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Ileus caused by obstructing colorectal cancer—impact on long-term survival

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Abstract

Purpose It is unclear whether obstructing colorectal cancer (CRC) has a worse prognosis than non-obstructing CRC. Of CRC patients, 10–28% present with symptoms of acute obstruction. Previous studies regarding obstruction have been primarily based on short-term outcomes, risk factors and treatment modalities. With this study, we want to determine the long-term survival of patients presenting with acute obstructive CRC.

Methods This single-centre observational retrospective cohort study includes all CRC patients who underwent surgery between December 2004 and 2010. Patients were divided into two groups: ileus and no ileus. Survival analyses were performed for both groups. Additional survival analyses were performed in patients with and without synchronous metastases. The primary outcome was survival in months.

Results A total of 1236 patients were included in the analyses. Ileus occurred in 178 patients (14.4%). The 5-year survival for patients with an ileus was 32% and without 60% ($P < 0.01$). In patients without synchronous metastases, survival with and without an ileus was 40.9 and 68.4%, respectively ($P < 0.01$). If ileus presentation was complicated by a colon blowout, 5-year survival decreased to 29%. No significant difference was found in patients with synchronous metastases. Survival at 5 years in this subgroup was 10 and 12% for patients with and without an ileus, respectively ($P = 0.705$).

Conclusions Patients with obstructive CRC have a reduced short-term overall survival. Also, long-term overall survival is impaired in patients who present with acute obstructive CRC compared to patients without obstruction.

Keywords Colorectal cancer · Obstruction · Emergency surgery · Survival · Oncological outcome

Introduction

Colorectal cancer (CRC) is the third most common type of cancer in the Netherlands [1].

Patients with CRC are often analysed because of abdominal symptoms such as bowel habit changes, bloody stool, unintentional weight loss and anaemia. Approximately 10–28% of the patients with CRC present with symptoms of an acute obstruction [2].

Symptoms of colorectal obstruction are abdominal (cramping) pain and severe constipation [3]. Obstruction leads to distension of the colorectal wall, which may cause insufficient circulation that in some cases leads to ischaemia and perforation. These patients deteriorate within days after the acute obstruction with poor intake, vomiting and weight loss. In some cases, this is accompanied by severe abdominal pain and sepsis [4].

In cases with obstructing CRC, several treatment modalities can be used. The Dutch Colorectal Audit (DCRA), a nationwide database consisting of all CRCs, shows that the most common treatment options are emergency resection of the tumour (82%), followed by stenting prior to surgery (11%) and two-staged surgery (first decompressing colostomy followed by elective resection, 7%) [5]. These surgical treatment options are mainly applied for obstructive left-sided CRC.

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The short-term results after emergency surgery in obstructing CRC show higher morbidity and mortality rates [6, 7]. Emergency surgery is an independent risk factor for mortality, which may increase to 41% in elderly patients with two or more additional risk factors [8, 9]. The long-term results show a lower 5-year disease-free survival rate for patients who had emergency colorectal resections versus elective resections [10]. Disease recurrence in patients with obstructing CRC seems to be higher [11]. From the fact that the recurrence rate is significantly higher and the 5-year disease-free survival rate is lower, one may speculate that the overall survival is also impaired in the obstructing CRC group. Limited data is available regarding long-term survival between cases of obstructing and non-obstructing CRCs [12].

The aim of this study is to assess the long-term survival of patients with acute obstructive CRC causing an ileus compared to patients without obstructing CRC.

Materials and methods

Database and definitions

This is a single-centre retrospective observational cohort study. The database consisted of patients who underwent surgery for CRC in our hospital between December 2004 and December 2010. This included surgery with curative intent or palliative resections. Patients who underwent oncologic colorectal resection because of an appendix carcinoma or pseudomyxoma peritonei (PMP) were excluded. Demographic-, clinical- and tumour-related data were ascertained from patients' medical charts. Surgical data consisted of resection type; these were classified as emergency or elective. In case of an emergency, surgery was performed within 24 h after diagnoses of acute obstruction. Additionally, follow-up data on systemic metastases and duration of follow-up were collected. Metastases could be diagnosed preoperatively, perioperatively, and during follow-up by imaging and, whenever possible, with histologic confirmation or when described in autopsy reports. Metastases diagnosed before, during and 6 weeks after surgery were defined as synchronous metastases. Metastases diagnosed after 6 weeks were classified as metachronous.

