BJA

British Journal of Anaesthesia, 126 (5): 921–930 (2021)

doi: 10.1016/j.bja.2020.11.019
Advance Access Publication Date: 30 December 2020
Clinical Practice

CLINICAL PRACTICE

Inhalation or total intravenous anaesthesia and recurrence after colorectal cancer surgery: a propensity score matched Danish registry-based study

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An abstract of this study has been submitted as an oral presentation at the Danish Surgical Society's annual conference 2020.

Abstract

Background: During colorectal cancer surgery, the immune-modulating effects of inhalation anaesthesia may create a favourable environment for metastasis formation, leading to increased risk of recurrence. Our aim was to assess the association between inhalation *vs* intravenous anaesthesia and cancer recurrence in patients undergoing colorectal cancer surgery.

Methods: Patients undergoing colorectal cancer surgery in 2004–18 were identified in the Danish Colorectal Cancer Group Database and Danish Anaesthesia Database. After exclusion of patients with residual tumour registered in postoperative pathology reports, local endoscopic resections, and stent insertions, we classified patients according to exposure to inhalation anaesthesia. The primary outcome was recurrence (time to recurrence), whereas secondary outcomes were all-cause mortality (time to death) and disease-free survival (time to either recurrence or death). Events of recurrence and death were identified using The Danish Civil Registration System, Danish National Pathology Registry, and Danish National Patient Registry. The sub-distribution hazards approach was used to estimate hazard ratios (HRs) for recurrence, and Cox regression was used for all-cause mortality and disease-free survival.

Results: We identified 5238 patients exposed to inhalation anaesthesia and 6322 to intravenous anaesthesia. Propensity score matching yielded 4347 individuals in each group with balanced baseline covariates. We found a weak association between recurrence and exposure to inhalation anaesthesia (HR=1.12; 95% confidence interval [CI], 1.02–1.23). The HR estimates for all-cause mortality and disease-free survival were 1.00 (95% CI, 0.93–1.07) and 1.04 (95% CI, 0.98–1.11) respectively.

Conclusion: Exposure to inhalation anaesthesia was associated with increased risk of recurrence after colorectal cancer surgery.

Keywords: cancer recurrence; colorectal cancer; epidemiology; inhalational anaesthesia; onco-anaesthesia

Editor's key points

- The immune-modulating effects of inhalation anaesthesia may create a favourable environment for metastasis formation in curative cancer surgery.
- The association between inhalation *vs* total intravenous anaesthesia and cancer recurrence in patients undergoing colorectal cancer surgery was assessed in a retrospective registry-based study.
- From 4347 individuals in each group with balanced baseline covariates, the authors found a weak

Received: 21 September 2020; **Accepted:** 17 November 2020

association between recurrence and exposure to inhalation anaesthesia, but none for all-cause mortality or disease-free survival.
- Besides the need for large randomised clinical trials, future research should focus on the underlying mechanisms of inhalation anaesthesia in patients with malignancy.

Surgical resection under general anaesthesia remains the best treatment for colorectal cancer. With an estimated 1.7 million new cases and 830 000 deaths annually, this is an enormous disease burden worldwide.[1] Up to one-third of patients who are primarily cured by surgery experience relapse.[2,3] Studies suggest that the surgical stress response, treatments, and events in the perioperative period can facilitate metastasis formation and residual tumour growth.[4]

The two main agents used for general anaesthesia are inhalation and intravenous anaesthetics. The two approaches, inhalation anaesthesia and TIVA, result in appropriate general anaesthesia for surgery. However, the mechanisms of action differ and are not fully understood. Emerging evidence suggests that anaesthetic techniques affect long-term survival after cancer surgery and inhalation anaesthesia has particularly been associated with mortality after various types of cancer surgery.[5]

The immune system is affected by inhalation anaesthesia by suppression of both the innate and adaptive immune response with decreased activity of neutrophils and natural killer cells as well as impaired T cell proliferation.[6] Exposure to inhalation anaesthesia also induces hypoxia inducible factor, which promotes cancer cell proliferation, migration, and angiogenesis.[7–10] This in combination may create a favourable microenvironment for residual tumour cells, enabling them to escape immune surveillance and thereby seed, spread, and grow after surgery. Thus, perioperative metastasis formation may explain the association between mortality and inhalation anaesthesia.[5] Nevertheless, the association between inhalation anaesthesia and cancer recurrence is ambiguous, and there is a need for further studies. Our aim was to estimate the effect of exposure to inhalation anaesthesia on cancer recurrence in patients undergoing colorectal cancer surgery. Owing to the known immune modulating features of these agents, we hypothesised that exposure to inhalation anaesthesia is associated with an increased recurrence rate.

