ANESTHESIOLOGY

Epidural Analgesia and Recurrence after Colorectal Cancer Surgery: A Danish Retrospective Registry-based Cohort Study

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- There are conflicting data regarding the association between epidural analgesia and cancer recurrence after colorectal cancer surgery

What This Article Tells Us That Is New

- In a retrospective cohort analysis of 11,618 patients in Danish national colorectal cancer surgery and anesthesia registries, 30% had an epidural catheter inserted for analgesia
- The comparison of 2,980 patients receiving general anesthesia with epidural analgesia matched to 2,980 patients with general anesthesia alone demonstrated that the rates of cancer recurrence were not significantly different: 19.0% *versus* 20.5%

ABSTRACT

Background: Surgery is the main curative treatment for colorectal cancer. Yet the immunologic and humoral response to surgery may facilitate progression of micro-metastases. It has been suggested that epidural analgesia preserves immune competency and prevents metastasis formation. Hence, the authors tested the hypothesis that epidural analgesia would result in less cancer recurrence after colorectal cancer surgery.

Methods: The Danish Colorectal Cancer Group Database and the Danish Anesthesia Database were used to identify patients operated for colorectal cancer between 2004 and 2018 with no residual tumor tissue left after surgery. The exposure group was defined by preoperative insertion of an epidural catheter for analgesia. The primary outcome was colorectal cancer recurrence, and the secondary outcome was mortality. Recurrences were identified using a validated algorithm based on data from Danish health registries. Follow-up was until death or September 7, 2018. The authors used propensity score matching to adjust for potential preoperative confounders.

Results: In the study population of 11,618 individuals, 3,496 (30.1%) had an epidural catheter inserted before surgery. The epidural analgesia group had higher proportions of total IV anesthesia, laparotomies, and rectal tumors, and epidural analgesia was most frequently used between 2009 and 2012. The propensity score–matched study cohort consisted of 2,980 individuals in each group with balanced baseline covariates. Median follow-up was 58 months (interquartile range, 29 to 86). Recurrence occurred in 567 (19.0%) individuals in the epidural analgesia group and 610 (20.5%) in the group without epidural analgesia. The authors found no association between epidural analgesia and recurrence (hazard ratio, 0.91; 95% CI, 0.82 to 1.02) or mortality (hazard ratio, 1.01; 95% CI, 0.92 to 1.10).

Conclusions: In colorectal cancer surgery, epidural analgesia was not statistically significantly associated with less cancer recurrence.

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Colorectal cancer is frequent with an estimated 1.8 million global cases per year,[1] and as the incidence is expected to increase further, it is becoming a substantial global health challenge.[2,3] Surgery remains the primary curative treatment for colorectal cancer. Nevertheless, postoperative cancer recurrence is frequent, and it is the primary cause of death for people suffering from this disease.[4,5]

Paradoxically, the physiologic stress impact of curative surgery on the immune and neuro-humoral system may generate a favorable microenvironment for cancer progression.[6,7] While activation of the hypothalamus-pituitary-adrenal axis and systemic inflammation facilitates wound healing,[8] it reduces the ability of the immune system to detect and eliminate tumor cells.[9] Hence, attenuating the disruptive impact of surgery on physiologic homeostasis may mitigate the risk of circulating tumor cells seeding and dormant micro-metastases being activated.[10,11]

Epidural analgesia can be used to reduce intraoperative opioid requirements and postoperative pain in abdominal

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surgery. Epidural analgesia of the midthoracic level provides analgesia to the abdomen by inhibiting afferent transmission of pain impulses to the brain, causing reduced cerebral activation of the sympathetic nervous system. Moreover, thoracic epidural analgesia inhibits sympathetic tone by blocking the efferent fibers from the brain to the sympathetic trunc.[7] This results in reduced postoperative pain and attenuated neuro-humoral response to surgery.[12,13] Thus, the reduction in surgery-induced physiologic stress may reduce metastasis formation.[9,14,15] It has also been proposed that opioids[9] and inhalational anesthesia[16] may promote metastases and that reduced requirements of these drugs can reduce the risk of cancer recurrence.

Based on the mitigating effects of epidural analgesia on the surgical stress response, we hypothesized that epidural analgesia decreases the risk of cancer recurrence after colorectal cancer surgery. We aimed to assess the association between use of epidural analgesia and postoperative cancer recurrence in patients undergoing surgery for colorectal cancer using data from Danish registries of prospectively collected data.

Materials and Methods

This was an observational cohort study based on prospective and routinely collected data from Danish health registries. It included patients curatively operated for colorectal cancer in Denmark 2004 to 2018. According to Danish law, use of data from health registries does not require patient consent or approval from ethics review boards. The study was approved by the Danish Data Protection Agency (Copenhagen, Denmark; file no. 2012-58-0003, REG-038-2017). The Strengthening The Reporting of Observational Studies in Epidemiology (STROBE) and REporting of studies Conducted using Observational Routinely-collected Data (RECORD) Statements were adhered to for reporting.[17,18]

Data Sources

The use of the Central Person Registration number, which is a unique identification number of all residents of Denmark, allowed us to link Danish health registries. The cohort was defined using the Danish Colorectal Cancer Group Database[19] and the Danish Anesthesia Database,[20] which were linked using the Central Person Registration number and operation date available in both registries. The completeness of the Danish Colorectal Cancer Group Database is more than 95%, and about 60% for the Danish Anesthesia Database.[19,20] Events of recurrence were obtained from the Danish National Patient Registry,[21] the Danish National Pathology Registry,[22] and the Danish Cancer Registry.[23] Data on mortality were obtained from the Danish Civil Registration System.[24] Prescriptions filled within 3 months before surgery were identified in the Danish National Prescription Registry.[25] Descriptions of data sources are provided in Supplemental Digital Content 1 (http://links.lww.com/ALN/C778).