Surgery-related mortality was defined as death within 30 days after surgery. Pathological classification was based on the fifth edition of the TNM classification [13]. The date of death was ascertained by using the Social Security number of the patient in the Municipal Personal Records Database (Gemeentelijke basisadministratie persoonsgegevens (GBA)). Follow-up time was determined from the date of surgery until the date of death or the last date of follow-up. Patients were divided into two groups: ileus and no ileus. Ileus was defined as clinical obstruction and distension of the abdomen. In some cases, this clinical finding could be confirmed by the presence of a dilated colon with computed tomography (CT scan) or an X-ray of the abdomen; the presence of a dilated colon could also be determined perioperatively. A blowout was diagnosed on a CT scan showing a perforation of the colon with pneumoperitoneum and/or free fluid or intra-abdominal fluid and signs of tumour perforation of the colon during surgery.

Statistics

We analysed patients' demographics by using the Kolmogorov-Smirnov model to determine if the variables were normally distributed. Data are presented as the means and SD for normally distributed data and as the medians and interquartile ranges (IQR) for non-normally distributed data. The relationships between categorical variables were analysed by a χ^2 test. Kaplan-Meier curves were constructed to compare the survival rates between patients with and without an ileus. The statistical outcome between these groups was determined by using the log-rank test. The Mann-Whitney U test was performed to determine the survival rates between patients with and without an ileus at 5 years after surgery. Additional survival analyses were performed in patients with an ileus complicated by a blowout and in patients without synchronous metastases. The primary outcome was overall survival in months. A P value of less than 0.05 was used to indicate significance. We used IBM SPSS Statistics program, version 24.

Results

A total of 1249 patients underwent surgery for CRC between December 2004 and December 2010. Nine patients were excluded because of incorrect or missing Social Security number. Four patients were excluded because of appendix carcinoma or PMP. The remaining 1236 patients were included in the analysis (Fig. 1).

Demographics

Of the 1236 patients, 688 were male (55.6%) (Table 1). The median age of the patients at the time of diagnosis was 71 years (IQR 62–78 years); median follow-up time was 72 months (IQR 21–97 months). The incidence of patients presenting with an ileus was 178 (14.4%). The most frequently reported location of the tumour was the rectum, followed by the sigmoid and the caecum (Table 2). Metastases were found in 393 patients (32%), of which 212 (54%) were synchronous metastases (Table 1). pTNM stadium was missing in 90 (7.3%) patients because of numerous reasons. In 69 patients, no resection was performed (76.7%); in these patients, only

Fig. 1 Flowchart of included patients
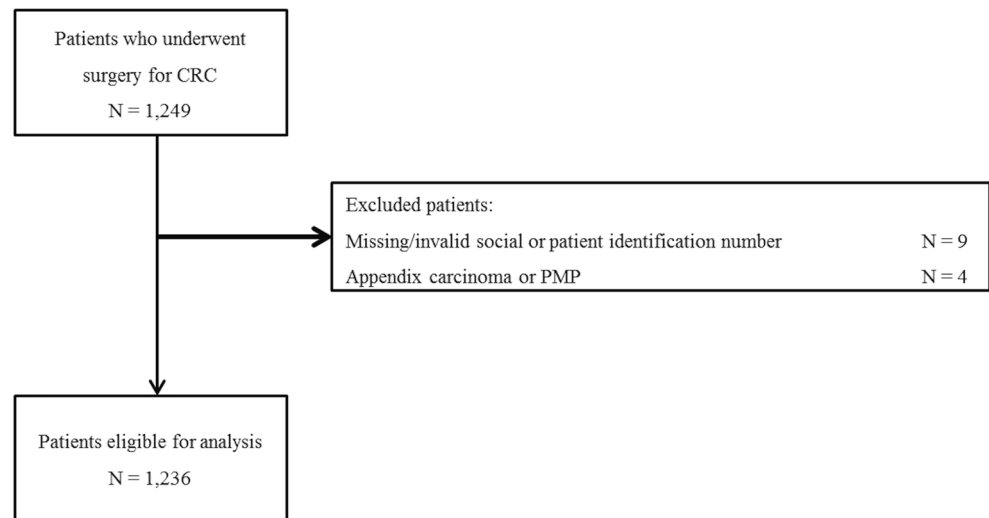
colostomy ($N = 58$, 64.4%), exploratory laparotomy ($N = 3$, 3.3%) or palliative bypass ($N = 8$, 8.9%) was performed. In 16 patients (17.8%), no vital tumour cells were found. In the remaining five (5.6%) patients, a preventive colostomy was performed. However, no curative resection could occur because of postoperative death in two patients and progressive disease in the other three patients.

