Clinics in Oncology

Research Article
Published: 22 Jul, 2022

Postoperative 5-Year Survival and Related Risk Factors of Colon Cancer Patients Undergoing Propofol *vs*. Sevoflurane Anesthesia: A Retrospective Cohort Study

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Abstract

Purpose: Anesthetic agents affect the biological behavior of tumor cells and long-term oncologic outcomes. We investigated the association of anesthetics and 5-year survival of colon cancer patients.

Methods: The data from patients underwent colon cancer surgery from July 01st, 2009 to July 31st, 2014 were analyzed. Patients were grouped according propofol or sevoflurane used during surgery. Five-year survivals were analyzed with Kaplan-Meier method, and Cox regression models were used to identify risk factors of death.

Results: Of 1,289 colon cancer patients, 913 patients with propofol anesthesia and 376 with sevoflurane anesthesia were eligible for analysis. After propensity score matching, 375 patients remained in each group, and 5-year overall survival was 79.7% (95% Confidence Interval [CI], 0.76-0.84) in the propofol group, and 78.1% (95% CI, 0.74-0.82) in the sevoflurane group, and 5-year recurrence-free survival was 73.4% (95% CI, 0.69-0.78) and 70.4% (95% CI, 0.66-0.75), respectively. Type of anesthetic did not affect 5-year overall survival and recurrence-free survival with the log-rank test (P=0.513, 0.293, respectively). Related risk factors were age, anesthesia duration, open surgery, CEA and CA199 values, vascular or nerve infiltration, TNM, and adjuvant therapy.

Conclusion: There were no benefits in 5-year survival in propofol anesthesia *vs*. sevoflurane anesthesia after colon cancer surgery.

Keywords: Propofol; Sevoflurane; Colon cancer; Surgery; Survival; Risk factors

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Received Date: *24 Jun 2022*
Accepted Date: *16 Jul 2022*
Published Date: *22 Jul 2022*

Citation:
Xu J, Gao Z, Coburn M, Ma D, Wang K. Postoperative 5-Year Survival and Related Risk Factors of Colon Cancer Patients Undergoing Propofol vs. Sevoflurane Anesthesia: A Retrospective Cohort Study. Clin Oncol. 2022; 7: 1933.

ISSN: 2474-1663

Introduction

Surgical resection remains the most effective treatment for curable colon cancer [1]. At the time of excision, surgical manipulation itself can lead to local or even systemic spreading tumor cells during surgery. If any factors including systemic inflammation affect those cell survival or even proliferation, they more or less contribute surgical outcomes or postoperative tumor metastasis [2-4]. Anesthetic agent or technique was reported to influence surgical cancer outcomes because they are administered during the greatest risk of transmission, i.e. surgical removal of the tumor [5]. Anesthetic agent or technique affected directly *via* changing biological behaviors of tumor cells or indirectly through altering host immune defense [6-8]. It has been reported that anesthetics affected indirectly the serum milieu and the potential for cancer cell biology; indeed, serum from patients receiving propofol anesthesia inhibited proliferation and invasion of colon cancer cells and induced apoptosis [9]. Previous studies also suggested that the volatile anesthetic-induced immunosuppression may be involved in cancer recurrence and metastasis, whereas propofol-based anesthesia has the opposite effect [10].

Propofol and sevoflurane are commonly used for anesthesia during cancer surgery. Propofol may have anti-inflammatory, anti-oxidative and anti-tumor properties [11-13]. Studies indicated that propofol appeared to promote the apoptosis of tumor cells and inhibit the proliferation, invasion

and migration *in vitro* [7], and decrease the growth of tumor in mice [14], and propofol was associated with better survival of colon cancer patients [15]. By contrast, volatile anesthetics, such as isoflurane and sevoflurane promote the proliferation and migration of cancer cells *in vitro* [16], increase the tumor load *in vivo* [17]. Interestingly, a clinical study showed that sevoflurane increased the recurrence of postoperative colon cancer, which was associated with poor survival [15]. Thus, different anesthetics might have the different influence on oncologic outcomes after surgery.

However, clinical evidence in this regarding is not still insufficient. Thus, we performed a retrospective cohort study to assess whether the choice of anesthetics, propofol versus sevoflurane, used during surgery influences the long-term survival after colon cancer surgery. Other risk factors related to postoperative recurrence or death were also analyzed in this study.