Population and Setting

The study cohort consisted of patients identified in the Danish Colorectal Cancer Group Database undergoing colorectal cancer surgery in Denmark with available anesthesia data from the Danish Anesthesia Database from 2004 to 2018. In Denmark, all colorectal cancer resections are performed in public hospitals that are required to report to the Danish Colorectal Cancer Group Database and the Danish Anesthesia Database. We excluded procedures where no tumor was resected, and to include only patients with relevant surgical trauma, we excluded individuals undergoing endoscopic polyp resections and stent insertions. Only complete micro- and macro-radical resections, where no cancer tissue was left after surgery based on postoperative pathology reports, were included. To avoid confounding from other cancer types, we excluded all patients with previous cancer registered in the Danish National Prescription Registry or the Danish Cancer Registry except nonmelanoma skin cancer.

The treatment group consisted of all patients receiving general anesthesia supplemented with insertion of an epidural catheter for analgesia. All catheters were placed preoperatively, but no data were available on timing of administration of epidural medication. The comparator group consisted of individuals receiving general anesthesia without neuraxial analgesia.

Outcomes

Cancer recurrence was the primary study outcome. Based on a validated algorithm,[26] we defined recurrence as a specific code for colorectal local cancer recurrence registered in the Danish National Patient Registry any time after surgery, or metastatic cancer, chemotherapy, or recurrence registered in the Danish National Pathology Registry, Danish National Patient Registry, or the Danish Cancer Registry more than 180 days from surgery without a new postoperative cancer diagnosis different from colorectal cancer and nonmelanoma skin cancer in between. The 180-day limit was used to distinguish adjuvant oncologic therapy from new regimens of chemotherapy for recurrence. Overall mortality, defined as time to death registered in the Danish Civil Registration System, served as a secondary outcome. Since metastatic disease is the primary cause of death in cancer, differences in long-term mortality rates are likely to be attributable to cancer progression. In addition, numerous studies within this field have used mortality as the main outcome, and including this outcome improves comparability with other studies.

Patients that emigrated and therefore were excluded from the Danish Civil Registration System were censored at the day of emigration. Follow-up was until death or September 7, 2018.

Other Variables

We obtained data on preoperative clinical characteristics including age, sex, body mass index, lifestyle factors, and

tumor characteristics from the Danish Anesthesia Database and Danish Colorectal Cancer Group Database. Patient frailty, which we considered to be a key confounder, was described by three individual parameters in combination. First, the Charlson Comorbidity Index[27,28] served as a measure of severity of diseases in the patient history. Second, American Society of Anesthesiologists (ASA; Schaumburg, Illinois) Physical Status[29,30] was used to describe the physical status at the time of surgery, and third, prescriptions filled within 3 months before surgery described the current comorbidities requiring medical treatment. Details and definitions of all variables are available in Supplemental Digital Content 2 (http://links.lww.com/ALN/C779).

Confounders and Bias

To estimate the treatment effect in patients receiving epidural analgesia (average treatment effect on the treated), we used propensity score matching to adjust for confounders. Propensity scores were calculated by logistic regression with epidural analgesia as outcome and the following covariates as exposure: age, sex, body mass index, tobacco use, alcohol consumption, Charlson Comorbidity Index, ASA Physical Status, filled prescriptions within the past 3 months (platelet inhibitors, anticoagulants, digoxin, thiazide, β-blockers, calcium antagonists, drugs acting on the renin angiotensin system, lipid-lowering drugs, estrogen replacement therapy, steroids, nonsteroid anti-inflammatory drugs, urate-lowering drugs, bisphosphonates, opioids, benzodiazepines, antidepressants, drugs for obstructive pulmonary disease, and number of individual drugs dispensed), preoperative metastases, tumor localization, neoadjuvant therapy, intended surgical approach (laparotomy or laparoscopy), urgency (elective or acute), general anesthesia type (inhalational or total IV anesthesia), and year. We did not include intra- or postoperative factors in the propensity score model as these cannot affect the choice of preoperative epidural analgesia and may potentially be part of the causal pathway between epidural analgesia and recurrence.[31] By visually inspecting density plots for the exposure groups, we ensured that there was sufficient overlap between the two groups to perform propensity score matching. Using the MatchIt[32] package in R (R Foundation for Statistical Computing, Austria), specified with "nearest neighbor," "caliper 0.25 of the SD of logit," "ratio 1:1," and "random order," we matched patients into groups with and without epidural analgesia. This constituted the study cohort. Covariate balance was assessed using standardized mean differences for each covariate category,[33] and acceptable covariate balance was defined as a standardized mean difference less than 0.1 for any covariate included in the propensity score.

Statistical Analysis

The study cohort was classified according to preoperative epidural analgesia, and characteristics were summarized with absolute numbers and percentages for categorical variables and medians with interquartile ranges for continuous variables. Missing data for categorical variables were classified as separate subgroups of the variable.

Postoperative events were displayed as cumulative incidence curves using the Aalen–Johansen estimates for recurrence and Kaplan–Meier estimates for mortality. We used Cox regression with the subdistribution hazards approach[34] to estimate hazard ratios for recurrence with death as a competing risk. The regular Cox proportional hazards approach was used to estimate hazard ratio for mortality. The proportional hazards assumption for recurrence was verified by visually inspecting cumulative incidence curves and using the plotEffects function in the "RiskRegression" package in R. For mortality, proportionality was inspected visually in Kaplan–Meier curves and in plots of residuals using the ggcoxzph function in the "survminer" package in R. Effect estimates were presented with 95% CI. By inserting subgroup covariates as interaction terms with epidural analgesia in regression models of the total cohort with all baseline covariates included, we formally tested effect modification. R version 3.6.3 was used for the analyses.

As data used in this study are routinely collected in health databases and have been available and used in previous publications by our research group, it was not possible to submit a statistical analysis plan before data access. Hence, a data analysis and statistical plan were written after the data were accessed. However, statistical analyses were specified before initiating analyses and were, therefore, driven by the study hypothesis. Since our study was based on all available routinely collected data in the registries used, we did not perform a prestudy statistical sample size calculation.