Ileus versus no ileus

The median age of patients presenting with an ileus was 74 years (IQR 65–80 years) compared to 70 years (IQR 62–77 years) for patients without an ileus ($P < 0.01$). In the patients with ileus, emergency surgery was performed in 144 (81.0%) of the cases compared to 44 (4.0%) patients without ileus ($P < 0.01$). The median follow-up time for patients with and without an ileus was 21 months (IQR 3–77 months) and 76 months (IQR 27–100 months), respectively ($P < 0.01$). A statistical difference in tumour location was found for the sigmoid colon, hepatic and splenic flexures. Adjuvant chemotherapy was administered in 274 patients (25.6%). Patients with an ileus received chemotherapy more frequently than patients without an ileus. Palliative chemotherapy was indicated in 20 of the 50 patients (40%) with an ileus. For the patients without an ileus, in 76 out of the 224 patients (33.9%), palliative chemotherapy was indicated ($P = 0.06$; Table 2).

Table 1 Patient characteristics of 1236 included patients with colorectal carcinoma

Patient characteristics ($N = 1236$)	No ileus ($N = 1058$)	Ileus ($N = 178$)	P value
Gender			0.54
Male	593 (56.0%)	95 (53.4%)	
Female	465 (44.0%)	83 (46.6%)	
Median age years (IQR)	70 (62–77)	74 (65–80)	< 0.01
Surgery < 24 h	44 (4.2%)	144 (80.9%)	< 0.01
Re-operation	150 (14.8%)	30 (16.9%)	0.35
R1/R2 resection	14 (1.3%)	11 (6.2%)	< 0.01
Comorbidity (ASA)			
I	142 (13.4%)	10 (5.6%)	< 0.01
II	577 (54.5%)	72 (40.4%)	< 0.01
III	325 (30.7%)	82 (46.1%)	< 0.01
IV	14 (1.4%)	14 (7.9%)	< 0.01
Metastases			
Synchronous	161 (15.2%)	51 (28.7%)	< 0.01
Metachronous	143 (13.5%)	38 (21.3%)	< 0.01
No metastases	754 (71.3%)	89 (50.0%)	< 0.01

IQR interquartile range, *ASA* American Society of Anaesthesiologists

Table 2 Tumour characteristics of included patients categorised as ileus and no ileus

