Anaesthetic technique and outcomes after colorectal cancer surgery

Vera Crone, Rune Petring Hasselager, Tina Fransgaard & Ismail Gögenur

ABSTRACT

INTRODUCTION: Previous studies have suggested that choice of anaesthesia can affect long-term outcome. In this study, the association between type of anaesthesia and outcomes in terms of survival, recurrence, post-operative complications and recovery after surgery for colorectal cancer was investigated in an Enhanced Recovery after Surgery (ERAS) setting.

METHODS: This was a retrospective study including patients undergoing elective curative-intended surgery for colorectal cancer between April 2013 and May 2015 at Zealand University Hospital, Denmark. Patients were stratified by anaesthetic technique. The primary outcome was cancer recurrence. Cox regression analyses were used for time-to-event variables; recurrence, disease-free survival, mortality, length of hospitalisation and time to bowel movement. Odds ratios for post-operative complications and time to discharge were estimated using logistic regression.

RESULTS: A total of 534 patients were included, 51 were exposed to inhalational anaesthesia and 483 had total intravenous anaesthesia. We found no statistically significant difference in recurrence (hazard ratio (HR) = 0.70; 95% confidence interval (CI): 0.21-1.68; p = 0.421). Patients in the inhalational aneasthesia group had a significantly lower chance of discharge per post-operative day (HR = 0.66; 95% CI: 0.48-0.91; p = 0.012). The same was seen for time to bowel movement (HR = 0.65; 95% CI: 0.46-0.90; p = 0.011). No statistically significant differences were seen for the other outcomes.

CONCLUSION: Anaesthetic technique might influence time to discharge and bowel function in an ERAS setting.

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TRIAL REGISTRATION: The study was approved by the Danish Data Protection Agency (record number 2008-58-0020). Under Danish law, consent from participants is not required in observational studies.

Colorectal cancer is one of the most frequent types of cancer with 1.7 million cases worldwide in 2016 [1]. Surgery is the first choice of treatment in most cases and improves chances of long-term survival. Even when surgery is intended to be curative, recurrence is common and remains a source of high mortality. Recurrence within five years is seen in up to 25% of patients [2].

The exact mechanism for metastatic recurrence remains unknown. One hypothesis is that cancer cells are released to the bloodstream during surgery; and due to modulation of the immune function caused by surgical stress, a favourable environment for metastasis formation is created [3]. Recently, several studies have supported the theories about anaesthetic agents and their ability to modulate the neuroendocrine stress response and interact with the immune system [4].

In elective cancer surgery, the Enhanced Recovery after Surgery (ERAS) regime has improved outcomes in terms of post-operative complications, morbidity and length of hospitalisation [5-7].

The aim of our study was to explore the relationship between inhalation anaesthetics and cancer recurrence, mortality and complication rates as well as length of post-operative recovery in patients undergoing surgery for colorectal cancer in a standardised ERAS setting.

In line with previous studies, we hypothesised that, in an ERAS setting, recurrence, mortality and post-operative complications were less frequent in patients anaesthetised with total intravenous anaesthesia than in patients anaesthetised with inhalational anaesthesia [8], and that post-operative recovery would be shorter in the group anaesthetised with total intravenous anaesthesia.

METHODS

This was a retrospective cohort study. The study was based upon data from a specialised colorectal cancer surgery centre at the Zealand University Hospital, Denmark.

Since 2006, the ERAS principles have been the foundation of care at our facility with more than 90% of procedures performed using a minimally invasive approach. Patients were informed about the ERAS programme, which is described in the following. General anaesthesia was induced with propofol and maintained with either sevoflurane or propofol. The latter as used routinely, but the choice was made by the attending anaesthetist. Remifentanil or sufentanil was given as supplementary opioid. Rocuronium was used for relaxation with neostigmine or sugammadex as reversal.