In the primary analyses, differences between groups were considered statistically significant if they were outside 95% CI, and a two-tailed approach was used for hypotheses testing. In subgroup analyses, we tested 29 hypotheses. Thus, applying Bonferroni correction for multiple hypothesis testing resulted in a *P* value threshold for statistical significance of 0.002 in the subgroup analyses.

Prespecified Subgroup Analyses

The relation between epidural analgesia and recurrence was explored within the following prespecified subgroups: age (70 or greater *vs.* less than 70 yr, which was the median age in the cohort), intended surgical approach (laparoscopy *vs.* laparotomy), sex (male *vs.* female), ASA Physical Status (I–II *vs.* III–IV), urgency (emergency *vs.* elective surgery), localization (rectum tumor *vs.* right-sided colon tumor *vs.* left-sided colon tumor), and use of neoadjuvant chemo therapy (yes *vs.* no). The analyses were performed in subgroups with separate propensity score matchings using the same specifications as the main analysis. If the definition of fine covariate balance was not met in a subgroup (at least one covariate standardized mean difference exceeding 0.1), we included imbalanced covariates in the Cox regression model used to

estimate hazard ratios. This double-adjustment approach has been shown to sufficiently reduce bias caused by covariate imbalance after propensity score matching.[35]

Sensitivity Analyses

We performed a number of sensitivity analyses to inspect the robustness of our results. First, we performed a crude analysis of the association between epidural analgesia and recurrence to assess if confounder adjustment changed the estimates substantially. This was also performed for the secondary outcome. Large discrepancies between the crude and adjusted estimates would be an indicator of potential residual confounding.

Some tumor characteristics such as approximate size and lymph node involvement are known before initiation of surgery and could influence the choice of performing epidural analgesia. Nonetheless, the tumor-specific data in the Danish Colorectal Cancer Group Database are from postoperative pathology reports that to a certain degree are influenced by the surgical quality of the resected specimen. Therefore, pathology data were not included in the primary analysis. Since tumor stage is substantially associated with cancer recurrence, we performed a sensitivity analysis including this covariate.

Last, as the propensity score matching method was not able to find matches for all treated patients, we also estimated the association between epidural analgesia and recurrence using multivariable regression on the full dataset without propensity score matching. All baseline covariates were selected as independent variables, and the outcome was cancer recurrence. Similar to the primary analysis, we used Cox regression with the subdistribution hazards approach to account for mortality as a competing risk for recurrence.

Post Hoc Analyses

Based on relevant suggestions during peer review, we chose to include additional analyses after performing the prespecified analyses. First, the study population was subdivided according to whether the tumor was located in the rectum or colon as the disease pathologies are different. Separate propensity score matchings were performed for these subgroups. Similar to the prespecified study population, analyses of recurrence and mortality were performed for colon and rectal cancer patients. Additionally, since there were imbalances in the follow-up time between the study groups, we performed a sensitivity analysis where the population was restricted by a minimum 1 year of follow-up postoperatively. For this cohort, a separate propensity score matching was performed, and the starting point was 1 year postoperatively. Next, the choice of anesthetic agent used for general anesthesia was assumed to be determined preoperatively and was therefore included in the main analyses. However, in the Danish Anesthesia Database, the intended type of general anesthesia is not registered, and if intended total IV anesthesia was converted to inhalational anesthesia during surgery, it was registered as inhalational anesthesia in the Danish Anesthesia Database. In theory, the decision to convert anesthetic technique could be a result of intraoperative events such as bleeding or hemodynamic instability caused by epidural analgesia. Because of the potential causal effect of epidural analgesia leading to conversion of general anesthesia type, we added a sensitivity analysis excluding type of general anesthesia. Moreover, even though all patients had complete excision of tumor tissue, some had metastases preoperatively. Since it is plausible that these patients had more circulating tumor cells in the perioperative period, and thereby, a higher risk of metastasis formation, we added patients with and without preoperative metastases to the subgroup analyses. Also, by request of reviewers, we performed analyses of subgroups classified according to Union for International Cancer Control (Geneva, Switzerland) Stage. Last, since we were unable obtain data from the Danish Anesthesia Database for a large proportion of the cohort identified in the Danish Colorectal Cancer Group Database, there were concerns about whether our cohort sufficiently represented patients undergoing colorectal cancer surgery in Denmark. Therefore, we performed a comparison of the baseline covariates between patients included in the study and patients without anesthesia data.

Results

From the Danish Colorectal Cancer Group Database, we identified 26,745 patients operated for colorectal cancer with microscopically completely resected tumor tissue. In the Danish Anesthesia Database, we identified 11,634 of these. The 15,127 patients who were not identified in the Danish Anesthesia Database were compared with the included patients. A larger proportion of the patients without anesthesia data were operated in the beginning of the study period. Also, they more frequently underwent laparotomy, and slightly fewer had Union for International Cancer Control Stage IV compared with the included patients. Differences between the populations with and without anesthesia data are presented in Supplemental Digital Content 3 (http://links.lww.com/ALN/C780).

