excluded from analyses. Of 698 patients undergoing NAC,

30 (4.3%) developed obstruction of whom 22 (3.2%) had radiologically proven and 8 (1.1%) had progressive symptoms suggestive of obstruction. *Figure 1* demonstrates the inclusion patients in this analysis from the FOxTROT trial participants.

Natural history of obstruction

Figure 2 displays the distribution from time of randomisation to obstruction, grouped by tumour regression grade. The median time from randomisation to bowel obstruction was 1.6 months (IQR: 1.1 to 2.0 months). The frequency of obstruction increased over time. There was no clear association between regression grade and timing of obstruction.

One patient was deemed to be obstructed immediately after randomisation so was taken straight for surgery and didn't start NAC. Of the remaining 29 patients, 20 (69.0%) completed NAC and 9 (31.0%) didn't finish NAC. Of those who started NAC, 5 (17.2%) were deemed to have moderate or marked regression, and 23 (79.3%) mild or no regression (2 missing data). There were 2 patients with mismatch repair deficient tumours amongst the 30 patients with obstruction (6.7%). We did not identify an association between tumour regression grade (p=0.22) or MMR status and obstruction (p=0.381) in this sample.

Analysis 1: Comparison of obstructed and unobstructed patients receiving NAC

Table 1 displays a comparison of patient and tumour characteristics between the groups. Obstructed patients were more likely to have a tumour at the hepatic flexure (16.7% versus 5.7%), splenic flexure (13.3% versus 2.8%) or in the transverse colon (23.3% versus 7.2%, p<0.001) than unobstructed patients. There was a numerically higher proportion of T4 tumours in obstructed patients, but this was not statistically significant (37.9% versus 23.8%, p=0.145).

Outcomes of obstruction

Of the obstructed patients (n=30), no perforation with frank peritonitis was seen at operation. Microperforation (contained and sealed) was seen in 5 patients (16.7%); representing a low absolute risk in patients undergoing NAC (1 in 139 [5/698]). Obstruction was managed with colonic stenting for 8 patients (26.7%) and expedited surgery for 21 (70.0%). 1 patient died preoperatively of an occlusive stroke; site investigators reported a concurrent symptomatic obstruction in this patient. All other patients (n=29) went on to primary tumour resection.

Table 2 displays outcomes of surgery in obstructed versus unobstructed patients. There was an increased frequency of open surgery (65.4% versus 38.0%, p=0.01) and occurrence of pR1 resections (12.0% versus 3.8%, p=0.004) in the obstructed group; however, only one pR2 resection was observed in an obstructed patient. There were no significant differences observed in the rates of stoma formation, anastomotic leak, reoperation, overall recurrence or death up to 30-days after surgery.

Obstructed patients were less likely to start adjuvant chemotherapy than non-obstructed patients (70.0% versus 88.0%, p<0.001), and fewer that successfully completed 18 weeks of AC (30.0% versus 65.3%, p=0.015). The 2-year overall recurrence rate was numerically higher in obstructed versus unobstructed patients, but this was not statistically significant (23.3% [7/30] versus 17.8% [119/668]; p=0.599).

Analysis 2: Comparison of obstructed cases and unobstructed controls

Table 3 describes the clinical, radiological and endoscopic features of the cases and controls. Cases and controls were well matched on both age and sex. Cases were more likely to be observed to have:

(1) obstructing disease on baseline endoscopy and/or be unable to pass past the lumen with the endoscope (53.3% versus 20.0%, p=0.008)

(2) stricturing disease on baseline radiology or endoscopy (78.3% versus 26.2%, p=0.002).

There were numerically more cases at the flexures and in the transverse colon than controls, although this was not statistically significant (p=0.051). This relationship could be explained through more frequent occurrence of endoscopic obstruction (p=0.004) or stricturing disease in these locations (p=0.006, *Supplementary Figure 1*, Supplemental Digital Content 1, http://links.lww.com/SLA/E942). There was also a trend towards an increased rate of radiological T4 disease in cases (p=0.056).

In the Bayesian mixed effects model (*Table 4, Supplementary Table 1*, Supplemental Digital Content 1, http://links.lww.com/SLA/E942*, Supplementary Figure 2*, Supplemental Digital Content 1, http://links.lww.com/SLA/E942 *and 3*, Supplemental Digital Content 1, http://links.lww.com/SLA/E942), the two features that remained strongly associated with obstruction after risk adjustment were:

(1) obstructing disease on endoscopy and/or being unable to pass through the lumen with the endoscopy (OR: 9.09, 95% CI 2.34 to 39.66)

(2) stricturing disease on radiology or endoscopy (OR: 7.18, 95% CI 1.84 to 32.34).