Methods

This nationwide observational register-based cohort study was based on a propensity score for matched groups. It included Danish residents undergoing surgery for colorectal cancer from 2004 to 2018. The study was approved by the Danish Data Protection Agency (file no. 2012-58-0003/REG-038-2017; April 5, 2019) and reported according to the STROBE Statement.[11]

Data sources

The present study was based upon data from national Danish registries. Patients undergoing surgery for colorectal cancer were identified in Danish Colorectal Cancer Group Database,[12] and data on anaesthesia type was obtained from the Danish Anaesthesia Database,[13] Danish National Patient Registry,[14] Danish National Pathology Registry,[15] Danish Civil Registration System,[16] and Danish Cancer Registry[17] were used to identify events of recurrence and death. To determine current medication use, the Danish National Prescription Database[18] served to identify prescriptions filled within 3 months before surgery for the population. Data on comorbidities were available from Danish Colorectal Group Database, which uses data from Danish National Patient Registry to compute the Charlson Comorbidity Index.[19] ASA physical status[20] at the time of surgery was derived from the Danish Anaesthesia Database. A detailed summary of the data sources and definitions of the variables used in the present study is presented in Supplementary Tables S1 and S2.

Population and setting

We included all patients undergoing colorectal cancer surgery from 2004 to 2018 in the Danish Colorectal Cancer Group Database. We disregarded endoscopic polyp resections, intestinal stent insertions, and procedures in which tumour resections were not performed. We excluded patients with residual tumour left after surgery; and to avoid interference with other cancer types, we excluded patients with a previous cancer diagnosis except non-melanoma skin cancer. Lastly, we excluded patients where no data on the type of anaesthesia were available in Danish Anaesthesia Database. Patients were stratified according to whether they were exposed to inhalation anaesthesia or to TIVA during their primary resection. Patients were followed up until death, emigration, or September 7, 2018.

In Denmark, the choice of type of anaesthesia depends on the attending anaesthesiologist guided by local standard operating procedures. Drug sales data in Denmark (medstat.dk[21]) indicate that the most commonly used inhalation agent was sevoflurane whereas the most commonly used intravenous agent was propofol throughout the study period (Supplementary Table S3).

Outcomes

Our primary outcome was cancer recurrence. Based on a validated algorithm,[22] we defined recurrence as the earliest of the following events:

1. Codes for metastatic cancer registered in the Danish National Patient Registry or Danish Cancer Registry more than 180 days from surgery without a new postoperative cancer diagnosis different from colorectal cancer and non-melanoma skin cancer in between.
2. Chemotherapy codes registered in Danish National Patient Registry more than 180 days after surgery or 60 or more days after their last chemotherapy code without a new primary cancer diagnosis registered in between.
3. Systematized Nomenclature Of Medicine Clinical Terms (SNOMED) (Danish SNOMED for Pathology available at www.patobank.dk) combinations in the Danish National Pathology Registry for metastasis or recurrence of colorectal cancer 180 or more days after surgery without new primary cancer registrations in between.
4. A registration specific for local colorectal cancer recurrence in the Danish National Patient Registry any time after surgery.

The 180 day quarantine was introduced to avoid manifestations of incompletely removed primary tumours being

Table 1 Characteristics of patients undergoing colorectal cancer surgery 2004–18 stratified by anaesthesia techniques before and after propensity score matching.