After excluding 16 patients with spinal anesthesia, the study cohort consisted of 11,618 patients. Of the total cohort, 5,337 (45.9%) were women, and the median age was 70 yr (interquartile range, 63 to 77). The first patient was operated October 26, 2004, and the last March 13, 2018. Median follow-up was 53 months (interquartile range, 27 to 86 months). There were low rates of missing data with a maximum of 3.0% in the variable "tobacco use." In the population, 3,496 (30.1%) had an epidural catheter inserted preoperatively. Baseline covariate analyses found that patients with rectum tumors were more likely to receive epidural analgesia, while patients with left-sided tumors were less likely to receive epidural

Table 1. Balance of Main Covariates of Individuals Undergoing Colorectal Cancer Surgery with Anesthesia Data in Denmark 2004 to 2018 before and after Propensity Score Matching

	Before Propensity Score Matching			After Propensity Score Matching		
	Epidural Analgesia	No Epidural Analgesia	Standardized Mean Difference	Epidural Analgesia	No Epidural Analgesia	Standardized Mean Difference
No.	3,496	8,122		2,980	2,980	
Median age, yr (interquartile range)	70 (63–77)	70 (63–77)	0.022	70 (63–77)	70 (63–77)	0.009
Sex			0.009			0.030
Male	1,901 (54.4)	4,380 (53.9)		1,631 (54.7)	1,587 (53.3)	
Female	1,595 (45.6)	3,742 (46.1)		1,349 (45.3)	1,393 (46.7)	
Body mass index, kg/m^2			0.081			0.021
<18.5	138 (3.9)	274 (3.4)		108 (3.6)	111 (3.7)	
18.5–25	1,596 (45.7)	3,487 (42.9)		1,343 (45.1)	1,322 (44.4)	
25–30	1,157 (33.1)	2,977 (36.7)		1,008 (33.8)	1,007 (33.8)	
>30	595 (17.0)	1,352 (16.6)		511 (17.1)	528 (17.7)	
Missing	10 (0.3)	32 (0.4)		10 (0.3)	12 (0.4)	
ASA Physical Status			0.031			0.032
I	638 (18.2)	1,522 (18.7)		552 (18.5)	528 (17.7)	
II	2,074 (59.3)	4,789 (59.0)		1,767 (59.3)	1,775 (59.6)	
III	726 (20.8)	1,653 (20.4)		610 (20.5)	616 (20.7)	
IV+	51 (1.5)	132 (1.6)		45 (1.5)	53 (1.8)	
Missing	7 (0.2)	26 (0.3)		6 (0.2)	8 (0.3)	
Charlson Comorbidity Index			0.023			0.012
0	2,344 (67.0)	5,379 (66.2)		1,988 (66.7)	1,975 (66.3)	
1	684 (19.6)	1,613 (19.9)		580 (19.5)	593 (19.9)	
2	257 (7.4)	600 (7.4)		228 (7.7)	231 (7.8)	
>2	211 (6.0)	530 (6.5)		184 (6.2)	181 (6.1)	
Tobacco			0.028			0.041
Smoker	721 (20.6)	1,587 (19.5)		596 (20.0)	619 (20.8)	
Nonsmoker	2,673 (76.5)	6,283 (77.4)		2,306 (77.4)	2,266 (76.0)	
Missing	102 (2.9)	252 (3.1)		78 (2.6)	95 (3.2)	
Alcohol, weekly units			0.091			0.020
0	942 (26.9)	2,191 (27.0)		787 (26.4)	795 (26.7)	
1–21	2,222 (63.6)	5,190 (63.9)		1,912 (64.2)	1,899 (63.7)	
>21	223 (6.4)	594 (7.3)		202 (6.8)	198 (6.6)	
Missing	109 (3.1)	147 (1.8)		79 (2.7)	88 (3.0)	
Tumor localization			0.200			0.004
Right hemicolon	1,166 (33.4)	2,721 (33.5)		974 (32.7)	968 (32.5)	
Left hemicolon	1,011 (28.9)	2,992 (36.8)		932 (31.3)	934 (31.3)	
Rectum	1,319 (37.7)	2,405 (29.6)		1,074 (36.0)	1,078 (36.2)	
Unspecified	<5 (0.0)	<5 (0.0)		<5 (0.0)	<5 (0.0)	
Preoperative metastases			0.027			0.024
Yes	124 (3.5)	261 (3.2)		112 (3.8)	116 (3.9)	
No	3,333 (95.3)	7,786 (95.9)		2,833 (95.1)	2,836 (95.2)	
Missing	39 (1.1)	75 (0.9)		35 (1.2)	28 (0.9)	
Cancer stage*			0.105			0.044
I	694 (19.9)	1,798 (22.1)		604 (20.3)	635 (21.3)	
II	1,506 (43.1)	3,173 (39.1)		1,271 (42.7)	1,216 (40.8)	
III	1,080 (30.9)	2,550 (31.4)		904 (30.3)	910 (30.5)	
IV	141 (4.0)	337 (4.1)		127 (4.3)	142 (4.8)	
Missing	75 (2.1)	264 (3.3)		74 (2.5)	77 (2.6)	
Neoadjuvant oncologic treatment			0.074			0.011
No	3,079 (88.1)	7,339 (90.4)		2,653 (89.0)	2,643 (88.7)	
Yes	417 (11.9)	783 (9.6)		327 (11.0)	337 (11.3)	
Urgency			0.040			0.022
Elective	3,225 (92.2)	7,543 (92.9)		2,726 (91.5)	2,707 (90.8)	
Acute	271 (7.8)	575 (7.1)		254 (8.5)	273 (9.2)	
Missing	<5 (0.0)	<5 (0.0)		<5 (0.0)	<5 (0.0)	
Intended surgical approach			0.307			0.032
Laparotomy	1,672 (47.8)	2,674 (32.9)		1,159 (38.9)	1,205 (40.4)	
Laparoscopy	1,824 (52.2)	5,448 (67.1)		1,821 (61.1)	1,775 (59.6)	
General anesthesia type			0.188			0.024
Inhalation	1,370 (39.2)	3,869 (47.6)		1,200 (40.3)	1,231 (41.3)	
Total IV anesthesia	2,117 (60.6)	4,195 (51.6)		1,771 (59.4)	1,742 (58.5)	
Missing	9 (0.3)	58 (0.7)		9 (0.3)	7 (0.2)	
Year			0.600			
2004–2008	392 (11.2)	2,110 (26.0)		392 (13.2)	434 (14.6)	0.049
2009–2012	1,868 (53.4)	2,170 (26.7)		1,364 (45.8)	1,378 (46.2)	
2013–2018	1,236 (35.4)	3,842 (47.3)		1,224 (41.1)	1,168 (39.2)	

Data are absolute numbers (%) unless stated otherwise.