| Tumour characteristics (N = 1236)	No ileus (N = 1058)	Ileus (N = 178)	P value
Tumour location			
caecum	128 (12.1%)	31 (17.4%)	0.05
ascending colon	118 (11.2%)	12 (6.7%)	0.08
hepatic flexure	57 (5.4%)	17 (9.7%)	0.03
transversal colon	38 (3.6%)	7 (3.9%)	0.82
splenic flexure	31 (2.9%)	15 (8.4%)	< 0.01
descending colon	35 (3.3%)	6 (3.4%)	0.96
Sigmoidal colon	237 (22.4%)	67 (37.6%)	< 0.01
rectum	374 (35.3%)	16 (9.0%)	< 0.01
double tumour	40 (3.8%)	7 (3.9%)	0.92
Tumour stage			
T1	76 (7.2%)	4 (2.2%)	< 0.01
T2	247 (23.3%)	20 (11.3%)	< 0.01
T3	589 (55.7%)	98 (55.1%)	0.79
T4	79 (7.5%)	33 (18.5%)	< 0.01
T missing	67 (6.3%)	23 (12.9%)	< 0.01
Nodal stage			
N0	649 (61.3%)	79 (44.4%)	< 0.01
N1	209 (19.8%)	50 (28.1%)	0.02
N2	133 (12.6%)	26 (14.6%)	0.48
N missing	67 (6.3%)	23 (12.9%)	< 0.01
M stage			
M0	863 (81.6%)	117 (65.7%)	< 0.01
M1	162 (15.3%)	53 (29.8%)	< 0.01
M missing	33 (3.1%)	8 (4.5%)	< 0.01
Tumour stadium AJCC			
Stage I	260 (24.6%)	14 (7.9%)	< 0.01
Stage II	360 (34.0%)	55 (30.8%)	0.38
Stage III	243 (23.0%)	48 (27.0%)	0.39
Stage IV	162 (15.3%)	53 (29.8%)	< 0.01
Missing	33 (3.1%)	8 (4.5%)	< 0.34
30-day mortality	47 (4.4%)	28 (15.7%)	< 0.01
Adjuvant chemotherapy			0.04
Yes	224 (21.2%)	50 (28.1%)	
No	834 (78.8%)	128 (71.9%)	
Palliative chemotherapy	76 (33.9%)	20 (40.0%)	0.06
Neo adjuvant therapy	277 (26.2%)	12 (6.7%)	< 0.01

AJCC American Joint Committee on Cancer

Survival

The median overall survival was 82 months (95% CI 72–92), and 5-year overall survival was 56%. Five-year overall survival was significantly decreased in patients with an ileus compared to patients without (32.0 versus 59.8%, respectively, $P < 0.01$) (Fig. 2). Median overall survival for patients with and without an ileus was 22 months (95% CI 13–31) and 95 months (95% CI 82–107), respectively. When ileus presentation was complicated by a blowout ($N = 28$), 5-year overall survival decreased to 28.6% with a median overall survival of 6 months (95% CI 0–18) (Table 3). In an additional subgroup analysis, patients with synchronous metastases were excluded. Overall survival was improved in both groups. The 5-year overall survival rates of patients with ($N = 127$) and without an ileus ($N = 897$) were 40.9 and 68.4%, respectively ($P < 0.01$). The median overall survival was 128 months (95% CI 116–140) in the patients without an ileus and 40 months (95% CI 21–59) in patients with an ileus. When ileus presentation was complicated by a blowout, 5-year overall survival was 32% with a median overall

Fig. 2 Overall survival (ileus versus no ileus). Kaplan-Meier curve of patients with (dashed line) and without (solid line) an ileus caused by colorectal carcinoma (log-rank test $P < 0.01$)
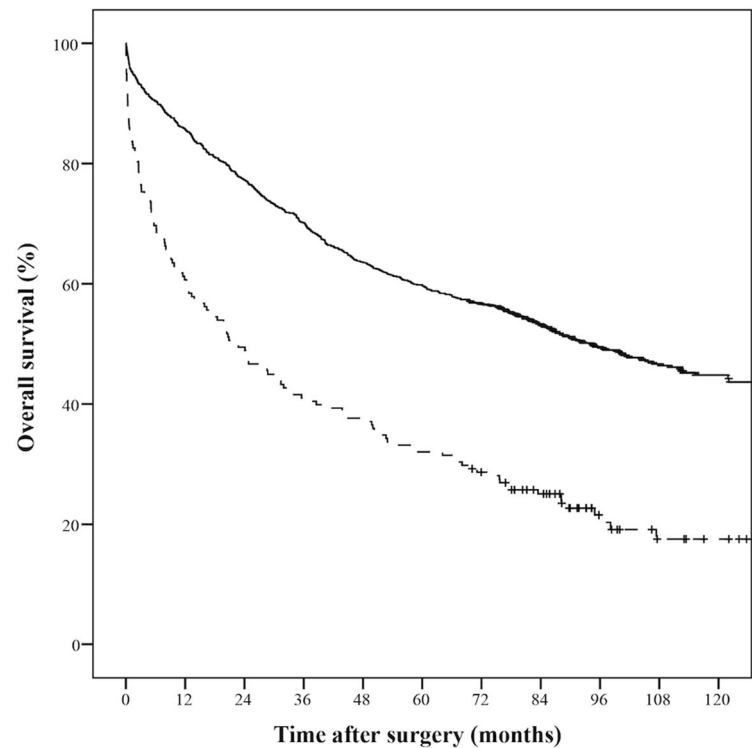
Numbers at risk