Methods

Ethical approval

The Ethics committee of the Harbin Medical University Cancer Hospital approved this retrospective study and waived off informed consent. The information was retrieved from the electronic database and medical records of Harbin Medical University Cancer Hospital.

Patients and data sources

Data from 1,826 consecutive cases with ASA physical status of I to III who received colon cancer (Tumor-Node-Metastasis (TNM) I to III) radical resection from July 01st, 2009 to July 31st, 2014 were retrospectively analyzed. 537 patients were excluded from the analysis. The exclusion criteria were: Propofol and sevoflurane in combination anesthesia; M1 cancer stage; History of colon surgery; Data in completion; Age <18 yr (Figure 1).

Anesthesia

According to anesthesia regimen used during surgery, patients were divided into two groups: Propofol-based intravenous anesthesia (the Propofol group, n=913) and sevoflurane-based inhalational anesthesia (the Sevoflurane group, n=376). No premedication was given before anesthesia induction. Routine monitoring, including noninvasive blood pressure, electrocardiography, pulse oximetry, end-tidal carbon dioxide, and body temperature were applied for each patient. Anesthesia was induced with sufentanyl, propofol, and cisatracurium in all patients. After tracheal intubation, patients were maintained with either propofol or sevoflurane together with a continuous infusion of remifentanil. Repeated bolus injections of cisatracurium and sufentanyl were given when necessary. No patients receive regional including epidural anesthesia.

In the propofol group, anesthesia was maintained with Target-Controlled Infusion (TCI) (Fresenius Orchestra Primea; Fresenius Kabi AG, Germany) using propofol at an effect-site concentration of 3 μg/mL to 4 μg/mL, and patients received FiO_2 of 100% oxygen at a flow rate of 300 mL/min. In the sevoflurane group, anesthesia was maintained with 1 to 4 vol% sevoflurane under a 100% oxygen flow of 300 mL/min in a closed system. Maintenance of the effect-site concentration with propofol or sevoflurane was adjusted upward and downward by 0.2 μg/mL to 0.5 μg/mL, or 0.5 to 2 vol%, according to the hemodynamics, bis monitoring or minimum alveolar concentration. Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) were used for postoperatively self-controlled analgesia, and the formula was flurbiprofen axetil (Beijing Taide Pharmaceutical Co., Ltd.) 400 mg and appropriate normal saline, a total of 200 mL analgesic solution, and the background dose was 2 mL/h, and the additional dose of automatic analgesia was 0.5 mL/15 min. Patients in severe pain were given sufentanyl at single bolus of 5 μg as rescue. After surgery, patients were transferred to the post-anesthesia care unit and then discharged to general wards.

Variables

The patients' data including demographics, ASA physical status, comorbidities, lifestyle, family disease history, anesthesia type and duration, blood transfusion, use of NSAIDs or sufentanyl, TNM stage, tumor localization, and tumor marker (preoperative serum CEA and CA19-9 values), type of surgery, vascular or nerve infiltration, and adjuvant chemotherapy or radiation therapy were collected.

Outcomes

The primary outcome measures were 5-year overall survival and recurrence-free survival. Overall survival was defined as the period up to 5 year from the day of surgery to the day of death, and recurrence-free survival was defined as the period up to 5 year from the day of surgery to the day of first evidence of tumor progression or death. The secondary outcome measures were potential risk factors for colorectal cancer recurrence or death. The recurrence and death data were obtained from follow-up center of Harbin Medical University Cancer Hospital or telephone interview with patients or their relatives. The follow-up was completed at December 31st, 2019.

Statistical analysis

Continuous variables were presented as mean ± Standard Deviation (SD), median (Inter-Quartile Range, IQR) or n (portion, %) as appropriate. The Shapiro-Wilk test was used to assess the normality of data distribution. Differences between the two groups for categorical variables were compared with Chi square test. Continuous variables were analyzed with the independent t-test or Mann-Whitney U. To adjust for possible selection bias and confounding factors, 1:1 ratio Propensity Score Matching (PSM) was performed. The propensity scores were obtained without regard to the outcome variables by logistic regression analysis. Nearest neighbor matching was performed, which matches the absolute differences of the estimated propensity scores of all subjects in the both groups from the smallest to the largest difference. Absolute Standardized Difference (ASD) was calculated to validate the suitability of propensity score matching balance diagnostics between groups, with ASD <0.1 for the covariate indicating that two groups were sufficiently balanced.