*Based on Union for International Cancer Control classification.

ASA, American Society of Anesthesiologists; IV, intravenous.

analgesia. When the intended operative approach was laparotomy or total IV anesthesia was used, epidural analgesia was used more frequently. In the timespan 2009 to 2012, epidural analgesia was used more frequently than before and after.

Propensity scores were distributed with a substantial overlap between the groups (Supplemental Digital Content 4, http://links.lww.com/ALN/C781), and propensity score matching yielded 2,980 pairs. The highest standardized mean difference was 0.049, which was well below the threshold of 0.1, indicating fine covariate balance between groups (Supplemental Digital Content 5, http://links.lww.com/ALN/C782). In the matched cohort, 2,742 (46.0%) were female, the median age was 70 yr (interquartile range, 63 to 77), and median follow-up was 58 months (interquartile range, 29 to 86). The epidural analgesia group had a median follow-up of 59 months (interquartile range, 29 to 86 months), while the group without epidural analgesia had a median follow-up of 56 months (interquartile range, 28 to 87 months). Baseline characteristics before and after propensity score matching are presented in table 1 and Supplemental Digital Content 6 (http://links.lww.com/ALN/C783). A flow chart of the study cohort is presented in figure 1.

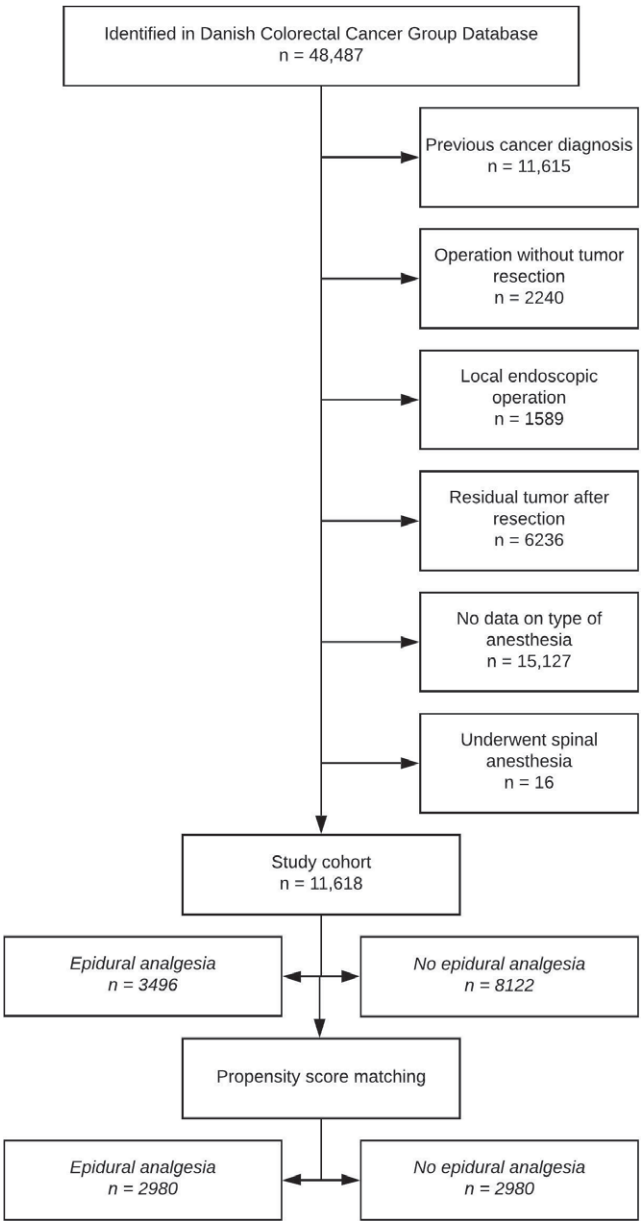

Fig. 1. Flow chart of study cohort.

Recurrence

In the propensity score–matched cohort, there were 567 (19.0%) events of recurrence in the epidural analgesia group and 610 (20.5%) in the group with general anesthesia alone. In the group with epidural analgesia, we found a hazard ratio of 0.91 (95% CI, 0.82 to 1.02) for recurrence compared with the group without epidural analgesia. The cumulative incidence of recurrence is presented in figure 2, and figure 3 summarizes results.

Mortality

After propensity score matching, 957 (32.1%) died in the epidural analgesia group during the follow-up period, whereas 959 (32.2%) died in the group without epidural analgesia. In the epidural analgesia group, the hazard ratio for mortality was 1.01 (95% CI, 0.92 to 1.10) compared with the group without epidural analgesia. Kaplan–Meier curves are presented in Supplemental Digital Content 7 (http://links.lww.com/ALN/C784). Results are summarized in figure 4.

Subgroup Analyses

After separate propensity score matchings, covariate imbalances between the study groups were present in the groups undergoing acute surgery, treated with neoadjuvant therapy, and with preoperative metastases. The imbalanced covariates were adjusted for in the effect size estimations, and an overview is available in Supplemental Digital Content 8 (http://links.lww.com/ALN/C785).

In patients under 70 yr, there were fewer recurrences in patients receiving epidural analgesia with a hazard ratio of 0.84 (95% CI, 0.72 to 0.99). However, after Bonferroni correction for multiple comparisons, this did not result in statistical significance. In the remaining subgroups, the effect estimates were not statistically significantly increased or reduced and were similar to the overall estimate. Further, all interaction tests between subgroups and epidural analgesia revealed no sign of effect modification.