Post-operative analgesia was achieved with paracetamol 1g and ibumetin 400 mg four times daily supplemented by oral morphine 10 mg on demand. Ondansetron 4 mg was given intravenously during surgery. Oral nutrition was given from the day of surgery

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Center for Surgical Science, Department of Surgery, Zealand University Hospital, Køge, Denmark

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and nasogastric tubes were removed before emergence. Urinary bladder catheters were removed within 24 hours after surgery.

Chewing gum five minutes three times daily was used as prophylaxis for ileus, and patients were mobilised to bedside on the day of surgery.

The discharge criteria were: patients able to take care of themselves, able to sit and have a sufficient oral intake enough cover daily needs, sufficient pain treatment on oral medical treatment, gastrointestinal function (flatus or stool) and no signs of complications. The ERAS regime including the discharge criteria has previously been described in detail by Munk et al [9].

Participants and variables

We included all patients above 18 years of age undergoing primary elective operations for colorectal cancer with a curative intent from April 2013 to May 2015 at Zealand University Hospital, Denmark. Patients were identified in a database containing information about patient demographics, American Society of Anesthesiologists (ASA) score, preoperative comorbidities, operative findings and approach (metastases, localisation, neoadjuvant radiation or chemotherapy, tumour, node, metastasis stage), pathology results, post-operative recovery and complications.

Anaesthesia records were searched retrospectively from January to March 2018. Patients were stratified into two groups according to anaesthetic technique (total intravenous anaesthesia or inhalational anaesthesia). Inhalational anaesthesia was defined as any exposure to inhalational anaesthesia during surgery.

Follow-up was performed in the above-mentioned period using the regional electronic patient file (OPUS), which contains all contacts to hospitals in the Zealand Region. Patients were followed-up for recurrence, radical resection and death until 24 November 2017 when a new patient file system was implemented. Recurrence was defined as recurrence described in the patient file (regardless if it was verified by a biopsy). If residual disease was described, this was not registered as recurrence. Data on mortality were available through linkage of the electronic patient file to the Danish Personal Registration System [10].

The pre-specified primary outcome of this study was recurrence-free survival and secondary outcomes were all-cause mortality, disease-free survival, post-operative complications (medical and surgical) and post-operative recovery (length of hospitalisation after surgery and time to post-operative bowel function). The protocol was not published.

Statistical methods

Patients were stratified by type of anaesthesia and differences analysed using the χ^2 test (or Fisher's exact test for small samples) for categorical data. The T-test was used to analyse differences for normally distributed continuous variables and the Mann-Whitney U test was used for non-normally distributed data.

We computed time at risk for recurrence and death from the day of the primary operation until 24 November 2017. All-cause mortality was defined as time to death of any cause during the follow-up period and disease-free survival was defined as time from surgery to death or recurrence. For recurrence, patients were censored in the event of death. Cox regression was performed to estimate hazard ratios (HR) for inhalational anaesthesia versus total intravenous anaesthesia with 95% confidence intervals (CI) for these outcomes.

Risk of 30-day complications for the inhalational anaesthesia group compared to total intravenous anaesthesia was estimated using logistic regression and results are presented as odds ratios with CI.

Time to discharge and first bowel movement were estimated using Cox regression and presented as HR with CI for inhalational anaesthesia versus total intravenous anaesthesia.

We performed univariate and multivariate analyses in the regression models. Multivariate analyses were adjusted for age, sex, ASA score (I-II or III-IV) and tumour location (rectum or colon). These variables were pre-specified and chosen because they were thought to influence both the choice of anaesthesia and the risk of recurrence. Multivariable analyses were performed on observations with complete data.

Data were analysed using the R software version 3.5.1. Tests were two-sided and p-values below 0.05 were considered statistically significant.

Trial registration: The study was approved by the Danish Data Protection Agency (record number 2008-58-0020). Under Danish law, consent from participants is not required in observational studies.

RESULTS

A total of 607 patients were included in the study, 73 patients were excluded due to palliative or emergency surgery or missing data. A flowchart of the study cohort is presented in **Figure 1**.

