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ORIGINAL ARTICLE

Increased long-term mortality after open colorectal cancer surgery: A multicentre population-based study

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Abstract

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

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

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

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

KEYWORDS
colorectal cancer, laparoscopic, mortality, open, surgery

INTRODUCTION

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

Several meta-analyses, however, have failed to show a significant difference in 30-day mortality between laparoscopic surgery and open surgery. The COLOR trial, which reported 10-year outcomes after laparoscopic and open surgery, also showed no mortality difference [8]. This may be partially explained by the strict eligibility criteria of the RCTs. For example, the COLOR trial had several exclusion criteria such as body mass index (BMI) higher than 30 kg/m^2, signs of bowel obstruction and previous ipsilateral surgery. On the other hand, several nationwide population-based studies demonstrated reduced 30-day and 90-day mortality after laparoscopic surgery compared with open surgery [9, 10].

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

What does this paper add to the literature?

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

METHOD

Study design and data collection

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

Patient population

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

Definitions of exposure and outcomes

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

Postoperative complications were classified using the Clavien–Dindo classification [13]. Adequate lymph node yield was defined as ten or more lymph nodes according to the national CRC guideline formulated by the Dutch Federation of Medical Specialists [14]. Mortality outcomes were 90-day mortality and 1-, 3- and 5-year mortality.

Statistical analysis

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

Results are presented as hazard ratio (HR) and odds ratio (OR) with corresponding 95% confidence interval (CI). One-, 3- and 5-year HRs were calculated to prevent possible relevant information from being compressed into a single overall HR. All the *p*-values reported are two-sided. A *p*-value of <0.05 was considered significant. Case exclusion took place in cases with missing data after supplementing by the primary researcher. Missing data were not random and therefore multiple imputation was not possible. Patients who died within 90 days of their operation were excluded from the survival analysis and the Cox regression models. The proportional hazards assumption of the Cox regression model was assessed by eyeballing the Kaplan–Meier plot and the log minus log plot [16]. Statistical analysis was performed using SPSS v.24.0 (IBM, Armonk, NY, USA).

RESULTS

Patients

A total of 6157 CRC patients in three hospitals who received resection for primary CRC were evaluated for inclusion (Figure 1). After excluding patients who met the exclusion criteria, 4531 patients remained (hospital A, *n* = 1606; hospital B, *n* = 1374; hospital C, *n* = 1551). The median follow-up was 43 months [interquartile range (IQR) 23–71 months] for the entire cohort, 37 months (IQR 20–63 months) for the laparoscopic cohort and 54 months (IQR 32–82 months) for the open cohort. Case exclusion took place in 2.7% of these cases due to missing data; this was not different between the open and laparoscopic groups (chi-square test, $p = 0.28$). In the participating hospitals 1298 out of 4531 patients (29%) underwent open surgery and the percentage of open surgery in these hospitals decreased from 51% (170 out of 334) in 2009 to 4% (22 out of 523) in 2018. Baseline data are shown in Table 1. All the TNM Stage 4 patients who were included had a pT1–3 tumour in combination with a metastasis for which no additional resection took place. There was no difference in BMI and previous abdominal surgery between the open and laparoscopic groups. These factors were therefore not included in the following Cox regression analyses.

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

Long-term mortality

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

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

After adjusting for the same variables as before, the 1-, 3- and 5-year HRs were 1.16 (95% CI 1.01–1.34, $p = 0.04$), 1.21 (95% CI 1.06–1.39, $p = 0.007$) and 1.26 (95% CI 1.09–1.44, $p = 0.001$), respectively.