For mortality, all subgroup analyses had CI including a hazard ratio of 1.0. Results are presented in figure 3 for recurrence and figure 4 for mortality. No tests of interaction

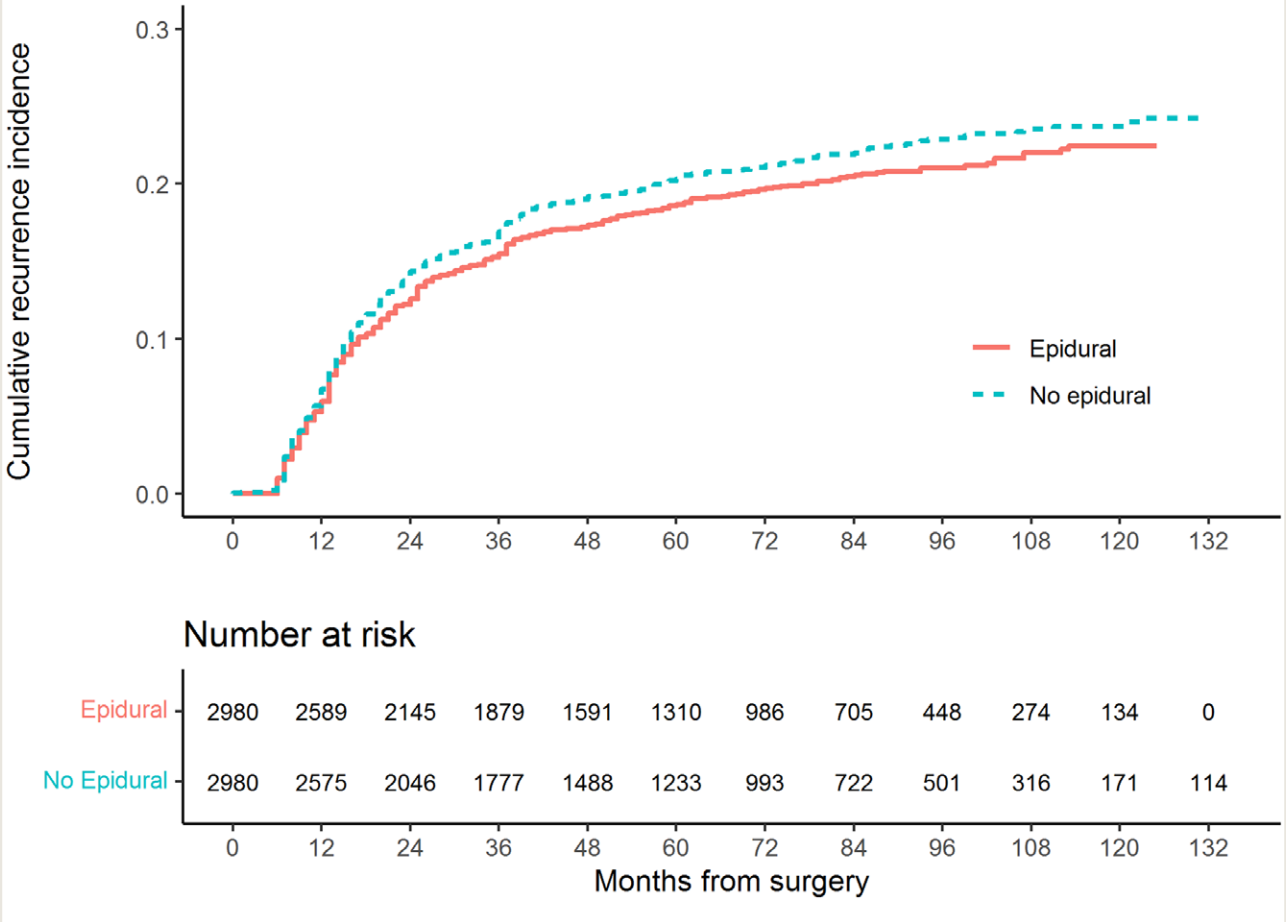

Fig. 2. Cumulative incidence of recurrence for patients with and without epidural analgesia in propensity score–matched cohort.