There was no independent association between tumour location or T-stage and obstruction. This was consistent across sensitivity analyses, including for proven obstruction only

(*Supplementary Table 2*, Supplemental Digital Content 1, http://links.lww.com/SLA/E942). These were defined as 'risk criteria' for the remainder of this analysis.

Risk criteria in cases and controls

The prevalence of both risk criteria in cases and controls can be found in *Supplementary table 3*, Supplemental Digital Content 1, http://links.lww.com/SLA/E942. A high proportion of obstructed cases had one or more risk criteria (28/30), and half had both risk criteria (15/30). Over half the controls had neither (48/90). Of patients with available data for both parameters (N=77), 14 patients were reported to have stricturing disease and 40 not to have stricturing disease on both radiological and endoscopic evaluation. 4 patients were reported to have stricturing disease on radiological and not on endoscopic evaluation, and 19 patients on endoscopic but not on radiological evaluation. There was 59.7% agreement between modalities with a Cohen's Kappa value of 0.37.

Risk stratification and implementation

The estimated proportion of patients randomised to NAC with one or both risk criteria and the rate of obstruction is summarised by tumour location in *Table 5*. The baseline risk for patients with neither high risk feature was 0.2% (0.0% to 0.6%) across different tumour locations. Identification of one high risk feature increased the obstruction risk (0.0% to 9.9%). Presence of both risk criteria concurrently conveyed the highest risk of obstruction. There was considerable variation in the absolute obstruction risk by tumour location: tumours at the flexures carried the highest risk (67.8%, 95% C.I. 34.3% to 93.8%) whilst sigmoid or rectosigmoid tumours had the lowest risk (7.6%, 95% C.I. 0.0% to 15.5%). Three risk classifications were defined for all patients undergoing NAC according to the presence or

absence of these criteria: 63.4% (443/698) of patients were at very low risk (<1%), 30.7% (214/698) at low risk (1-10%), and 5.9% (41/698) at high risk (>10%).

Discussion

This nested case-control study within an international randomised trial identifies two risk criteria features that target a small group of patients (5.9%) at substantial risk of colonic obstruction during NAC for colon cancer. There was considerable variation in the absolute risk of obstruction by tumour site. Importantly, these features are readily available to the MDT before treatment initiation and can be used to inform NAC decision making. We propose that these data can be used in four ways. Firstly, to inform patient consent. Secondly, to provide enhanced monitoring for patients at risk. Thirdly, to inform a decision to proceed straight to surgery, if appropriate. Fourthly, to provide support for colonic stenting or diversion to facilitate NAC, particularly where there is concern that the primary tumour may be unresectable.

Uniquely, this study was able to prospectively observe a large patient cohort who had a planned delay before undergoing resectional surgery. We did not detect an association between the occurrence and timing of obstruction and treatment response (assessed using tumour regression grade) nor dMMR status. The study did however identify physical tumour factors identifiable by endoscopy and radiology that could define tumours at higher risk of obstruction. As care pathways for colon cancer increase in complexity, this study has implications for the safe implementation of novel chemotherapy pathways for colon cancer[8,12].

The two risk criteria identified here are anatomical properties of a colonic tumour, rather than related to their treatment response, histopathological subtype or genomic profile. Specifically,

transmural disease (causing stricturing and scarring) noted on radiology or endoscopy, and an obstructing phenotype noted at the point of endoscopy. Obstruction was most common in tumours at the hepatic and splenic flexures; it is plausible that this is related to peritoneal tethering and reduced compliance of the colon in these locations, although multivariable analysis suggested tumour stricturing and/or obstructing disease were the most influential features. A description of obstructive features at endoscopy before patients undergo NAC has not previously been reported. We suggest that complete luminal assessment could be added to MDT assessment criteria for high-risk colon cancer. Being unable to traverse a tumour should not be considered a contraindication to NAC in the absence of clinical symptoms suggestive of acute obstruction (only 3 of 28 patients (10.7%) where this was attempted went on to obstruct). With the high rate of tumour regression seen this higher risk group may in fact benefit most from NAC where the tumour is chemo-sensitive. The presence of a circumferential tumour alone was not associated with risk of obstruction during NAC, but where it had reached the point that a circumferential tumour caused luminal stricturing that visible radiologically or endoscopically, this reached statistical significance. As would be expected in a pragmatic study, with a degree of subjectivity in tumour evaluation despite quality assurance measures, there was some disagreement in characteristics reported using different treatment modalities. This highlights the important of having all information related to multi-modal assessment available to the multidisciplinary team at the time a treatment decision is made.

The rate of stoma formation, anastomotic leak, reoperation and early postoperative mortality were all comparable between obstructed and non-obstructed patients. This contrasts with a wealth of previous literature[1,3,5,13,14]. We hypothesise that the favourable outcomes we have seen may be related to the enhanced monitoring provided to patients attending the hospital

for neoadjuvant therapy, enabling early intervention in the event of obstructive signs and symptoms. Importantly, this benefit should continue to be realised in routine practice beyond the trial itself[15]. Improved perioperative outcomes (for example, reduced rates of anastomotic leak) were also seen following NAC in the FOxTROT trial in comparison with patients randomised to proceed directly to surgery[8]. This may also reflect the benefits of preoperative patient care in the oncology outpatient setting[7,8].