Ileus	178	106	84	73	66	57	51	45	40	38	38
No ileus	1058	902	815	737	672	630	599	567	540	525	520

survival of 9 months (95% CI 0–34) (Fig. 3; Table 3). In a second subsequent analysis, only patients with synchronous metastases were included. Survival rates at 5 years with ($N = 51$) and without an ileus ($N = 161$) were 9.8 and 11.7%, respectively ($P = 0.705$; Fig. 4). The median overall survival was 6 months (95% CI 4–9) in patients with an ileus compared to a median overall survival of 19 months (95% CI 15–23) in patients without an ileus (Table 3).

Discussion

This single-centre retrospective observational study compared the long-term survival of patients with obstructing CRC to patients without obstructing CRC. We found a lower 5-year overall survival rate in patients with obstructing CRC. If obstruction was complicated by a blowout, survival was even worse with a 5-year survival rate of 28.6%. A significant

Table 3 Overall survival of included patients, with- and without synchronous metastases

	5-year survival (%)	Median overall survival (months)	95% CI (months)
Complete group ($N = 1236$)	55.8	82	72–91
No ileus ($N = 1058$)	59.8	95	82–107
Ileus ($N = 178$)	32.0	22	13–31
Complicated by blowout ($N = 28$)	28.6	6	0–18
Patients without synchronous metastases ($N = 1024$)	65.0	107	93–121
No ileus ($N = 897$)	68.4	128	116–140
Ileus ($N = 127$)	40.9	40	21–59
Complicated by a blowout ($N = 22$)	31.8	9	0–34
Patients with synchronous metastases. ($N = 212$)	11.3	16	12–20
No ileus ($N = 161$)	11.7	19	15–23
Ileus ($N = 51$)	9.8	6	4–9

Fig. 3 Overall survival in patients without synchronous metastases (ileus versus no ileus). Kaplan-Meier curve of patients with (dashed line) and without (solid line) an ileus caused by colorectal carcinoma after exclusion of patients with synchronous metastases (log-rank test $P < 0.01$)
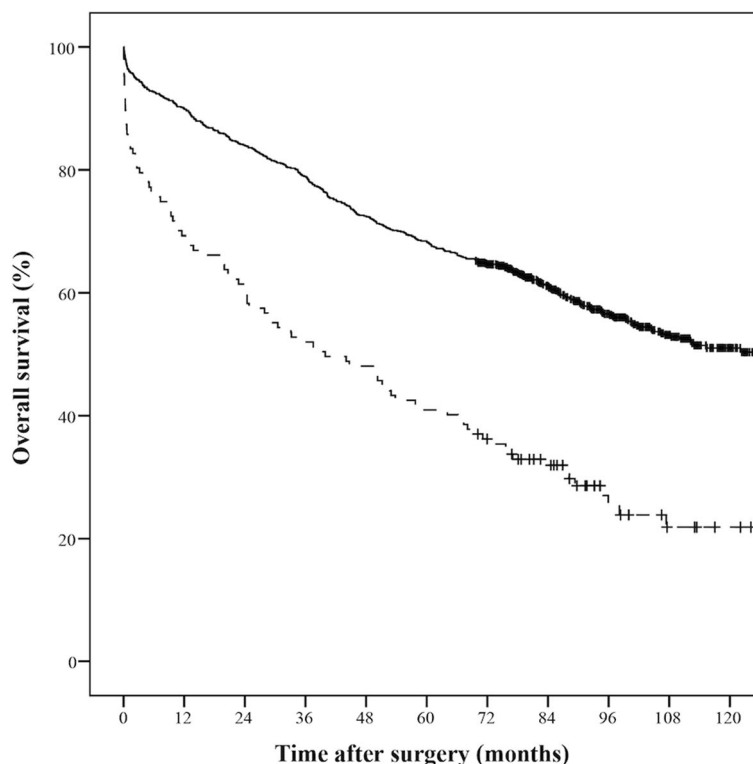
Numbers at risk											
Ileus	127	87	74	66	61	52	46	41	36	34	34
No ileus	897	804	756	708	653	615	584	555	528	513	508