Table 1 shows the baseline characteristics of the study population stratified by anaesthetic technique.

Overall, 90 patients were reported to have recurrence; six patients in the inhalational anaesthesia group and 84 patients in the total intravenous anaesthesia group. The unadjusted risk of recurrence was not statistically significantly different between the groups (HR = 0.86; 95% CI: 0.37-1.96; p = 0.711), nor after adjusting for confounders (HR = 0.70; 95% CI: 0.21-1.68).

In total, 90 patients died during the period. A significantly higher mortality in the inhalational anaesthesia

group was found (HR = 2.15; 95% CI: 1.24-3.75; p = 0.007) but not after adjusting for confounders (HR = 1.52; 95% CI: 0.84-2.76; p = 0.172). Results are summarised in **Table 2**.

A total of 105 (19.7%) patients were reported to have medical complications and 83 (15.5%) to have surgical complications in the post-operative period. No significant difference in odds ratio for complications before and after adjusting for confounders was found (Table 2).

Patients in the inhalational anaesthesia group had a significantly lower chance of discharge per post-operative day both before and after adjusting for confounders (adjusted HR = 0.66; 95% CI: 0.48-0.91; p = 0.012). Furthermore, a significantly lower chance of bowel function per post-operative day in the inhalational anaesthesia group (adjusted HR = 0.65; 95% CI: 0.46-0.90; p = 0.011) was found. Cumulative incidence curves for post-operative recovery are presented in **Figure 2**.

DISCUSSION

In this observational study in an ERAS setting, we found a correlation between inhalational anaesthesia and mortality. Since inhalational anaesthetics are primarily given to the weakest of patients, this comes as no surprise, and the effect was not significant after adjusting for potential confounders. No relation was found between exposure to inhalational anaesthesia and recurrence, or post-operative complications.

A significantly more rapid discharge and return of bowel function rates was found in the total intravenous anaesthesia group than in the inhalational anaesthesia group.

Firstly, a key strength of the study was that it covered patients enrolled in an ERAS protocol. Secondly, baseline data, data on operation type and post-operative complications were collected in a database with a standardised pre-specified form, which reduces the risk of information bias. Only colorectal cancer surgery was included, which makes the cohort homogenous regarding the surgical stress response. There are limitations that should be addressed. Only 51 patients (9.6%) were exposed to inhalational anaesthesia. In Denmark, inhalational anaesthesia is primarily reserved for patients with heart or lung disease because of its potentially protective properties in these patients [11]. The substantial difference in crude and adjusted estimates also confirms that there is a high degree of confounding. We adjusted our estimates for age and ASA score, which is based on a subjective perception of the patient's overall comorbidity burden with some degree of inter-rater variability [12]. These variables cover the concept of overall frailty related to choice of anaesthesia, death and recurrence. We were unable to include more variables reflecting patient frailty in more detail in the multivariable model without risking to over-fit the regression model because of the limited number of patients in the inhalational anaesthesia group. The multivariable results are therefore prone to residual confounding and there is a risk of confounding by indi-

FIGURE 1 / Flow chart of the study cohort illustrating the inclusion and exclusion criteria of participants.