Cox proportional hazards model analyses were conducted to assess risk factors for postoperative recurrence or death, and assess the Hazard Ratios (HR) with 95% Confidence Interval (CI). The univariable analysis evaluated all predictor variables independently. Thereafter, the correlation between anesthetics and oncologic outcomes (P<0.1 by univariable analysis) were assessed using multivariate analysis. Kaplan-Meier curve was used to compare overall survival and relapse-free survival. All data were analyzed using R software version 3.6.1 and the difference of P<0.05 was considered to be of statistical significance.

Results

A total of 1,826 patient cases were manually searched for inclusion, of which 537 were excluded (Figure 1). 1,289 patients were eligible for analysis, 913 patients received propofol and 376 received sevoflurane anesthesia. After propensity score matching, 375 patients

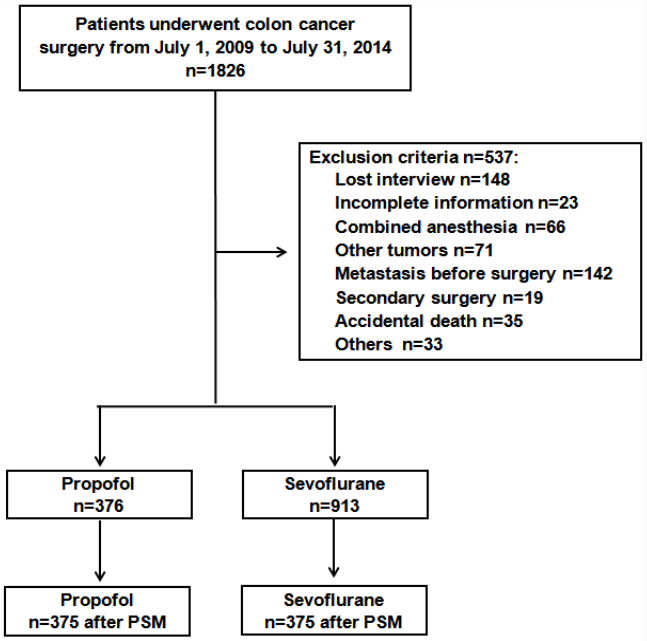

Figure 1: Flow chart detailing the selection of patients included in the retrospective cohort analysis PSM, propensity score matching.

remained in each group.

Table 1 showed characteristics of all patients before and after PSM. Before PSM, blood transfusion rate in the sevoflurane group was higher than that in the propofol group (P<0.05). Patients in the propofol group received more NSAIDS than those in the sevoflurane group (P<0.05). After PSM, there was no significant difference in all variables between groups, and the confounding factors were evenly distributed between groups, with P>0.05. The standardized mean differences of all variables were greater than 0.1, indicating that two groups of variables matched well.

We revealed that 5-year overall survival was 79.5% (95% CI, 0.76-0.84) in the propofol group and 77.9% (95% CI, 0.75-0.81) in the sevoflurane group (Figure 2). After PSM, the 5-year overall survival was 79.7% (95% CI, 0.76-0.84) and 78.1% (95% CI, 0.74-0.82), respectively. There was no significant difference in overall survival between groups in the total study cohort (Figure 2a) and the propensity-matched cohort (Figure 2b); 5-year recurrence-free survival was 73.6% (95% CI, 0.69-0.78) in the propofol group and 71.4% (95% CI, 0.69-0.74) in the sevoflurane group; After PSM, these numbers were 73.4% (95% CI, 0.69-0.78) and 70.4% (95% CI, 0.66-0.75), respectively. There was no significant difference in recurrence-free survival between groups in the total study cohort (Figure 2c), and the propensity-matched cohort (Figure 2d).

In the total study cohort, univariable and multivariable Cox proportional hazards model was constructed to compare 5-year overall survival according to anesthetics and other variables (Table 2). After adjusting for confounding factors, there was no significant correlation between anesthetics and 5-year overall survival after colorectal cancer surgery (HR=0.86, 95% CI, 0.66-1.11, P=0.236). Cox proportional hazards model of 5-year recurrence-free survival in the total study cohort, and multivariable Cox proportional hazards model revealed that anesthetics had no effect on 5-year recurrence-free survival after colorectal cancer surgery (HR=0.86, 95% CI, 0.69-1.08, P=0.184), (Table 3).