difference was found in median survival between patients with and without an ileus.

It is already known that the morbidity and mortality rates in patients with obstructing CRC is worse than in patients with non-obstructing CRC [6, 7, 9]. From our large series with a follow-up longer than 5 years, it has become clear that the overall survival of patients with acute obstructing CRC is half that of patients without an acute obstruction. Limited data are available in the current literature regarding long-term survival in obstructing CRC. One study showed no difference in long-term survival between obstructing or non-obstructing CRC. In this small cohort, there was a non-significant difference in survival rate in patients with ($N = 80$) and without ($N = 171$) an ileus [12]. Patients who underwent emergency surgery for other reasons than blowout were excluded (perforation or abscess). This might be the reason why their study demonstrated a higher 5-year survival rate in the patients with obstruction compared with our series. In addition, patients with middle or low rectal carcinomas were excluded because none of them presented with large bowel obstruction at the time of diagnosis, which can induce selection bias. Wang et al. showed that obstruction is an independent prognostic factor for long-term survival. The 5-year cancer-specific survival rate was significantly lower in patients with an obstruction (46%) than in

patients without an obstruction (83%) ($P = 0.0001$) [14]. Poor survival outcomes were also found in a recently published retrospective study from Japan. They analysed 234 patients with obstructive CRC with similar tumour locations as those found in our study. The 5-year disease-free survival and cancer-specific survival rates were 50.6 and 80.3%, respectively [15]. They excluded all patients with stage I disease and patients who did not undergo primary resection.

The low survival rate in patients with a blowout was different from the study by Biondo et al. In this small cohort, they specifically determined a difference in outcome between patients with obstructive ($N = 117$) and perforated colonic cancer ($N = 38$) who were managed with emergency curative surgery. No differences were found in overall- and cancer-related survival at 5 years [16]. However, they excluded all patients with rectal cancer < 15 cm from the anal verge and patients who underwent palliative surgery. In our study, three locations (sigmoidal colon, the hepatic and splenic flexures) were more frequently reported in patients with an ileus compared to patients without an ileus; the caecum location was borderline significant. These results are partly in line with those described by Moolla et al. in the South African study; only the sigmoid colon was the most common site [17]. Other authors suggest that the splenic flexure is at greatest risk of obstruction