	Before propensity score matching			After propensity score matching		
	TIVA	Inhalation	SMD	TIVA	Inhalation	SMD
N	6322	5238		4347	4347	
Age, yr (median [IQR])	69.00 [61.25, 76.00]	72.00 [64.00, 79.00]	0.271	71.00 [64.00, 78.00]	71.00 [63.00, 78.00]	0.014
Male	3405 (53.9)	2845 (54.3)	0.009	2366 (54.4)	2364 (54.4)	0.001
BMI, kg m^{-2}			0.099			0.028
<18.5	184 (2.9)	241 (4.6)		154 (3.5)	172 (4.0)	
18.5–25	2828 (44.7)	2241 (42.8)		1896 (43.6)	1895 (43.6)	
25–30	2261 (35.8)	1852 (35.4)		1542 (35.5)	1541 (35.4)	
>30	1032 (16.3)	897 (17.1)		746 (17.2)	733 (16.9)	
Missing	17 (0.3)	7 (0.1)		9 (0.2)	6 (0.1)	
Comorbidities						
Charlson comorbidity index			0.226			0.010
0	4492 (71.1)	3190 (60.9)		2832 (65.1)	2850 (65.6)	
1	1115 (17.6)	1167 (22.3)		907 (20.9)	900 (20.7)	
2	410 (6.5)	445 (8.5)		339 (7.8)	329 (7.6)	
>2	305 (4.8)	436 (8.3)		269 (6.2)	268 (6.2)	
ASA physical status			0.325			0.021
1	1342 (21.2)	806 (15.4)		736 (16.9)	763 (17.6)	
2	3939 (62.3)	2893 (55.2)		2630 (60.5)	2589 (59.6)	
3	961 (15.2)	1404 (26.8)		912 (21.0)	928 (21.3)	
4 and above	60 (0.9)	122 (2.3)		58 (1.3)	57 (1.3)	
Missing	20 (0.3)	13 (0.2)		11 (0.3)	10 (0.2)	
Lifestyle						
Tobacco			0.106			0.014
Smoker	1242 (19.6)	1053 (20.1)		874 (20.1)	893 (20.5)	
Non-smoker	4940 (78.1)	3975 (75.9)		3349 (77.0)	3324 (76.5)	
Missing	140 (2.2)	210 (4.0)		124 (2.9)	130 (3.0)	
Alcohol consumption (weekly units)			0.189			0.009
0	1537 (24.3)	1581 (30.2)		1221 (28.1)	1236 (28.4)	
1–21	4285 (67.8)	3097 (59.1)		2727 (62.7)	2711 (62.4)	
21	402 (6.4)	410 (7.8)		312 (7.2)	310 (7.1)	
Missing	98 (1.6)	150 (2.9)		87 (2.0)	90 (2.1)	
Prescriptions filled within the past 3 months (ATC code)						
Proton pump inhibitors (A02BC)	1034 (16.4)	1033 (19.7)	0.088	785 (18.1)	789 (18.2)	0.002
Antidiabetics (A10)	563 (8.9)	561 (10.7)	0.061	432 (9.9)	422 (9.7)	0.008
Acetylsalicylic acid (B01AC06)	849 (13.4)	895 (17.1)	0.102	686 (15.8)	666 (15.3)	0.013
Other platelet inhibitors (B01AC)	296 (4.7)	317 (6.1)	0.061	235 (5.4)	235 (5.4)	<0.001
Anticoagulants (B01A)	301 (4.8)	358 (6.8)	0.089	260 (6.0)	253 (5.8)	0.007
Digoxin (C01AA05)	133 (2.1)	195 (3.7)	0.096	116 (2.7)	111 (2.6)	0.007
Thiazides (C03)	1036 (16.4)	1040 (19.9)	0.090	798 (18.4)	772 (17.8)	0.016
Beta blockers (C07)	841 (13.3)	887 (16.9)	0.101	677 (15.6)	656 (15.1)	0.013
Calcium channel blockers (C08)	896 (14.2)	838 (16.0)	0.051	674 (15.5)	664 (15.3)	0.006
Drugs acting on renin angiotensin system (C09)	1549 (24.5)	1456 (27.8)	0.075	1160 (26.7)	1147 (26.4)	0.007
Lipid lowering drugs (C10)	1305 (20.6)	1210 (23.1)	0.059	988 (22.7)	963 (22.2)	0.014
Oestrogen hormone replacement (G03C)	274 (4.3)	207 (4.0)	0.019	180 (4.1)	182 (4.2)	0.002
Corticosteroids for systemic use (H02)	161 (2.5)	158 (3.0)	0.029	124 (2.9)	125 (2.9)	0.001
Non-steroid anti-inflammatory drugs (M01A)	454 (7.2)	373 (7.1)	0.002	314 (7.2)	315 (7.2)	0.001
Urate-lowering drugs (M04)	105 (1.7)	120 (2.3)	0.045	85 (2.0)	81 (1.9)	0.007
Bisphosphonates (M05BA, M05BB)	164 (2.6)	182 (3.5)	0.051	135 (3.1)	140 (3.2)	0.007
Opioids (N02A)	636 (10.1)	629 (12.0)	0.062	471 (10.8)	482 (11.1)	0.008
Benzodiazepines (N05CD, N05CF)	578 (9.1)	523 (10.0)	0.029	423 (9.7)	418 (9.6)	0.004
Antidepressants (N06A)	423 (6.7)	424 (8.1)	0.054	324 (7.5)	314 (7.2)	0.009
Drugs for obstructive airway diseases (R03)	461 (7.3)	509 (9.7)	0.087	373 (8.6)	368 (8.5)	0.004
Number of different drugs dispensed during the past 3 months			0.160			0.009
0–4	287 (4.5)	378 (7.2)		246 (5.7)	245 (5.6)	
5–9	4433 (70.1)	3314 (63.3)		2876 (66.2)	2894 (66.6)	
>10	1602 (25.3)	1546 (29.5)		1225 (28.2)	1208 (27.8)	