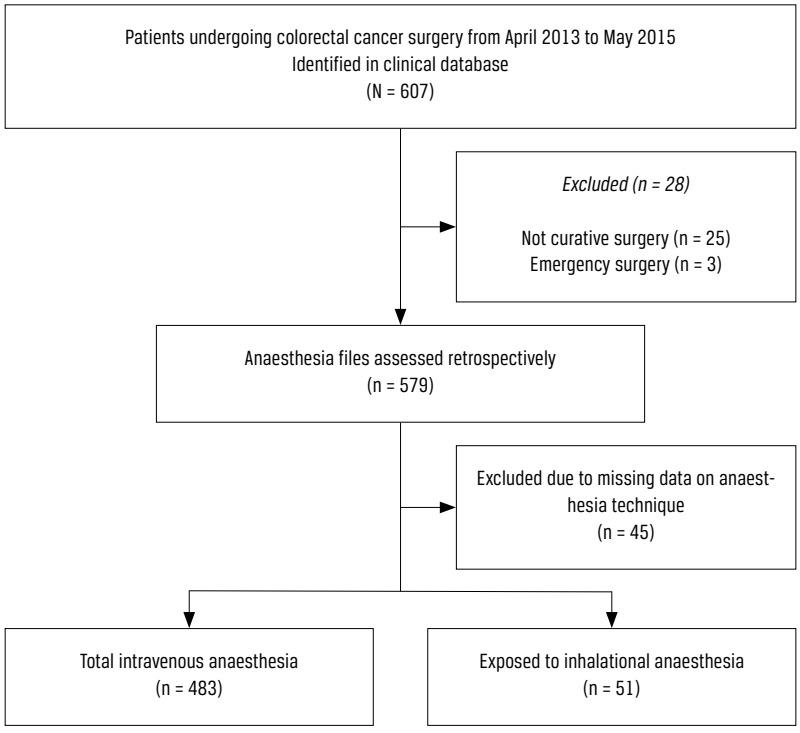

FIGURE 2 / Cumulative incidence curves for post-operative time to discharge (**A**) and post-operative ileus (**B**).

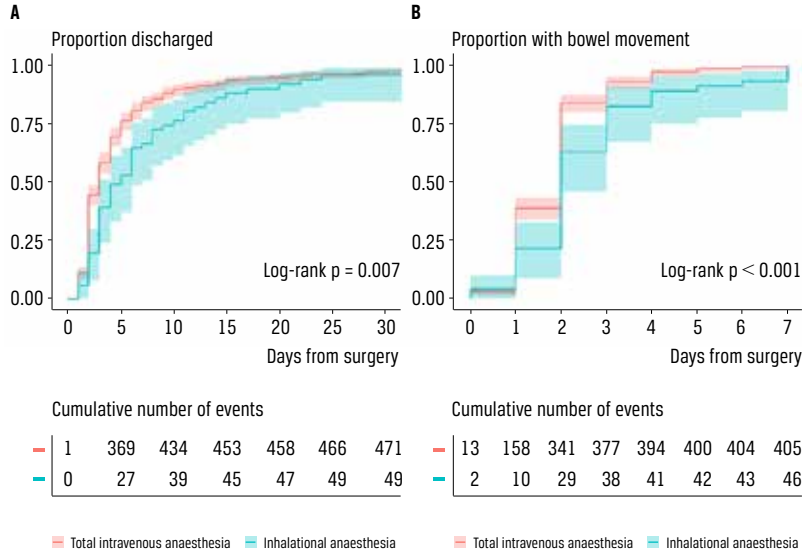

TABLE 1 / Characteristics of study population.