There were still adverse outcomes from obstruction observed in this series. The rate of initiation or completion of adjuvant therapy was lower in obstructed patients, which may reflect prolonged recovery after urgent surgery. Although there was no difference in advanced lymph node involvement (N2 rate in Analysis 1: 27.6% obstructed cases versus 28.3% unobstructed patients randomised to NAC), there was a higher proportion of T4 rather than T3 tumours seen in obstructed patients (Analysis 1: 37.9% versus 23.8% respectively). This may, in part, be due to poorly responsive disease, but potentially may represent an increased propensity for obstruction in more advanced disease. A higher proportion of T4 tumours may also explain the increased pR1 rate in obstructed patients. For patients developing progressive obstruction where there is a real concern for the resectability of the primary tumour, colonic defunctioning or stenting may be helpful to facilitate NAC[16,17].

This nested case-control study benefitted from high-quality data monitoring, governance and quality assurance within a randomised trial, and provides the best available evidence on this topic. Nonetheless, this study has several limitations. First, the absolute number of obstructions within this cohort was low (n=30), so inferential statistics are challenging. To account for this, we have adopted Bayesian methodology to allow us to interpret the probabilistic distributions of factors associated with obstruction. All model assumptions were

met, MCMC chains demonstrated no evidence of divergence, and the results were robust to sensitivity analyses. Second, case-control matching was performed using only two simple matching variables (age and sex) in a 3:1 ratio. This was done to ensure that no factors highly associated with obstruction were included in the case-matching process, therefore becoming uninterpretable. However, this pragmatic approach may have left residual sampling bias or confounding. There are several biases of conditional logistic regression which come under criticism, so unmatched logistic regression was selected for the primary analysis[10]. Third, the true impact of treatment response on risk of obstruction may be left unexplored here, as tumours that were highly anatomically unfavourable (i.e., obstructed early within the window to surgery) would not have had the opportunity to demonstrate regression at the time of resection; for example, no tumours demonstrating a pathological complete response obstructed. However, tumours obstructed throughout the treatment window even when displaying moderate regression, suggesting that this did not seem to be a key factor in its pathoaetiology. Fourth, the estimates of absolute risk rely on the assumption that the prevalence of risk criteria is similar in the control sample to the other unobstructed patients that received NAC. Fifth, whilst clinical and radiological data were collected prospectively, endoscopic characteristics were collected retrospectively (directly from prospectively recorded source data (e.g., endoscopy reports). Finally, we were unable to compare outcomes for patients that were not randomised in the trial because of obstructive symptoms with those in the trial that developed obstruction. This was because of a lack of consent and such patients would frequently be managed through an emergency pathway; the generalisability of our data relies of the assumption of similar disease biology.

This study defines a prospectively identifiable subgroup of patients at greater than 10% risk of obstruction and so provides a risk stratification tool that can assist oncologists in the safer introduction of neoadjuvant chemotherapy for patients with colon cancer.

References

1. Dahdaleh FS, Sherman SK, Poli EC, et al. Obstruction predicts worse long-term outcomes in stage III colon cancer: A secondary analysis of the N0147 trial. *Surgery*. Dec 2018;164(6):1223-1229. doi:10.1016/j.surg.2018.06.044

2. Koebrugge B, Vogelaar FJ, Lips DJ, et al. The number of high-risk factors is related to outcome in stage II colonic cancer patients. *Eur J Surg Oncol*. Nov 2011;37(11):964-70. doi:10.1016/j.ejso.2011.08.135

3. Manceau G, Mege D, Bridoux V, et al. Emergency Surgery for Obstructive Colon Cancer in Elderly Patients: Results of a Multicentric Cohort of the French National Surgical Association. *Dis Colon Rectum*. Aug 2019;62(8):941-951. doi:10.1097/dcr.0000000000001421

4. Webster PJ, Tavangar Ranjbar N, Turner J, El-Sharkawi A, Zhou G, Chitsabesan P. Outcomes following emergency colorectal cancer presentation in the elderly. *Colorectal Dis*. Jul 1 2020;doi:10.1111/codi.15229

5. Biondo S, Gálvez A, Ramírez E, Frago R, Kreisler E. Emergency surgery for obstructing and perforated colon cancer: patterns of recurrence and prognostic factors. *Tech Coloproctol*. Dec 2019;23(12):1141-1161. doi:10.1007/s10151-019-02110-x

6. Fahim M, Dijksman LM, van der Nat P, Derksen WJM, Biesma DH, Smits AB. Increased long-term mortality after emergency colon resections. *Colorectal Dis*. Jul 6 2020;doi:10.1111/codi.15238

7. FOxTROT-Collaborative-Group. Fluorouracil and Oxaliplatin With or Without Panitumumab In Treating Patients With High-Risk Colon Cancer That Can Be Removed by Surgery (FOxTROT).