Continued

Table 1 Continued

	Before propensity score matching			After propensity score matching		
	TIVA	Inhalation	SMD	TIVA	Inhalation	SMD
Tumour characteristics						
Metastases			0.006			0.010
No	6054 (95.8)	5010 (95.6)		4152 (95.5)	4161 (95.7)	
Yes	207 (3.3)	176 (3.4)		151 (3.5)	143 (3.3)	
Missing	61 (1.0)	52 (1.0)		44 (1.0)	43 (1.0)	
Localisation			0.048			0.027
Right hemicolon	2099 (33.2)	1769 (33.8)		1446 (33.3)	1455 (33.5)	
Left hemicolon	2242 (35.5)	1746 (33.3)		1483 (34.1)	1452 (33.4)	
Colon unspecified	<5 (0.0)	<5 (0.0)		<5 (0.0)	<5 (0.0)	
Rectum	1980 (31.3)	1721 (32.9)		1417 (32.6)	1440 (33.1)	
Preoperative oncologic treatment	607 (9.6)	581 (11.1)	0.049	458 (10.5)	467 (10.7)	0.007
Surgery characteristics						
Minimally invasive surgery	4293 (67.9)	2944 (56.2)	0.243	2659 (61.2)	2651 (61.0)	0.004
Urgency			0.139			0.004
Elective	5967 (94.4)	4754 (90.8)		4038 (92.9)	4034 (92.8)	
Acute	354 (5.6)	481 (9.2)		308 (7.1)	312 (7.2)	
Missing	<5 (0.0)	<5 (0.0)		<5 (0.0)	<5 (0.0)	
Converted from laparoscopy to laparotomy			0.173			0.009
Yes	389 (6.2)	328 (6.3)		285 (6.6)	277 (6.4)	
No	5811 (91.9)	4901 (93.6)		4054 (93.3)	4061 (93.4)	
Missing	122 (1.9)	9 (0.2)		8 (0.2)	9 (0.2)	
Intraoperative perforation of intestine			0.107			0.018
No	6117 (96.8)	4955 (94.6)		4167 (95.9)	4156 (95.6)	
Yes	199 (3.1)	277 (5.3)		177 (4.1)	186 (4.3)	
Missing	6 (0.1)	6 (0.1)		<5 (0.0)	5 (0.1)	
Intraoperative blood transfusion			0.170			0.018
Yes	572 (9.0)	664 (12.7)		478 (11.0)	466 (10.7)	
No	5695 (90.1)	4451 (85.0)		3814 (87.7)	3818 (87.8)	
Missing	55 (0.9)	123 (2.3)		55 (1.3)	63 (1.4)	
Anaesthesia characteristics						
Peripheral nerve block	468 (7.4)	247 (4.7)	0.113	231 (5.3)	229 (5.3)	0.002
Neuroaxial nerve block	2148 (34.0)	1384 (26.4)	0.165	1232 (28.3)	1265 (29.1)	0.017
Year group			0.239			0.009
2004–2008	1087 (17.2)	1404 (26.8)		981 (22.6)	986 (22.7)	
2009–2012	2270 (35.9)	1769 (33.8)		1529 (35.2)	1543 (35.5)	
2013–2018	2965 (46.9)	2065 (39.4)		1837 (42.3)	1818 (41.8)	
Postoperative pathology[*]						
T stage			0.079			0.050
T0	533 (8.4)	423 (8.1)		351 (8.1)	369 (8.5)	
T1	1133 (17.9)	879 (16.8)		755 (17.4)	745 (17.1)	
T2	3731 (59.0)	3025 (57.8)		2574 (59.2)	2504 (57.6)	
T3	851 (13.5)	846 (16.2)		613 (14.1)	678 (15.6)	
T4	56 (0.9)	47 (0.9)		38 (0.9)	39 (0.9)	
Missing	18 (0.3)	18 (0.3)		16 (0.4)	12 (0.3)	
N stage			0.060			0.046
N0	4126 (65.3)	3363 (64.2)		2849 (65.5)	2777 (63.9)	
N1	1385 (21.9)	1161 (22.2)		924 (21.3)	977 (22.5)	
N2	779 (12.3)	661 (12.6)		546 (12.6)	553 (12.7)	
Missing	32 (0.5)	53 (1.0)		28 (0.6)	40 (0.9)	
M stage			0.006			0.010
M0	6054 (95.8)	5010 (95.6)		4152 (95.5)	4161 (95.7)	
M1	207 (3.3)	176 (3.4)		151 (3.5)	143 (3.3)	
Missing	61 (1.0)	52 (1.0)		44 (1.0)	43 (1.0)	

Propensity scores were computed using logistic regression based on all variables above. Numbers in parentheses are percentages unless otherwise stated. ATC, Anatomical Therapeutic Chemical Classification; IQR, inter-quartile range; SMD, standardised mean difference.

[*] The postoperative T and N stages were not included in propensity score estimation.

confused with relapse. Secondary outcomes were all-cause mortality and disease-free survival. All-cause mortality was defined as death recorded in the Danish Civil Registration System, and disease-free survival was defined as time to either death or recurrence. Participants were censored in the event of emigration on the date registered in Danish Civil Registration System. Both primary and secondary endpoints were specified before data analysis.

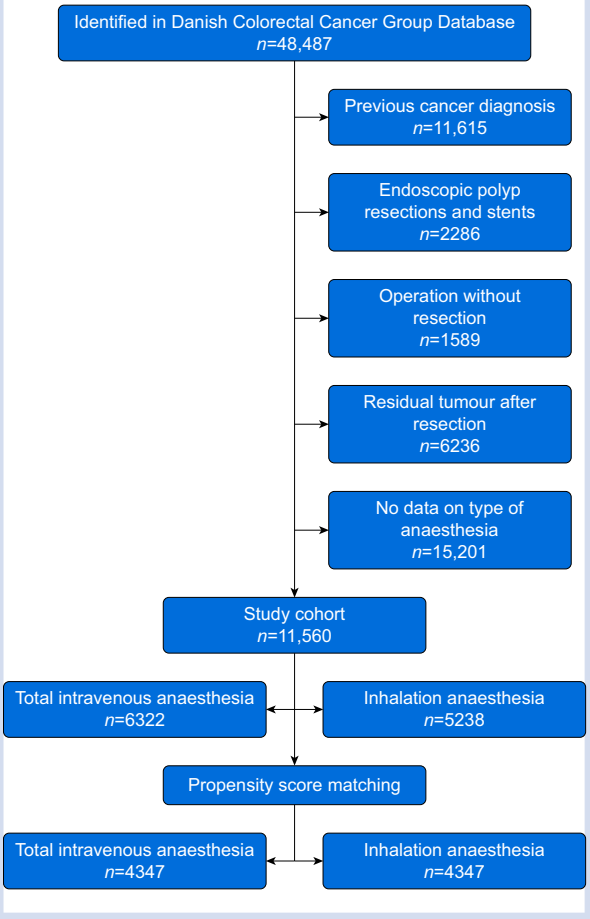

Fig 1. Flowchart of study cohort.