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

DISCUSSION AND CONCLUSION

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

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

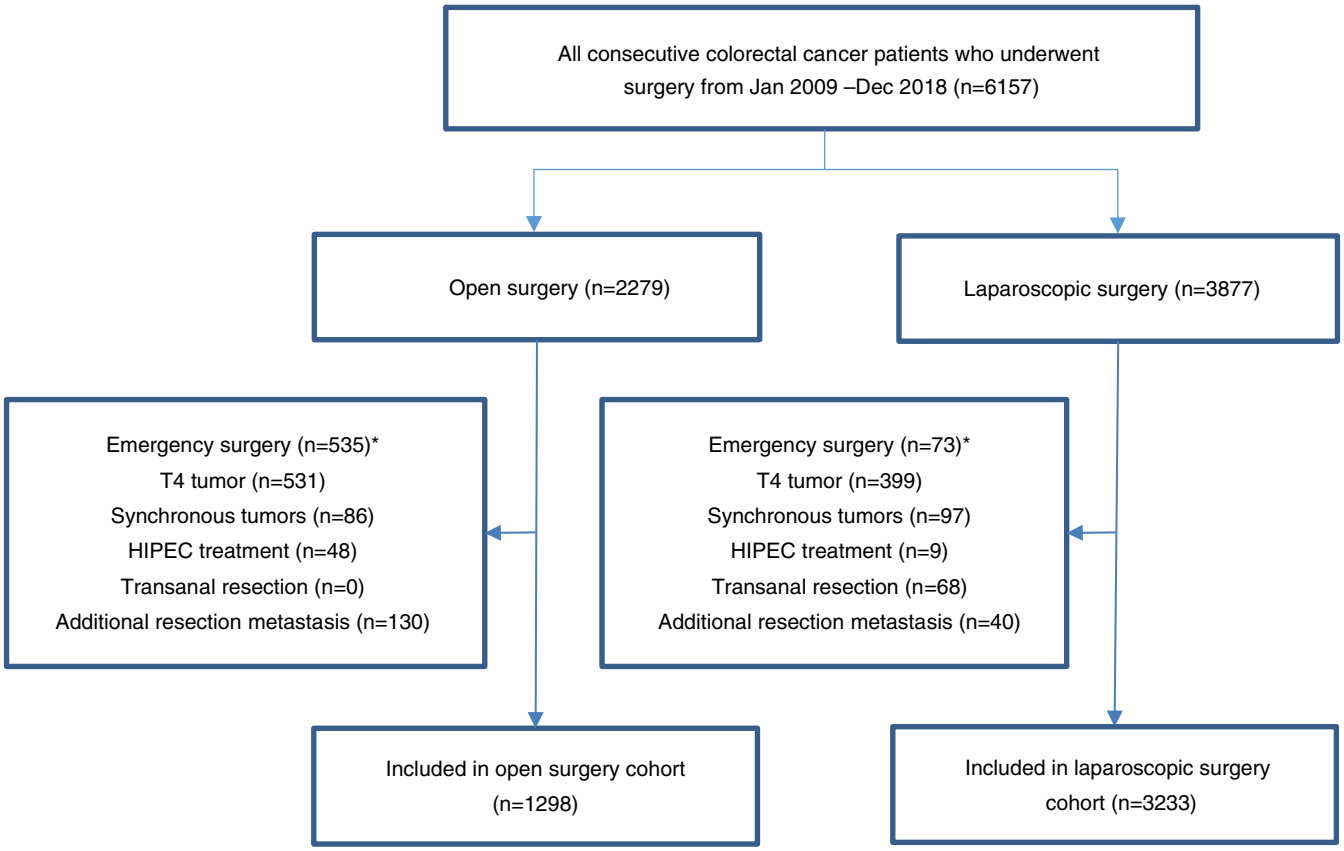

FIGURE 1 Study flowchart (HIPEC, hyperthermic intraperitoneal chemotherapy). *Some patients had multiple exclusion criteria

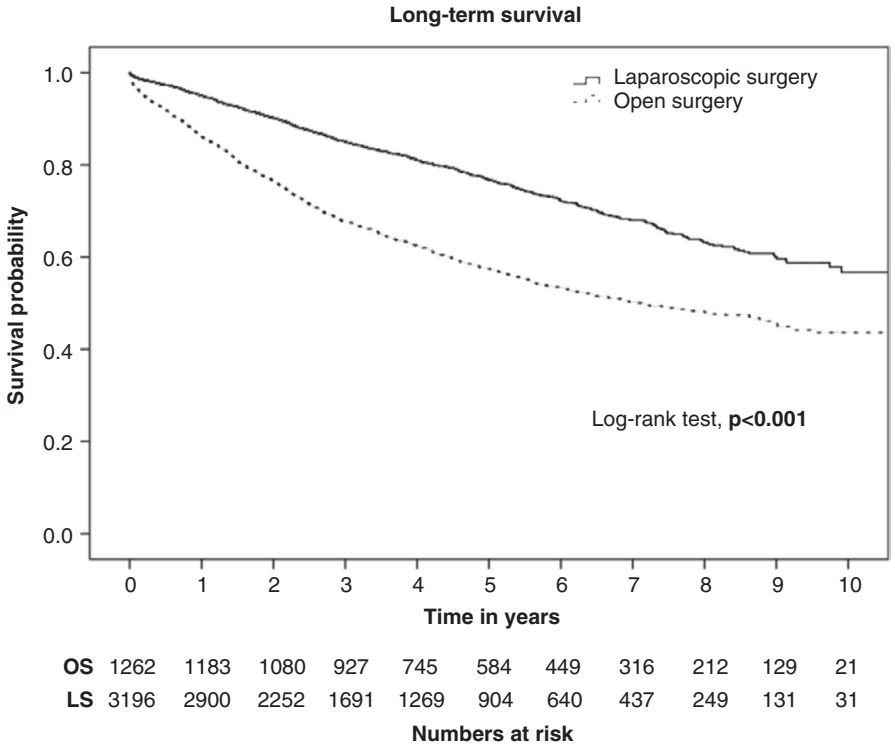

FIGURE 2 Kaplan–Meier survival curves of laparoscopic surgery versus open surgery

TABLE 1 Baseline characteristics

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

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

Abbreviations: ASA, American Society of Anesthesiologists; BMI, body mass index.