	Total IV anaesthesia (N = 483)	Inhalational anaesthesia (N = 51)	p-value[a]	Missing, %
Sex, n (%)			0.561	0.0
Female	211 (43.7)	25 (49.0)		
Male	272 (56.3)	26 (51.0)		
Age, yrs, median (IQR)	70.00 (64.00- 75.00)	75.00 (70.00-80.00)	< 0.00[b]	0.0
BMI, kg/m^2, median (IQR)	25.44 (23.05-28.72)	24.29 (22.57-29.48)	0.397[b]	2.8
ASA score, n (%)			< 0.001	1.3
I	119 (25.0)	7 (13.7)		
II	319 (67.0)	21 (41.2)		
III	38 (8.0)	23 (45.1)		
IV	0	0		
WHO performance score, n (%)			< 0.001	9.4
0	372 (84.7)	22 (48.9)		
1	43 (9.8)	13 (28.9)		
2	15 (3.4)	6 (13.3)		
3	1 (0.2)	3 (6.7)		
4	1 (0.2)	1 (2.2)		
5	7 (1.6)	0		
Surgical approach, n (%)			0.946	9.7
Laparoscopic	432 (98.6)	44 (100.0)		
Open	6 (1.4)	0		
Localisation, n (%)			0.121	0.0
Colon	322 (66.7)	40 (78.4)		
Rectum	161 (33.3)	11 (21.6)		
Liver metastases, n (%)			1.000[b]	1.9
No	442 (93.4)	48 (94.1)		
Yes	10 (2.1)	1 (2.0)		
Uncertain diagnosis	21 (4.4)	2 (3.9)		
Lung metastases, n (%)			0.002[b]	2.1
No	423 (89.6)	47 (92.2)		
Yes	2 (0.4)	3 (5.9)		
Uncertain diagnosis	47 (10.0)	1 (2.0)		
TNM stage, n (%)				
T-stage:			0.848[b]	0.7
0	5 (1.0)	0		
1	39 (8.1)	2 (3.9)		
2	116 (24.2)	12 (23.5)		
3	278 (58.0)	32 (62.7)		
4	41 (8.6)	5 (9.8)		
N-stage:			0.582[b]	0.2
0	319 (66.2)	36 (70.6)		
1	110 (22.8)	12 (23.5)		
2	53 (11.0)	3 (5.9)		
M-stage:			0.396[b]	0.0
0	479 (99.2)	50 (98.0)		
1	4 (0.8)	1 (2.0)		
Neoadjuvant therapy, n (%)				
Radiation therapy	27 (5.6)	3 (5.9)	1.000[b]	0.0
Chemotherapy	33 (6.8)	3 (5.9)	1.000[b]	0.0

CONTINUES ››

TABLE 1 CONTINUED / Characteristics of study population

	Total IV anaesthesia (N = 483)	Inhalational anaesthesia (N = 51)	p-value[a]	Missing, %
Preoperative co-morbidity, n (%)				
Steroid use	3 (0.6)	2 (3.9)	0.074[b]	0.0
Excessive alcohol consumption	11 (2.3)	2 (3.9)	0.357[b]	0.0
IDDM	52 (10.8)	6 (11.8)	1.000	0.0
Heart failure	104 (21.5)	20 (39.2)	0.008	0.0
Hypertension	170 (35.2)	13 (25.5)	0.217	0.0
COPD	35 (7.2)	17 (33.3)	< 0.001	0.0
Concomittant cancer	64 (13.3)	13 (25.5)	0.031	0.0
Other co-morbidity	90 (18.6)	13 (25.5)	0.320	0.0
Outcomes, n (%)				
Death	75 (15.5)	15 (29.4)	0.020	0.0
Recurrence	84 (17.6)	6 (12.5)	0.487	1.7
Follow-up, n, median (IQR)	1,199 (1,011.5-1396.5)	1,069 (931-1,346.5)	0.014	0.0

ASA = American Society of Anesthesiologists; COPD = chronic obstructive pulmonary disease; IDDM = insulin dependent diabetes mellitus; IQR = interquartile range; TNM = tumour, node, metastasis.
a) Kruskal-Wallis test.
b) χ^2- or Fisher's exact test.

TABLE 2 / Post-operative outcomes for inhalational versus total intravenous anaesthesia.

		Unadjusted		Adjusted[d]	
	n (%)	HR, mean (95% CI) [p-value]	OR (95% CI) [p-value]	HR (95% CI) [p-value]	OR (95% CI) [p-value]
Long-term outcomes					
Recurrence	90 (16.8)	0.86 (0.37-1.96) [0.711]		0.70 (0.21-1.68 [0.421]	
All-cause mortality	90 (16.9)	2.15 (1.24-3.75) [0.007]		1.52 (0.84-2.76) [0.172]	
Disease-free survival	133 (24.9)	1.46 (0.85-2.51) [0.167]		1.13 (0.63-2.01) [0.648]	
Complications					
Medical complications[a]	105 (19.7)		2.02 (1.05-3.76) [0.295]		1.94 (0.93-3.88) [0.066]
Surgical complications[b]	83 (15.5)		1.18 (0.52-2.43) [0.663]		1.12 (0.46-2.46) [0.794]
Post-operative recovery					
Hospital discharge rate[c]	-	0.66 (0.50-0.89) [› 0.006]		0.66 (0.48-0.91) [0.012]	
Return of bowel function rate[c]	-	0.58 (0.43-0.79) [› 0.001]		0.65 (0.46-0.90) [0.011]	