Confounders

We used propensity score matching as our primary tool for confounder adjustment. We included all preoperative variables in Table 1 in the model build. We did not include postoperative characteristics, as these could potentially lie in the causal pathway. Propensity scores, which represent the estimated probability of treatment given patient baseline characteristics, were calculated by logistic regression. It has been shown that matching on propensity score will achieve balance on all variables included in the propensity score model. We used the MatchIt package[23] in R (R Core Team (2019). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL: https://www.R-project.org/) to perform the propensity score matching with the following specifications: 'nearest neighbour', calliper 0.1 standard deviations of the logit of the propensity score, random matching order, and a ratio of 1:1. As cancer stage is highly predictive of recurrence, we specifically ensured that there was balance in baseline cancer stage, as judged from the postoperative pathology report.

To evaluate the effect of adjustments for confounders on our results, we reported analyses on data without propensity score adjustments. Large discrepancy between the crude and adjusted results would indicate substantial confounding and room for residual confounding.

Subgroup analyses

To explore potential effect modification, we performed analyses of the primary outcome in pre-specified subgroups. The subgroups were defined by the following: age older than 70 yr, age younger than 70 yr, male sex, female sex, ASA physical status 1–2, ASA physical status 3–4, right-sided colon tumour, left-sided colon tumour, rectal tumour, laparotomy, laparoscopy, elective operation, acute operation, neoadjuvant oncologic treatment, Charlson comorbidity index 0–1, and Charlson comorbidity index above 1. Analyses of patients stratified by frailty state using the Easter Cooperative Oncology Cooperation Score for physical performance was planned; however, data revealed more than 80% missing data on this variable in the Danish Colorectal Cancer Group Database. Instead, we included multi-drug use, defined as the number of different prescriptions dispensed within 3 months before surgery (0–4, 5–9, or more than 9).

Statistical analyses

The population was stratified and characterised with absolute numbers and percentages for categorical variables and medians with inter-quartile ranges (IQRs) for non-normally distributed continuous variables. Missing data were categorised as separate levels in categorical variables. The study groups were compared before and after propensity score matching using standardised mean differences. Acceptable covariate balance was defined as standardised mean difference <0.1 for the entire list of covariates. Risk of recurrence between the propensity score matched groups were estimated using Cox proportional hazard regression with the competing risk approach of Fine and Gray[24] with death as a competing event. Disease-free survival and mortality were estimated using Cox proportional hazards regression. Results are presented as hazard ratios (HRs) with 95% confidence intervals (95% CIs).

In the subgroup analyses, we performed analyses of recurrences in the subgroups of the propensity score matched cohorts. We also assessed whether covariate fine balance was achieved within each group; and if this was not the case, analyses were repeated in a separate propensity score matching of the subgroup. Statistical analyses were performed using R version 3.6.3 (R Core Team (2019). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL: https://www.R-project.org/).

Results

We identified 11,560 patients undergoing colorectal cancer resection without residual tumour registered in postoperative pathology reports and with information on the type of anaesthesia used. We found low rates of missing data, with the highest rates found in tobacco (350; 3.0%), and alcohol consumption (248; 2.1%). Median age was 70 yr (IQR, 63–77 yr), 6250 (54.1%) were male and 5238 (45.3%) were exposed to inhalation anaesthesia. The median follow-up time was 46.2 months (IQR, 25.0–80.1 months). A flowchart of the cohort is presented in Fig. 1.

Before propensity score matching, the group exposed to inhalation anaesthesia was older and with more comorbidity as reflected in higher Charlson comorbidity indices and ASA physical status. Furthermore, a smaller proportion of patients

in the inhalation anaesthesia group underwent minimally invasive surgery; and lastly, more patients underwent anaesthesia with inhalation anaesthesia in the beginning of the study period, whereas the majority underwent TIVA by the end of the study period (Table 1).

Propensity score matching and covariate balance

There was considerable overlap in propensity scores between the study groups; after propensity score matching, the distributions of propensity scores were similar between groups (Supplementary Fig. S1). The propensity score matched cohort consisted of 8694 individuals. In the propensity score matched cohort, 4730 (54.4%) were men, the median age was 71 yr (IQR 64–78), and characteristics were similar to the cohort before propensity score matching. The matched cohort had balanced characteristics for patients receiving inhalation anaesthesia and TIVA (Table 1). As an indication of fine covariate balance, no variable had a standardised mean difference >0.1 (Table 1 and Supplementary Fig. S2). The median follow-up time was 54.3 months (IQR, 26.9–88.2). Disease stage based on pathology reports were also balanced between groups (Table 1).

Recurrence

Cancer recurrence was observed in 1722 (19.8%) individuals during the study period: 902 (20.7%) in the group exposed to inhalation anaesthesia and 820 (18.9%) in the TIVA group. In the inhalation anaesthesia group, we found increased risk of recurrence (HR=1.12; 95% CI, 1.02–1.23) compared with the TIVA group. Based on the competing risk model for recurrence, the predicted 5 yr probability of recurrence was 20.8% and 18.8% for the inhalation anaesthesia and TIVA groups, respectively. The cumulative incidence function for recurrence is presented in Fig. 2. The results are summarised in Table 2.