8. Morton D, Seymour MT, FOxTROT-Collaborative-Group. FOxTROT: an international randomised controlled trial in 1052 patients (pts) evaluating neoadjuvant

chemotherapy (NAC) for colon cancer. presented at: American Society of Clinical Oncology (ASCO); 2019; Chicago, Illinois. Accessed 22 September 2020. https://ascopubs.org/doi/abs/10.1200/JCO.2019.37.15_suppl.3504

9. Mortensen LQ, Andresen K, Burcharth J, Pommergaard H-C, Rosenberg J. Matching Cases and Controls Using SAS® Software. Code. *Frontiers in Big Data*. 2019-May-08 2019;2(4)doi:10.3389/fdata.2019.00004

10. Pearce N. Analysis of matched case-control studies. *Bmj*. Feb 25 2016;352:i969. doi:10.1136/bmj.i969

11. Makowski D, Ben-Shachar M, Lüdecke D. bayestestR: Describing Effects and their Uncertainty, Existence and Significance within the Bayesian Framework. Journal of Open Source Software. 2019. p. 1541.

12. Karoui M, Gallois C, Piessen G, et al. Does neoadjuvant FOLFOX chemotherapy improve the prognosis of high-risk Stage II and III colon cancers? Three years' follow-up results of the PRODIGE 22 phase II randomized multicentre trial. *Colorectal Dis*. Feb 13 2021;doi:10.1111/codi.15585

13. Mege D, Manceau G, Beyer-Berjot L, et al. Surgical management of obstructive right-sided colon cancer at a national level results of a multicenter study of the French Surgical Association in 776 patients. *Eur J Surg Oncol*. Oct 2018;44(10):1522-1531. doi:10.1016/j.ejso.2018.06.027

14. Winner M, Mooney SJ, Hershman DL, et al. Management and outcomes of bowel obstruction in patients with stage IV colon cancer: a population-based cohort study. *Dis Colon Rectum*. Jul 2013;56(7):834-43. doi:10.1097/DCR.0b013e318294ed6b

15. Downing A, Morris EJ, Corrigan N, et al. High hospital research participation and improved colorectal cancer survival outcomes: a population-based study. *Gut*. Jan 2017;66(1):89-96. doi:10.1136/gutjnl-2015-311308

16. Harvey PR, Rees J, Baldwin S, et al. Outcomes of colorectal stents when used as a bridge to curative resection in obstruction secondary to colorectal cancer. *Int J Colorectal Dis*. Jul 2019;34(7):1295-1302. doi:10.1007/s00384-019-03302-5

17. Hill J, Kay C, Morton D, et al. CREST: Randomised phase III study of stenting as a bridge to surgery in obstructing colorectal cancer—Results of the UK ColoRectal Endoscopic Stenting Trial (CREST). *Journal of Clinical Oncology*. 2016;34(15_suppl):3507-3507. doi:10.1200/JCO.2016.34.15_suppl.3507