ASA = American Society of Anesthesiologists; CI = confidence interval; HR = hazard ratio, OR = odds ratio.
a) Pneumonia, atelectasis, pulmonary embolism, myocardial infarction, arrhythmia, sepsis, deep vein thrombosis, heart failure or stroke.
b) Surgical site infection requiring revision, intra-abdominal abscess, local peritonitis, anastomotic leakage, bleeding, stoma necrosis, ileus.
c) Represent time-to-event: the rate of hospital discharge and return of bowel function was lower in the group exposed to inhalational anaesthesia than in the group with total intravenous anesthesia.
d) Adjusted for age, sex, ASA score › II and localisation: colon or rectum.

cation. Moreover, the intended doses of anaesthesia used in both groups are not known. Knowledge hereof could have been used to establish a dose-response association. For the primary outcome, recurrence, there were only six events in the inhalational anaesthesia group. The small sample size is reflected in estimates with a wide CI for recurrence, making the results susceptible to type-II error (false negative results).

Furthermore, data on 45 patients were missing from an already small sample.

The entire cohort was enrolled in a structured ERAS programme with a high rate of minimally invasive surgery, which was demonstrated to reduce surgical stress response [13]. The effect of the type of anaesthesia may not be as substantial in a low surgical stress setting, which may be the reason for our statistically insignifi-

cant results. The estimates on recurrence and survival are, however, very imprecise and an effect of the type of anaesthesia on long-term outcomes after surgery in an ERAS setting cannot be ruled out based on this study. The findings of no difference in the association between post-operative complications and choice of anaesthesia are in line with findings reported in recent studies [14].

In the present study, the post-operative length of hospitalisation and time to post-operative bowel movements were considerably shorter than previously described in colorectal cancer patients [15]. The reason for this finding is likely adherence to the ERAS protocol [16]. Even though the setting was optimised for early resumption of transit, a significantly shorter time to bowel movement was found in the total intravenous anaesthesia group after adjusting for confounders. This was a secondary outcome parameter and should therefore be interpreted accordingly as there is a risk of random findings.

There are only few studies on bowel function and type of anaesthesia in humans and their results are divergent [17, 18]. A possible confounder of post-operative ileus may be the use of neostigmine for reverting neuromuscular blockade. Neostigmine has parasympathetic stimulatory properties [19]. The dose of neostigmine used for reverting neuromuscular blockade is low, and it is given in combination with atropine to reduce the parasympathetic side effects. The need of reversal of neuromuscular blockade is likely to be equal for both types of anaesthesia.

Post-operative vomiting and nausea (PONV) is known to be worse after anaesthesia with sevoflurane than after use of total intravenous anaesthesia, which could play a role in the time to discharge [20]. All patients received ondansetron as PONV prophylaxis before emergence.

CONCLUSION

Our results suggest that type of anaesthesia may have an influence on post-operative bowel function in an ERAS setting, but the possible mechanism remains unknown. Further research should focus on the different anaesthetic agents and their influence on perioperative pathophysiology. Furthermore, large cohort studies, with the ability to adjust for more confounders, and randomised trials are needed focusing on the effect of anaesthetic technique and risk of mortality and recurrence in patients operated for colorectal cancer, as our cohort was small and highly susceptible to imprecise estimates.

CORRESPONDENCE: *Vera Crone.* E-mail: Veracrone@gmail.com

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