All-cause mortality and disease-free survival

During the study period, 2948 (33.9%) patients died, 1475 (33.9%) in the inhalation anaesthesia group and 1472 (33.9%) in the TIVA group. For inhalation anaesthesia compared with TIVA, we observed an HR of 1.00 (95% CI, 0.93–1.07) for all-cause mortality and an HR of 1.04 (95% CI, 0.98–1.11) for disease-free survival. Results are summarised in Table 2. Survival curves are presented in Supplementary Fig. S3 and S4.

Crude estimates

The results of the analyses of data without propensity score adjustment revealed similar HR for inhalation anaesthesia for the primary outcome, recurrence, of 1.11 (95% CI, 1.02–1.21) *vs* 1.12 (95% CI, 1.02–1.23). The differences between crude and unadjusted estimates were substantial for mortality (crude HR=1.39 [95% CI, 1.30–1.48] *vs* adjusted HR=1.00 [95% CI 0.93–1.07] and disease-free survival (crude HR=1.33 [95% CI 1.25–1.49] *vs* adjusted HR=1.04 [95% CI, 0.98–1.11]). Crude results are presented in Table 3.

Subgroup analyses

The subgroup analyses showed estimates that were very similar to the main analysis in most subgroups. CIs were wider for smaller subgroups. Although confidence intervals included HR=1.00 in most subgroups, the estimates from the groups 'Charlson 0–1', 'elective surgery', and 'number of drugs dispensed 0–4' were statistically significant. The association between inhalation anaesthesia and recurrence was smaller in patients with Charlson Comorbidity scores >1 compared with lower scores. Moreover, the association was larger in patients with high ASA physical status and patients who had received neoadjuvant therapy. Nevertheless, no statistically significant effect modification was observed. The results are summarised in Fig. 3 and Supplementary Table S4.

There were covariate imbalances with maximum standardised mean differences >0.2 in three subgroups ('Number of different drugs dispensed during last 3 months >10', 'Acute surgery', and 'Neoadjuvant therapy'), and imbalances with maximum standardised mean difference >0.1 but <0.2 in another seven subgroups. After performing new propensity score matching within these groups, 'Acute surgery' yielded higher effect estimates than before, and 'neoadjuvant therapy' displayed a smaller effect estimate compared with the primary analyses. The remaining estimates were similar to the primary analyses (Fig. S5).

Discussion

In this retrospective registry-based study, we found an association between exposure to inhalation anaesthesia during colorectal cancer surgery and cancer recurrence. The association between inhalation anaesthesia and disease-free survival was less pronounced and not statistically significant. We did not find any association with all-cause mortality.

The hypothesis that the type of anaesthesia increases the risk of cancer recurrence has been proposed in recent years. The use of inhalation anaesthesia or TIVA has been studied in various populations with mortality and recurrence as outcomes.[5] In keeping with our results, some studies have reported increased recurrence rates related to inhalation anaesthesia in breast, colon, and oesophageal cancer

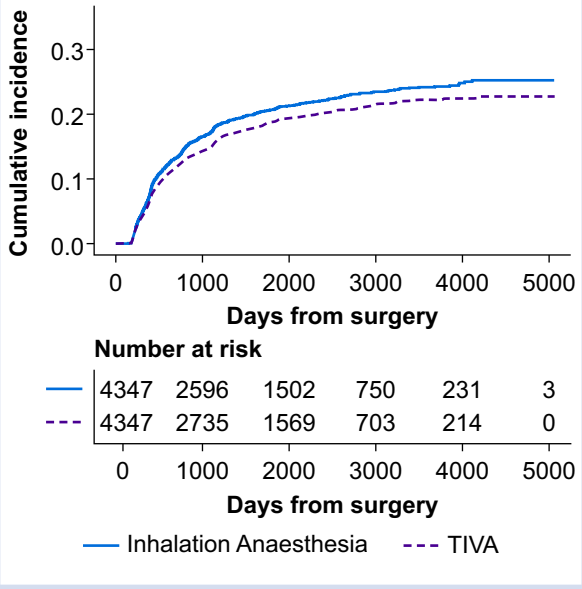

Fig 2. Cumulative incidence of recurrence after colorectal cancer surgery stratified by type of anaesthesia.

Table 2 Estimated association between exposure to inhalation anaesthesia during colorectal cancer surgery and cancer recurrence, all-cause mortality and disease-free survival in propensity score matched cohort.

	N	Median follow-up, months (IQR)	Events (%)	HR (95% CI)
Recurrence				
TIVA	4347	47.9 (19.2–82.4)	820 (18.9)	1.00 (reference)
Inhalation	4347	44.1 (17.9–84.4)	902 (20.7)	1.12 (1.02–1.23)
All-cause mortality				
TIVA	4347	55.5 (28.0–87.0)	1473 (33.9)	1.00 (reference)
Inhalation	4347	53.1 (26.3–90.0)	1475 (33.9)	1.00 (0.93–1.07)
Disease-free survival				
TIVA	4347	47.9 (19.2–82.4)	1777 (40.9)	1.00 (reference)
Inhalation	4347	44.1 (17.9–84.4)	1827 (42.0)	1.04 (0.98–1.11)

Hazard ratios (HRs) are estimated using Fine and Gray subdistribution hazards approach for recurrence and Cox proportional hazards approach for all-cause mortality and disease-free survival. 95% CI, 95% confidence interval; IQR, inter-quartile range.