[a]Fisher's exact test.

population-based study that included 16,378 rectal cancer patients and showed reduced 5-year survival after open surgery [17].

Several factors might explain the association between open surgery and increased long-term mortality. Firstly, patients often do not fully recover to their previous level of health, most notably elderly CRC patients [18]. Secondly, patients might need additional surgery for incisional hernia or adhesion-related bowel obstruction in the years following the initial open operation [4, 6].

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

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

	Univariable Cox regression		Multivariable Cox regression	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Gender				
Male	1		1	
Female	0.99 (0.87–1.12)	0.83	0.92 (0.81–1.06)	0.25
Age (years)				
<70	1		1	
70–80	1.88 (1.63–2.20)	<0.001	1.78 (1.52–2.09)	<0.001
>80	4.09 (3.48–4.82)	<0.001	3.58 (2.97–4.33)	<0.001
ASA classification				
I	1		1	
II	1.64 (1.34–2.01)	<0.001	1.36 (1.11–1.68)	0.004
III	3.57 (2.87–4.44)	<0.001	2.33 (1.84–2.95)	<0.001
IV	7.35 (4.73–11.41)	<0.001	3.31 (2.10–5.23)	<0.001
Tumour location				
Colon	1		1	
Rectum	1.01 (0.88–1.15)	0.95	1.05 (0.83–1.33)	0.67
TNM stage				
I	1		1	
II	1.41 (1.18–1.69)	<0.001	1.22 (1.01–1.47)	0.041
III	2.20 (1.83–2.65)	<0.001	2.15 (1.74–2.65)	<0.001
IV	6.91 (5.60–8.54)	<0.001	6.56 (5.23–8.23)	<0.001
Surgical approach				
Laparoscopic surgery	1		1	
Open surgery	1.52 (1.33–1.73)	<0.001	1.26 (1.10–1.45)	0.001
Additional intraoperative resection due to primary tumour growth				
No	1		1	
Yes	1.17 (0.85–1.61)	0.33	1.06 (0.76–1.46)	0.74
Adequate lymph node yield (<10)				
No	1		1	
Yes	0.92 (0.76–1.11)	0.39	1.00 (0.81–1.22)	0.99
Neoadjuvant treatment				
No	1		1	
Yes	0.91 (0.79–1.04)	0.17	1.30 (1.01–1.67)	0.04
Adjuvant treatment				
No	1		1	
Yes	0.89 (0.77–1.04)	0.15	0.98 (0.81–1.19)	0.81
Period of surgery				
2009–2012	1		1	
2013–2015	0.93 (0.80–1.08)	0.35	1.03 (0.88–1.20)	0.74
2016–2018	0.61 (0.47–0.77)	<0.001	0.74 (0.57–0.95)	0.018

Abbreviations: ASA, American Society of Anesthesiologists; HR, hazard ratio.

procedures were done in the last few years of the study. This caused a lower median follow-up time of the laparoscopic cohort.

An extensive body of literature exists regarding the effect of the surgical approach on short-term postoperative mortality and morbidity. Thus far, the meta-analyses of RCTs have shown trends

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

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

Since the implementation of the DCRA there has been a nationwide trend of steadily improving surgical outcomes in the Netherlands [20]. In recent years, we also saw the rise of value-based healthcare, which is seen as a possible method to continuously improve quality of care and deal with rising healthcare costs [21]. These developments might have influenced some outcomes in our study; however, we believe that both the laparoscopic and the open cohorts in our study are affected to the same extent.

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

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

CONCLUSION

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

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CONFLICT OF INTEREST

The authors declare no conflict of interest, funding or other sources of support.

AUTHOR CONTRIBUTIONS

Study proposal and design are attributed to Milad Fahim, Lea Dijksman and Anke Smits. Data collection and analysis is attributed to Milad Fahim. Drafting and revisal of the manuscript was done by Milad Fahim, Lea Dijksman, Anke Smits, Thijs Burghgraef, Paul van der Nat, Wouter Derksen, Hjalmar van Santvoort, Bareld Pultrum, Esther Consten, and Douwe Biesma.

ETHICAL APPROVAL

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

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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