Figure 1. Flowchart of included patients

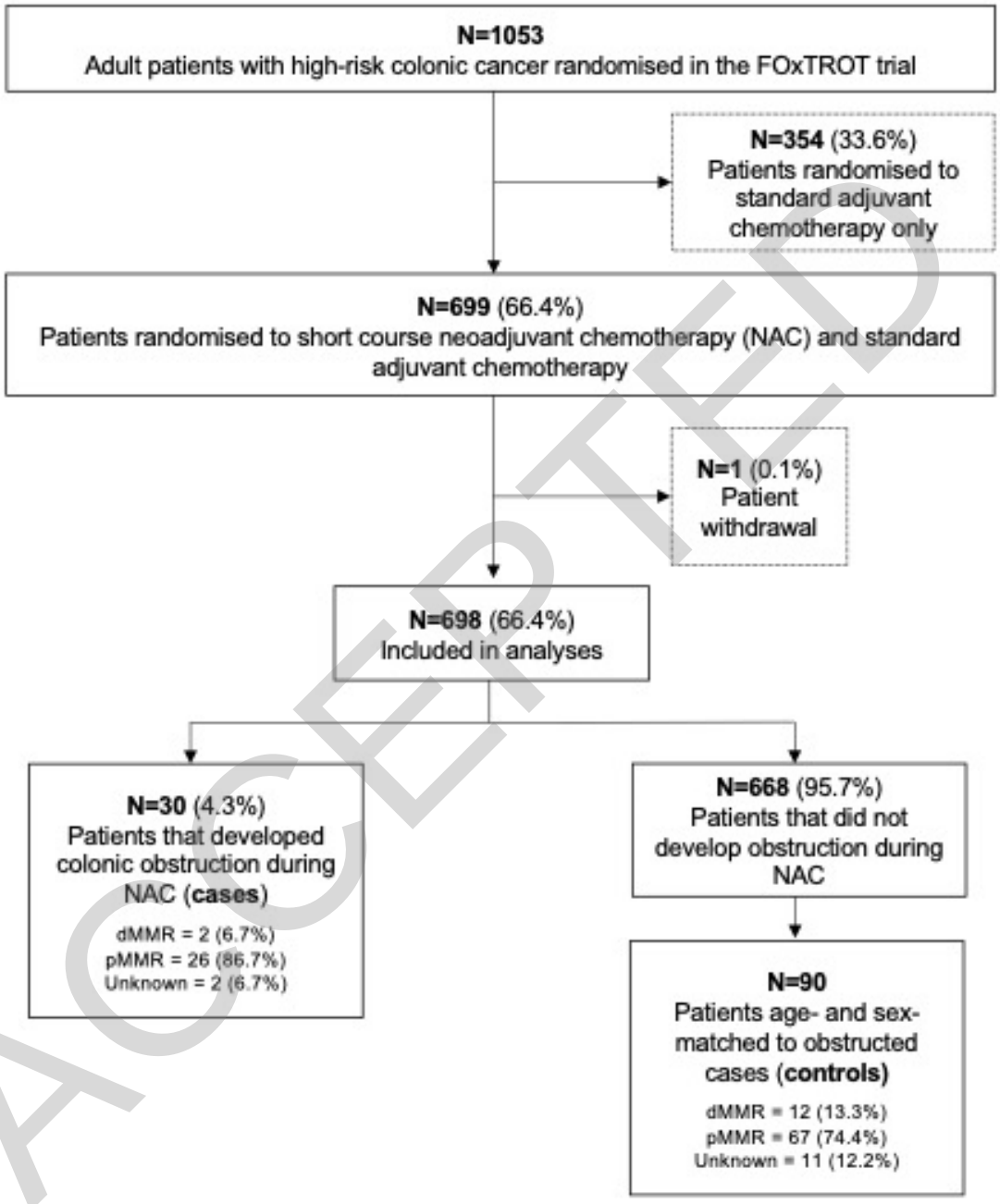

Figure 2. Timing from randomisation to obstruction in patients undergoing neoadjuvant chemotherapy grouped by pathological regression grade.

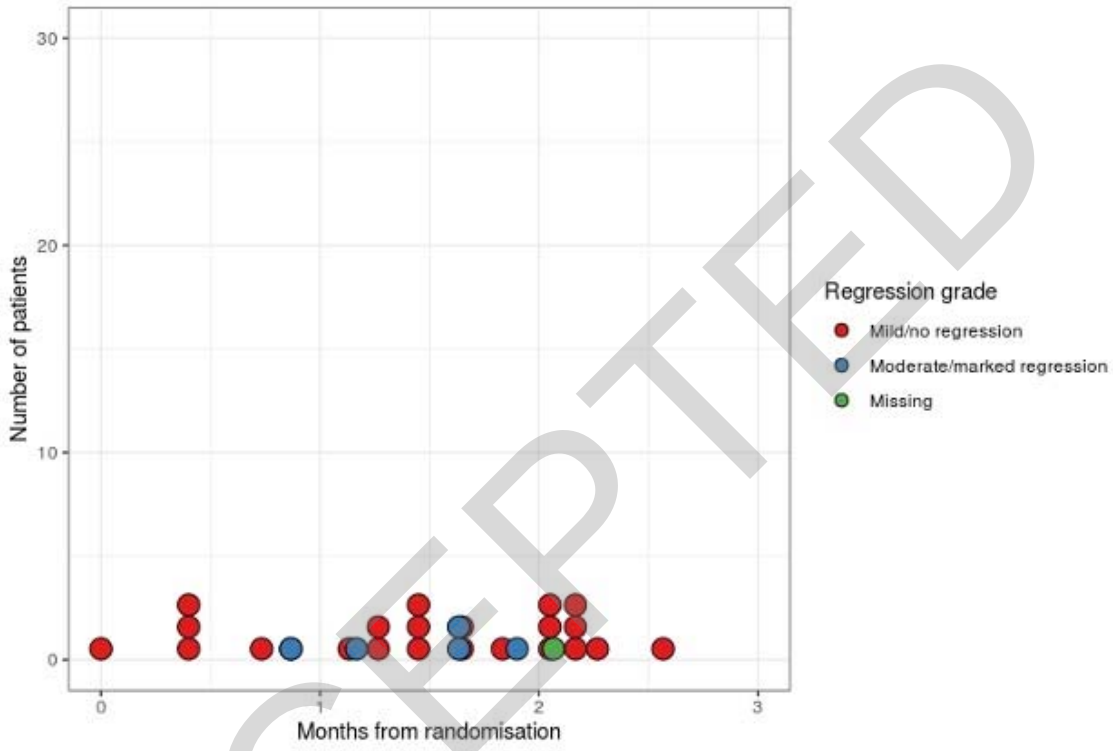

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Table 1. Characteristics of obstructed patients (cases) and other unobstructed patients randomised to receive NAC.