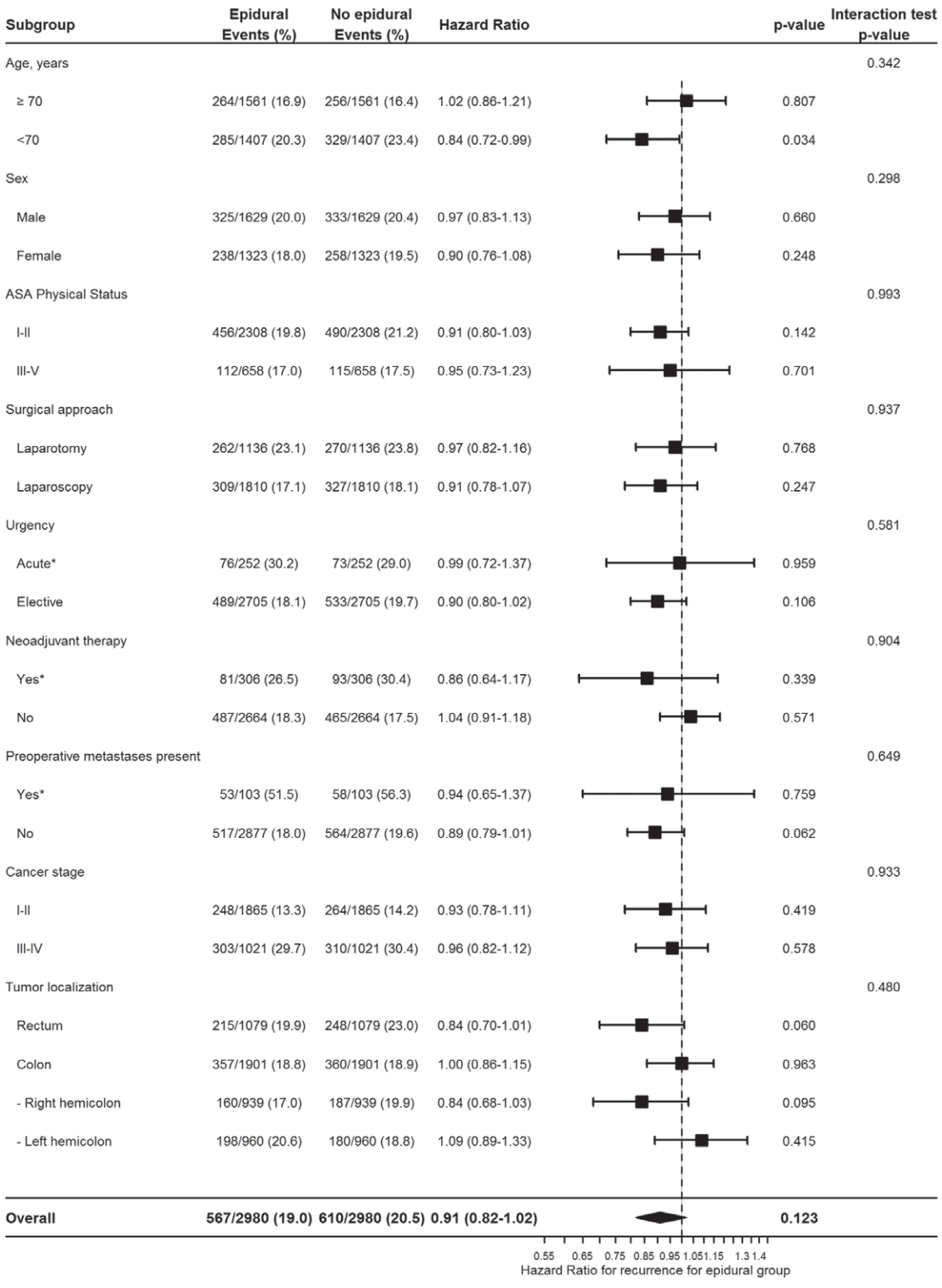

Fig. 3. Forest plot of estimates of association between epidural analgesia and recurrence. Separate propensity score matchings were performed for subgroups. Estimates and *P* values were obtained using Cox regression with the subdistribution hazards approach. No effect estimates remained statistically significant after Bonferroni correction for multiple comparisons. Interactions were tested by inserting the covariate as an interaction term with epidural analgesia in the regression model. Cancer stage was based on the Union for International Cancer Control (Geneva, Switzerland) classification. *Imbalanced covariates were adjusted for in regression model. ASA, American Society of Anesthesiologists.