Fig. 4 Overall survival in patients with synchronous metastases (ileus versus no ileus). Kaplan-Meier curve of patients with synchronous metastases categorised as patients with (dashed line) and without (solid line) an ileus caused by colorectal carcinoma (log-rank test $P = 0.02$)
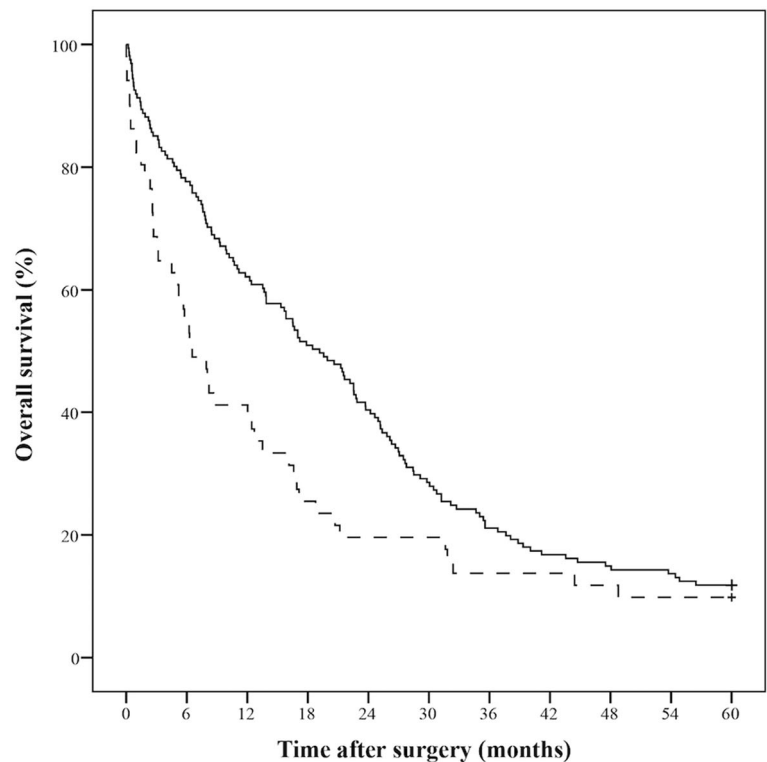
because of angulation [3]. Findings of our study confirm this suggestion. In recent literature, some studies demonstrate no difference between the overall incidences of left- and right-sided obstructing CRC [18, 19].

The definition of ileus varies in published literature, and without a universally accepted definition, tumour locations causing an ileus will continue to vary in future publications. In this study, an ileus was defined as a clinical finding that could be confirmed with radiological findings. Other authors define an ileus as a clinical finding, and when symptoms are vague, obstruction is then defined as colorectal disease requiring emergency surgery [17]. Differences in definition lead to misunderstanding and heterogeneous study populations. Previous studies have shown that obstructing CRC is associated with increased rates of distant metastases; this is confirmed in our data [6, 11, 20]. The overall incidence of both synchronous and metachronous metastases was significantly higher in patients with an ileus. Patient characteristics, subsequent patient and doctor delays, tumour biology and patient immune factors may contribute to this difference. Second, surgery quality may be impaired in patients who undergo emergency surgery compared to patients who undergo elective surgery. Emergency surgery has, as its priority, preserving life and is based on 'damage control'; this could lead to

irradical resection margins that cause further tumour proliferation and a higher probability of tumour spread. Emergency surgery could lead to inaccuracy in preoperative staging compared to elective operation patients. In these patients, occult metastases may already be present at the time of emergency surgery, causing a higher incidence rate in patients presenting with obstructive CRC [21]. These theories are based on assumptions and are not evidence-based.

Surveillance of patients after obstructing CRC, however, has a specific importance because of the higher incidence in distant metastases. Patients with obstructive CRC after curative surgery may benefit from a more intensive surveillance programme. Several authors have determined and shown the advantage of an intensive surveillance programme [22–25].

The strength of our study is the large population with a median follow-up of longer than 5 years. This retrospective study has several limitations. First, we used a database from patients who underwent surgery within a specific time period prior to 2011. It is important to realise that perioperative morbidity and 30-day mortality have decreased significantly ever since in the Netherlands and in our hospital. Second, patient demographics were significantly different between the ileus and no ileus groups. For example, patients presenting with an ileus were significantly older. Although the difference was

only 4 years, this might have influenced the long-term survival in this group negatively because of their lower overall survival profit. In addition, a higher ASA status was found in the ileus group, i.e. their physical condition was more critical than in patients without an ileus, and they were therefore more vulnerable to possible long-term and preoperative and postoperative complications.

This study provides evidence that patients with obstructive CRC not only have worse short-term survival but also have decreased long-term survival compared to patients who do not present with acute obstruction of the colon.

Compliance with ethical standards

The Medical Research Ethics Committees United (MEC-U) was consulted for ethical approval. They confirmed that this study (reference number W17,073), the Medical Research Involving Human Subject Act (WMO), does not apply. The institutional review board (AMOA) of Amphia Hospital confirmed that no formal written waiver for ethics approval was required.

Conflict of interest   The authors declare that they have no conflict of interest.

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