Factor	Level	Cases (N=30)	Other patients randomised to NAC (N=668)*	P-value
Clinical features				
Age at randomisation	Mean (SD)	61.6 (9.4)	63.1 (9.9)	0.414
Sex	Female	11 (36.7)	240 (35.9)	1
	Male	19 (63.3)	428 (64.1)	
Tumour location	Caecum	2 (6.7)	119 (17.8)	***<0.001***
	Ascending colon	1 (3.3)	120 (18.0)	
	Hepatic Flexure	5 (16.7)	38 (5.7)	
	Transverse colon	7 (23.3)	48 (7.2)	
	Splenic flexure	4 (13.3)	19 (2.8)	
	Descending colon	2 (6.7)	34 (5.1)	
	Sigmoid	7 (23.3)	240 (35.9)	
	Rectosigmoid	2 (6.7)	50 (7.5)	
Baseline radiological features				
T-stage	Muscularis propria (T2)	0 (0.0	1 (0.2)	0.145
	Beyond muscularis propria (T3)	18 (62.1)	505 (76.1)	
	Adjacent organs or peritoneum (T4)	11 (37.9)	158 (23.8)	
	Missing	1	4	
N-stage	N0	12 (41.4)	157 (23.6)	0.071
	N1 (1-3 nodes)	9 (31.0)	319 (48.0)	
	N2 (4+ nodes)	8 (27.6)	188 (28.3)	
	Missing	1	4	
Maximum tumour thickness (mm)	Mean (SD)	23.9 (21.7)	20.3 (11.7)	0.129
Maximum distance of spread beyond muscularis propria (mm)	Mean (SD)	9.9 (9.0)	9.2 (7.9)	0.622
Irregularly enhancing LNs	Mean (SD)	1.2 (1.8)	1.9 (2.1)	0.123

Peritonealisation	Non-peritonealised	3 (13.0)	163 (30.0)	0.129
	Peritonealised	20 (87.0)	380 (70.0)	
	Missing	7	125	
Extra-mural vascular invasion	No	10 (34.5)	270 (41.0)	0.322
	Minimal spreading	10 (34.5)	190 (28.8)	
	Nodular spread into small vessel	9 (31.0)	151 (22.9)	
	Spread along large vein	0 (0.0)	48 (7.3)	
	Missing	1	9	
Pathological features				
RAS status	Mutant	6 (27.3)	165 (34.0)	0.730
	Not determined	1 (4.5)	13 (2.7)	
	Wildtype	15 (68.2)	307 (63.3)	
	Missing	8	183	
Tumour subtype	Adenocarcinoma	27 (96.4)	550 (87.5)	0.209
	Mucinous	1 (3.6)	82 (11.4)	
	Signet ring	0 (0.0)	8 (1.1)	
	Missing	2	28	
Differentiation	Well/moderate	27 (96.4)	532 (85.3)	0.168
	Poor	1 (3.6)	92 (14.7)	
	Missing	2	44	

Chi-squared test calculations exclude missing data. *One patient randomised to NAC and AC withdrew from the FOxTROT trial and was excluded.

Table 2. Clinical and pathological outcomes in obstructed patients (cases) versus other unobstructed patients randomised to receive NAC.