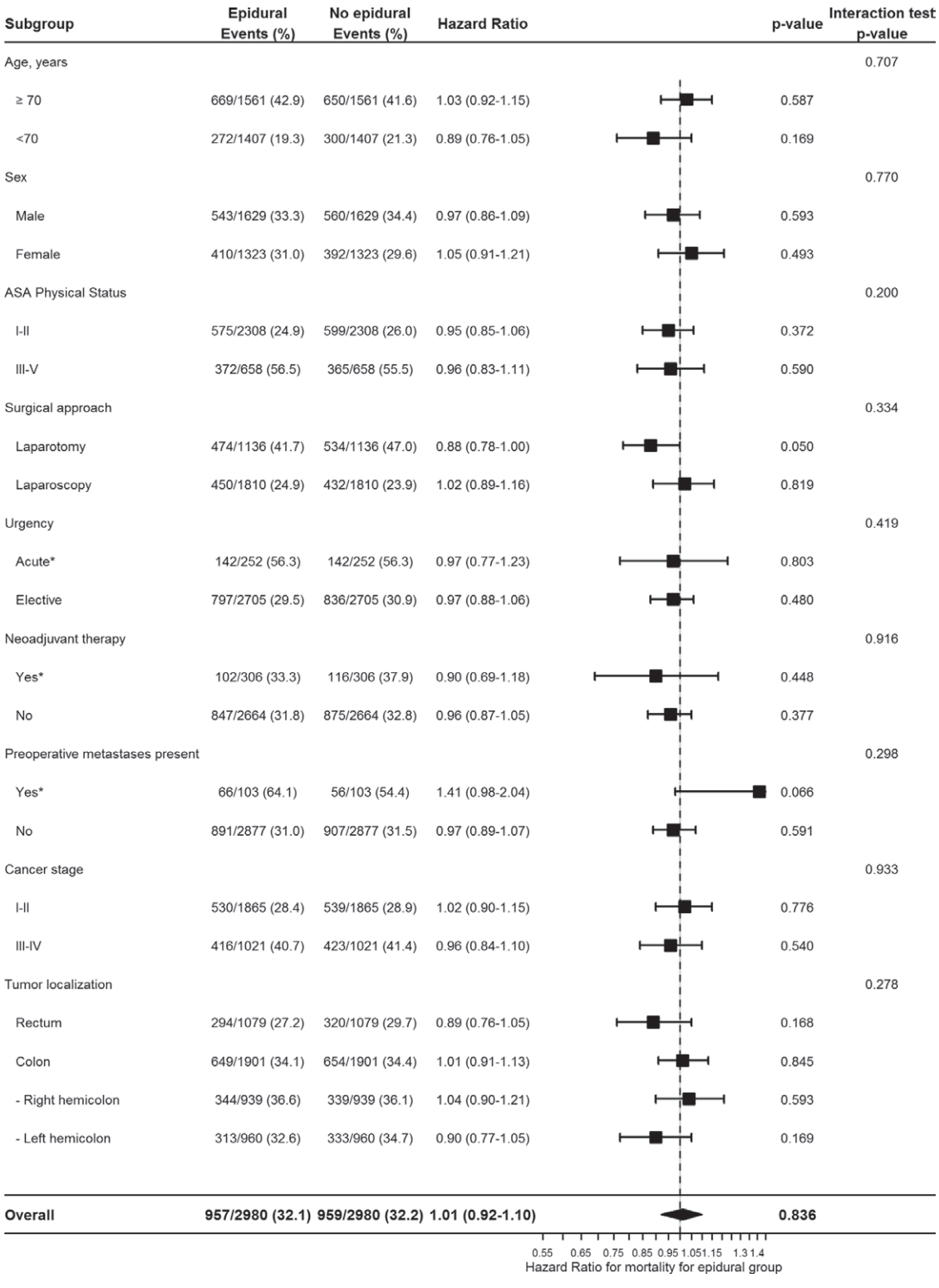

Fig. 4. Forest plot of estimates of association between epidural analgesia and mortality. Separate propensity score matchings were performed for subgroups. Estimates and *P* values were obtained using Cox regression. No effect estimates remained statistically significant after Bonferroni correction for multiple comparisons. Interactions were tested by inserting the covariate as an interaction term with epidural analgesia in the regression model. Cancer stage was based in the Union for International Cancer Control (Geneva, Switzerland) classification. *Imbalanced covariates were adjusted for in regression model. ASA, American Society of Anesthesiologists.

between subgroups and epidural analgesia were statistically significant.

Sensitivity Analyses

Crude estimates of hazard ratios for recurrence for patients with epidural analgesia showed results similar to the main analysis, with hazard ratio 0.97 (95% CI, 0.89 to 1.06) for recurrence and hazard ratio 0.98 (95% CI, 0.92 to 1.06) for mortality. All remaining subgroup analyses yielded results that were comparable to the overall estimates. The results are summarized in Supplemental Digital Content 9 (http://links.lww.com/ALN/C786).

Discussion

In this registry-based study using routinely collected health data, we found no association between epidural analgesia during colorectal cancer surgery and recurrence. Moreover, we did not find an association with long-term postoperative mortality.

Previously, the association between epidural analgesia and cancer recurrence has been investigated in observational studies with equivocal results. In contrast to our results, other studies found improved survival and recurrence rates related to epidural analgesia.[36,37] Moreover, one study found an association with mortality but not with recurrence,[38] whereas a systematic review suggested that evidence is inadequate.[39] Similar to our results, other studies of colorectal cancer surgery did not find statistically significant benefits of epidural analgesia.[40,41] Within this field, there is only little evidence from randomized clinical trials. One trial did not find differences between study groups across various types of cancer; however, since it was a follow-up study of a previous trial, it was only powered to detect very large reductions in recurrence.[42] A recent randomized controlled trial including 221 patients undergoing colorectal cancer surgery found no significant difference in a composite outcome of mortality and recurrence after 5 yr.[43] However, only 43 events of recurrence were recorded, and the study is likely to be underpowered to detect differences in recurrence. In a large randomized trial of the effect of regional anesthesia combined with propofol *versus* sevoflurane combined with opioids in breast cancer surgery, no difference in cancer recurrence was seen.[44] With more than 2,000 participants, this is the largest randomized trial to date within this field. Still, it can be argued that the adrenergic stress response to breast cancer surgery is smaller than colorectal cancer surgery; therefore, the results cannot be applied to surgery with more extensive surgical stress. In our results, we did not find an increased risk of recurrence in patients undergoing laparotomy compared with laparoscopy, which indicates no apparent effect modification of the extent of the surgical stress response in our observational data.

When interpreting these results, it is important to keep study limitations in mind. First, since cancer recurrence is rarely routinely registered in databases, it has proven challenging to determine cancer recurrence through healthcare databases of routinely collected data.[45] Even though the algorithm we used is robust, with a positive predictive value of 86% (95% CI, 75 to 93%) and a negative predictive value of 99% (95% CI, 97 to 100%),[26] there is a risk of misclassification of cancer recurrence. We therefore chose to include overall mortality as a secondary outcome, because the registration of death is considered complete in Denmark.[24] Mortality in this patient group is strongly affected by cancer recurrence. Still, we only assessed long-term outcomes, and it is possible that there are differences in short-term mortality related to postoperative recovery. Another clinical feature that is difficult to measure is patient frailty, which is defined as a phenotype with reduced tolerance to external stress such as surgery.[46] To assess frailty, we chose to include three key features: physical performance, measured by ASA Physical Status; disease history, measured by Charlson Comorbidity Index; and comorbidities, measured by recently filled prescriptions. The combination of these is likely to result in comparable distributions of patient frailty between the groups. Yet observational data still have an inherent risk of imbalance of unmeasured confounders. In addition, the need to cover the relevant sensory dermatomes may have resulted in epidural analgesia at a lower spinal level for patients undergoing rectal compared with colon surgery. Therefore, the extent of blockade of the thoracic sympathetic trunk and the physiologic impact of epidural analgesia might have varied according to the localization of the tumor. Additionally, our study groups were defined by preoperative insertion of epidural catheters; nonetheless, there is a risk that some epidural catheters were misplaced and did not result in adequate epidural analgesia. Moreover, the Danish Anesthesia Database does not contain data on the timing, duration, and dosing of epidural medication, which is essential for the quality of epidural analgesia. As all patients underwent general anesthesia and we did not have data regarding the efficacy of epidural analgesia, our results should be interpreted as estimates for the association between the intention to install epidural analgesia and cancer recurrence. Last, a limitation of the study is the lack of data on ethnicity in the registries used, which would be helpful when comparing these results with other populations.

Epidural analgesia is effective in reducing postoperative pain,[47] and the opioid sparing effect may play an important role by direct or indirect effects on metastasis formation.[9] Even though we did not find a statistically significant association between epidural analgesia and cancer recurrence, our results suggest that the association may range from 18% reduction to a 2% increase in cancer recurrence hazard. If causal evidence is established, even small improvements in cancer recurrence by epidural analgesia are clinically

meaningful and relevant to implement into guidelines. A definitive answer to whether epidural analgesia causes less cancer recurrence will require very large randomized trials with long-term follow-up. In total, in this observational study based on Danish registries, we did not find an association between epidural analgesia and cancer recurrence after colorectal cancer surgery.

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Competing Interests

The authors declare no competing interests.

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