Table 3 Crude estimates without propensity score adjustment of the association between exposure to inhalation anaesthesia during colorectal cancer surgery and cancer recurrence, all-cause mortality and disease-free survival.

	N	Median follow-up, months (IQR)	Events (%)	Crude HR (95% CI)
Recurrence				
TIVA	6322	48.0 (70.7–80.5)	1171 (18.5)	1.00 (reference)
Inhalation	5238	42.0 (16.9–83.2)	1076 (20.5)	1.11 (1.02–1.21)
All-cause mortality				
TIVA	6322	55.1 (30.2–84.5)	1790 (28.3)	1.00 (reference)
Inhalation	5238	50.9 (23.8–89.3)	2035 (38.9)	1.39 (1.30–1.48)
Disease-free survival				
TIVA	6322	48.0 (70.7–80.5)	2282 (36.1)	1.00 (reference)
Inhalation	5238	42.0 (16.9–83.2)	2428 (46.4)	1.33 (1.25–1.40)

Hazard ratios (HRs) are estimated using Fine and Gray subdistribution hazards approach for recurrence and Cox proportional hazards approach for all-cause mortality and disease-free survival. 95% CI, 95% confidence interval; IQR, inter-quartile range.

surgery.[25–27] Conversely, large studies of breast and lung cancer surgery did not find this association,[28–30] whereas other studies have lacked statistical power to detect any effect of inhalation anaesthesia on recurrence.[31,32] This may be because the magnitude of the adrenergic–inflammatory response to surgery is reduced in some types of surgery and that patients are immunologically competent to clear cancer cells in the perioperative phase.[33] In addition, it is plausible that the effect of inhalation anaesthesia on perioperative metastasis formation depends on the type of cancer. Lastly, it is noted that the association between anaesthesia type and cancer recurrence could be attributed to favourable effects of TIVA instead of adverse effects of inhalation anaesthesia.[10]

Large studies in breast, gastric, liver, colon, and rectal cancer have indicated increased mortality in cancer patients undergoing inhalation anaesthesia.[27,34–38] Nonetheless, the association to mortality found in these studies may not necessarily be caused by cancer recurrence. In our study, we did not find an association with mortality. As death can be caused by various other events than cancer recurrence, it would require a larger study population to see an effect on death caused by inhalation anaesthesia-induced recurrence. One retrospective study of patients undergoing oesophageal cancer resections found increased mortality related to inhalation anaesthesia but significantly fewer myocardial infarctions, which may be explained by the supposed protective effect of inhalation anaesthesia on reperfusion injury. [25,38,39] The lack of association between inhalation anaesthesia and mortality may be caused by a reduction of other postoperative events related to inhalation anaesthesia such as myocardial infarctions. In addition to cancer recurrence, further studies should focus on other possible explanations of the associations between inhalation anaesthesia and postoperative mortality such as postoperative complications.

The strengths of this study are its large size and detailed patient characteristics of patients undergoing the same types of surgery, which allowed us to perform detailed adjustments for potential confounders. Moreover, we included prospectively collected data, reducing the risk of recall bias. Comorbidities, which are a major confounder in the association between choice of anaesthesia and cancer outcome, were measured using three different approaches. First, the Charlson comorbidity index provided an overall score of disease history, and the method of using the Danish National Patient Registry to compute the score has been validated.[40] Secondly, the ASA physical status served as a valid marker of preoperative health status[41]; and thirdly, the use of the Danish National Prescription Database ensured the validity of actual prescription drug consumption. The combination of disease history, health status, and current medication ensured a detailed and universal assessment of comorbidities. Cancer stage is highly determining for cancer recurrence. After propensity score matching for preoperative covariates, we found fine covariate balance for postoperative T, N, and M stages. This means that the cancer stages were comparable between the groups and did not cause bias to our results. Finally, recurrence can be diagnosed in various ways and is therefore often difficult to define clearly. However, the algorithm used for detection of