Outcome	**Levels**	**Cases (N=30)***	**Other patients randomised to NAC (N=668)**	**P-value**
Surgical decision making				
Operative approach	Open	17 (65.4)	216 (38.0)	***0.01***
	Laparoscopic	9 (34.6)	352 (62.0)	
	Missing	4	100	
Stoma formation	No	24 (88.9)	569 (88.4)	1
	Yes	3 (11.1)	75 (11.6)	
	Loop stoma	2 (66.7)	45 (60.0)	1
	End stoma	1 (33.3)	30 (40.0)	
	Missing	3	24	
Pathological outcomes				
Resection plane	Mesocolic	16 (76.2)	133 (86.2)	0.324
	Intramesocolic	4 (19.0)	62 (11.0)	
	Muscularis propria	1 (4.8)	16 (2.8)	
	Missing	9	105	
Bowel perforation$^{\epsilon}$	No	26 (86.7)	615 (92.2)	0.454
	Yes	4 (13.3)	52 (7.8)	
	Missing	3	70	
Margin status	pR0	21 (84.0)	577 (95.8)	***0.004***
	pR1	3 (12.0)	23 (3.8)	
	pR2	1 (4.0)	2 (0.3)	
	Missing	5	66	
Clinical outcomes (up to 30 postoperative days)				
Death	No	27 (96.4)	651 (99.5)	0.396
	Yes	1 (3.6)	3 (0.5)	
	Missing	2	14	
Length of stay	Mean (SD)	10.8 (15.1)	7.3 (7.5)	***0.023***
Reoperation	No	27 (96.4)	626 (95.7)	1
	Yes	1 (3.6)	28 (4.3)	
	Missing	2	14	
Anastomotic leak	No	27 (96.4)	617 (96.7)	1
	Yes	1 (3.6)	21 (3.3)	
	No anastomosis$^{\$}$	1	30	
	Missing	2	14	
Adjuvant therapy				
Treatment status	Completed	10 (33.3)	436 (65.3)	***<0.001***
	Started did not finish	10 (33.3)	135 (20.2)	
	Did not start	10 (33.3)	80 (12.0)	
	Missing	0	17	
Oncological outcomes (at 2 years after randomisation)				
	No	22 (75.9)	549 (82.2)	0.599

Overall recurrence	Yes	7 (24.1)	119 (17.8)	

*1 case died preoperatively of an occlusive stroke, so postoperative outcome data is not available. [€]Included both macroscopic perforation (noted at operation) and microscopic (noted during pathological examination) [$]Patients with no anastomosis not included in proportion of patients with anastomotic leak. Chi-squared test calculations exclude missing data. NAC = Neoadjuvant therapy.

Table 3. Clinical, radiological, endoscopic and pathological features of obstructed cases versus matched controls. Chi-squared test calculations exclude missing or unavailable data.

Factor	Levels	Cases N=30	Controls N=90	P-Value
Clinical features				
Age at randomisation	Mean (SD)	61.6 (9.4)	61.6 (9.6)	0.974
Sex	Female	11 (36.7)	33 (36.7)	1
	Male	19 (63.3)	57 (63.3)	
Tumour location	Caecum	2 (6.7)	13 (14.4)	0.051
	Ascending colon	1 (3.3)	12 (13.3)	
	Hepatic Flexure	5 (16.7)	8 (8.9)	
	Transverse colon	7 (23.3)	11 (12.2)	
	Splenic flexure	4 (13.3)	2 (2.2)	
	Descending colon	2 (6.7)	3 (3.3)	
	Sigmoid	7 (23.3)	35 (38.9)	
	Rectosigmoid	2 (6.7)	6 (6.7)	
Baseline radiological features				
T-stage	Beyond muscularis propria (T3)	18 (62.1)	71 (78.9)	0.117
	Adjacent organs or peritoneum (T4)	11 (37.9)	19 (21.1)	
	Missing	1	0	
N-stage	N0	12 (41.4)	21 (23.3)	0.07
	N1 (1-3 nodes)	9 (31.0)	49 (54.4)	
	N2 (4+ nodes)	8 (27.6)	20 (22.2)	
	Missing	1	0	
Maximum tumour thickness (mm)	Mean (SD)	23.9 (21.7)	20.2 (12.0)	0.257
	Missing	1	1	
Maximum distance of spread beyond muscularis propria (mm)	Mean (SD)	9.9 (9.0)	8.1 (7.2)	0.248
	Missing	1	1	
Irregularly enhancing LNs	Mean (SD)	1.2 (1.8)	1.9 (2.1)	0.151
	Missing	2	2	
Peritonisation	Non-peritonealised	3 (13.0)	20 (27.0)	0.273

	Peritonealised	20 (87.0)	54 (73.0)	
	Missing	1	0	
Extra-mural vascular invasion	No	10 (34.5)	37 (41.1)	0.26
	Minimal spreading	10 (34.5)	29 (32.2)	
	Nodular spread into small vessel	9 (31.0)	17 (18.9)	
	Spread along large vein	0 (0.0)	7 (7.8)	
	Missing	1	0	
Circumferential (radiology)	No	18 (78.3)	54 (70.1)	0.619
	Yes	5 (21.7)	23 (29.9)	
	Missing	7	13	
Stricturing (radiology)	No	13 (56.5)	68 (88.3)	***0.002***
	Yes	10 (43.5)	9 (11.7)	
	Missing	7	13	
Obstructing (radiology)	No	20 (87.0)	76 (98.7)	0.055
	Yes	3 (13.0)	1 (1.3)	
	Missing	7	13	
Pathological features				
MMR status	Proficient	26 (96.3)	67 (84.8)	0.116
	Deficient	1 (3.7)	12 (15.2)	
	Missing	3	11	
RAS status	Mutant	6 (27.3)	19 (26.8)	0.996
	Not determined	1 (4.5)	3 (4.2)	
	Wildtype	15 (68.2)	49 (69.0)	
	Missing	8	19	
Tumour subtype	Adenocarcinoma	27 (96.4)	70 (84.3)	0.219
	Mucinous	1 (3.6)	12 (14.4)	
	Signet ring	0 (0.0)	1 (1.2)	
	Missing	2	7	
Differentiation	Well/moderate	27 (96.4)	72 (86.7)	0.282
	Poor	1 (3.6)	11 (13.3)	
Endoscopic features				

Unable to pass scope	No	3 (10.0)	25 (27.8)	***0.004***
	N/A – Caecal	3 (10.0)	17 (18.9)	
	N/A – Flexible sigmoidoscopy only	8 (26.7)	30 (33.3)	
	Yes	16 (53.3)	18 (20.0)	
Circumferential (endoscopy)	No	13 (59.1)	43 (71.7)	0.414
	Yes	9 (40.9)	17 (28.3)	
	Not available	9	30	
Stricturing (endoscopy)	No	6 (27.3)	41 (69.5)	***0.002***
	Yes	16 (72.7)	18 (30.5)	
	Not available	8	31	
Ulcerating (endoscopy)	No	18 (81.8)	47 (78.3)	0.97
	Yes	4 (18.2)	13 (21.7)	
	Not available	8	30	
Polypoid (endoscopy)	No	20 (90.9)	48 (78.7)	0.34
	Yes	2 (9.1)	13 (21.3)	
	Not available	1	29	
Obstructing (endoscopy)	No	14 (60.9)	71 (88.8)	***0.005***
	Yes	9 (39.1)	9 (11.2)	
	Not available	7	10	
Summary baseline features (radiological and endoscopic)				
Circumferential (all)	No	12 (48.0)	44 (53.7)	0.789
	Yes	13 (52.0)	38 (46.3)	
	Missing	5	4	
Stricturing (all)	No	5 (21.7)	59 (73.8)	***<0.001***
	Yes	18 (78.3)	21 (26.2)	
	Missing	7	10	

Table 4. Bayesian unconditional mixed-effects model demonstrating features associated with obstruction in the case-control matched data.

			95% credible interval	
		Odds ratio	*Lower*	*Upper*
Age	Years	0.97	0.91	1.05
Sex	Female	-	-	-
	Male	1.63	0.39	7.29
Tumour location*	Ascending or descending colon	-	-	-
	Hepatic or splenic flexure	1.39	0.18	9.83
	Transverse colon	0.55	0.05	4.99
	Sigmoid or rectosigmoid	0.36	0.06	2.25
Radiological T-stage	T3	-	-	-
	T4	1.61	0.39	6.60
Stricturing disease	No	-	-	-
	Yes	***7.18***	***1.84***	***32.34***
Obstructing (endoscopy) or unable to pass scope	No	-	-	-
	Yes	***9.09***	***2.34***	***39.66***

*Tumour locations were grouped anatomically by peritoneal covering of associated the large bowel: sigmoid and transverse on a mesentery; ascending/descending colon retroperitoneal; flexures tethered.

Table 5. Estimated absolute risk of obstruction in all patients receiving NAC in FOxTROT (n=698) with presence or absence of risk criteria.

	Tumour location			
	Ascending or descending colon	Hepatic or splenic flexure	Transverse colon	Sigmoid or rectosigmoid
No stricturing disease AND able to pass scope / non-obstructing	0.4% (0.0% to 1.3%) n=223	0.0% (0.0% to 0.0%) n=15	0.0% (0.0% to 0.0%) n=19	0.6% (0.0% to 1.8%) n=167
Stricturing disease (radiology or endoscopy)	3.3% (0.0% to 9.5%) n=31	6.8% (0.0% to 19.2%) n=16	0.0% (0.0% to 0.0%) n=13	2.5% (0.0% to 7.4%) n=41
Unable to pass scope / obstructing (endoscopy)	9.9% (0.0% to 27.4%) n=11	4.5% (0.0% to 13.0%) n=23	0.0% (0.0% to 0.0%) n=6	2.1% (0.0% to 6.1%) n=49
Stricturing disease (radiology or endoscopy) **AND** Unable to pass scope / obstructing (endoscopy)	19.8% (0.0% to 42.2%) n=12	67.8% (34.3% to 93.8%) n=12	31.4% (9.2% to 53.6%) n=17	7.6% (0.0% to 15.5%) n=43

Presented as estimated percentage risk with 95% confidence intervals in rounded brackets. N= represents the estimated number of patients from all patients receiving NAC in FOxTROT represented by each group. A suggested classification is presented by colour: green (very low risk <1%, including 443 patients (63.4%)); yellow (low risk 1% to 10%, including 214 patients (30.7%)); red (high risk >10%, including 41 patients (5.9%).