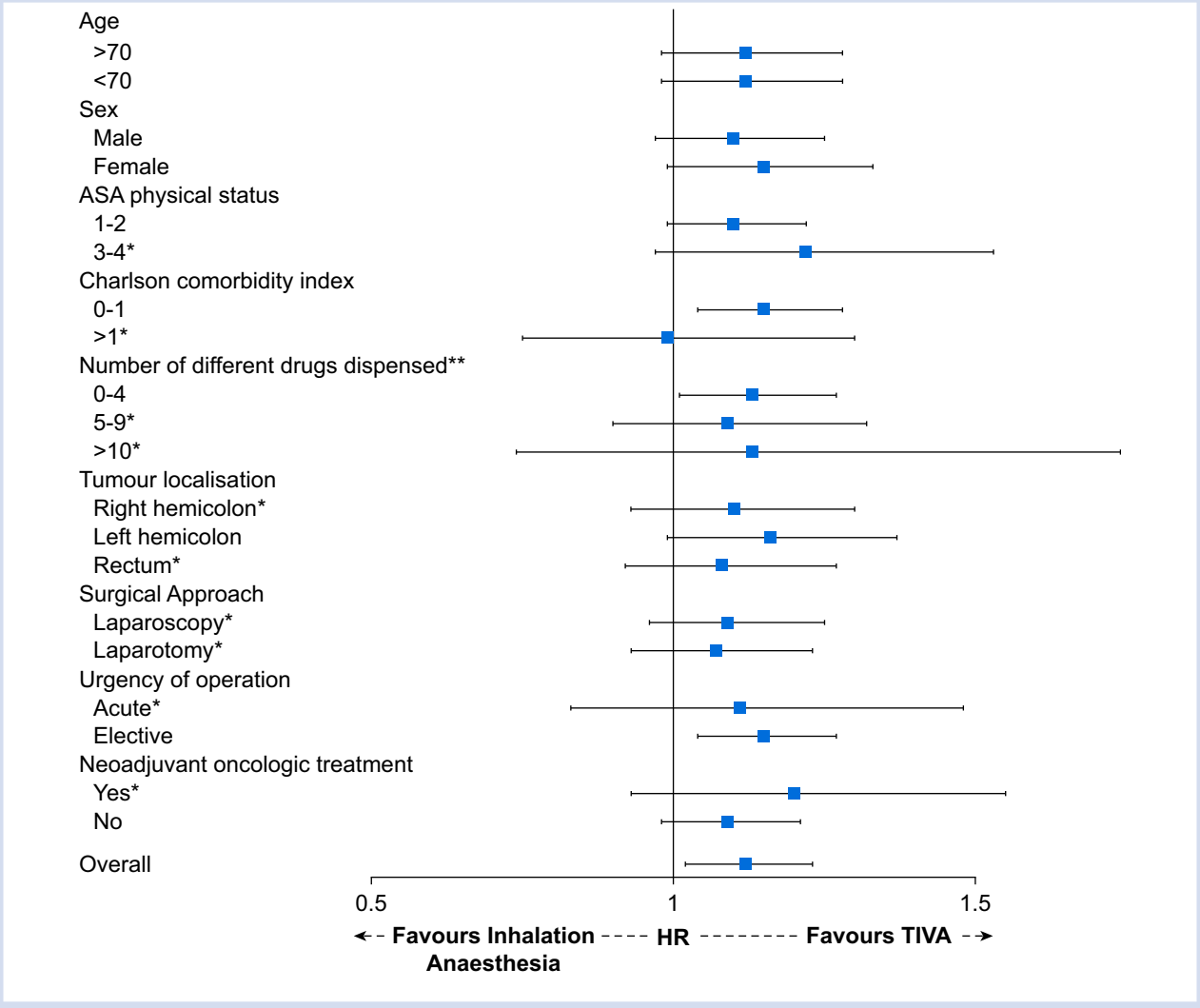

Fig 3. Forest plot of hazard ratios for recurrence for inhalation anaesthesia compared with total intravenous anaesthesia in patients undergoing surgery for colorectal cancer. *Owing to subgroup covariate imbalance, estimates are based on new subgroup propensity score matching. **During 3 months before surgery.

recurrences is highly reliable and has been validated previously with an estimated sensitivity of 95% and specificity of 97%.[22] In the validation study, the positive predictive value was 86% (95% CI, 75–93%) and the negative predictive value was 99% (95% CI, 97–100%).

There are important limitations to bear in mind when interpreting these results, and they cannot automatically be applied to other populations. There is a risk of different data reporting practices at the reporting institutions, which could lead to misclassification in the Danish registries. Moreover, by performing propensity score matching and stratification, we adjusted for measured variables that could have influenced the choice of anaesthesia technique. There is always an inherent risk of residual confounding by unmeasured covariates in observational studies. If data were available, it could have been indicated to adjust for clinical cancer stage, preoperative blood transfusions, and laboratory parameters such as haemoglobin level and intraoperative medication. In our crude analyses, we found large differences between crude and adjusted estimates of mortality and disease-free survival. This indicates substantial confounding effects on these outcomes and that further adjustments could have changed the results even more. The opposite can be stated about recurrence, as the effect of confounding on our estimates of recurrence was very limited. Prospective randomised trials are necessary to determine if a causal link between inhalation anaesthesia and cancer recurrence exists. Our results suggest that a potential effect of inhalation anaesthesia on recurrence is small, and therefore, future studies should be sizeable. However, the absolute risk reduction of 5 yr recurrence of 2.0% between groups, which corresponds to a number needed to treat of 50, has substantial clinical relevance.

In conclusion, we found increased risk of recurrence in patients undergoing colorectal cancer surgery with inhalation anaesthesia compared with TIVA. Besides the need for large randomised clinical trials, future research should focus on

understanding the underlying pathophysiologic and immunologic mechanisms of inhalation anaesthesia in patients with malignancy.

Authors' contributions

Conception and design: RPH, JH, IG
Data analysis: RPH
Interpretation of results: RPH, JH, IG
Drafting of the manuscript: RPH
Critical revision of the manuscript: JH, IG

Declarations of interest

The authors declare that they have no conflicts of interest.

Funding

Danish Cancer Research Fund (granted in 2018).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2020.11.019.

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Handling editor: Hugh C Hemmings Jr