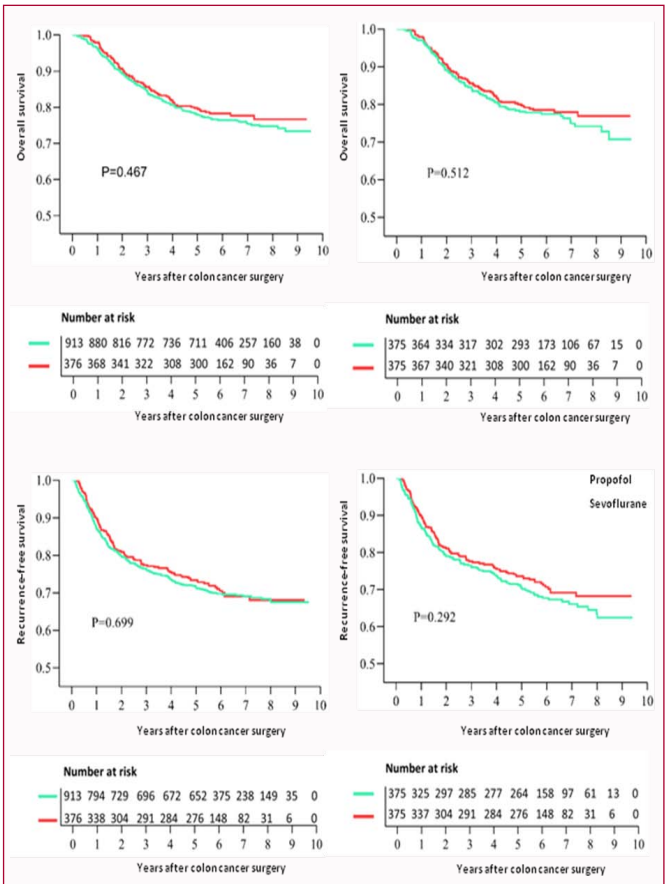

Figure 2: Survival cures of colon cancer patients after surgery. (a) Overall survival cures from the date of surgery by anesthetics in the total study cohort. (b) Overall survival cures from the date of surgery by anesthetics in the propensity-matched cohort. (c) Recurrence-free survival cures from the date of surgery by anesthetics in the total study cohort. (d) Recurrence-free survival cures from the date of surgery by anesthetics in the propensity-matched cohort.

In the total study cohort and the propensity-matched cohort, results of the subgroup analyses showed that there were no significant differences in overall survival or recurrence-free survival between two groups in each TNM stage.

The multivariable Cox regression analysis for other variables revealed that the risk factors of postoperative recurrence or death could be increased by the following factors, such as age, anesthesia duration, open surgery, increased CEA and CA19-9 values, vascular or nerve infiltration, TNM stage and adjuvant chemotherapy or radiation therapy (Table 2, 3).

There was no significant difference in 5-year overall survival of patients under propofol or sevoflurane-based anesthesia after surgery: Crude HR was 0.91 (95% CI, 0.71-1.17; P=0.467), PS-adjusted HR was 0.87 (95% CI, 0.67-1.12; P=0.283), and PS-matched HR was 0.91 (95% CI, 0.67-1.22; P=0.513). In addition, there was no significant difference in 5-year recurrence-free survival of patients under propofol or sevoflurane-based anesthesia after surgery: Crude HR was 0.96 (95% CI, 0.77-1.19; P=0.700), PS-adjusted HR was 0.90 (95% CI, 0.72-1.12; P=0.348), and PS-matched HR was 0.87 (95% CI, 0.68-1.13; P=0.293) (Table 4).

Discussion

In the present study, there was no difference of propofol

Table 1: Characteristics of patients before or after propensity score matching.

Parameter	Before propensity score matching			After propensity score matching			SMD
	Propofol (n=376)	Sevoflurane (n=913)	*P-value*	Propofol (n=375)	Sevoflurane (n=375)	*P-value*	
Age (yr)	58.5 (11.1)	58.2 (10.9)	0.663	58.4 (11.1)	58.6 (11.2)	0.751	0.023
Male	204 (54.3%)	518 (56.7%)	0.451	171 (45.6%)	169 (45.1%)	0.942	0.011
BMI (kg/m^2)	23.6 (3.2)	23.6 (3.6)	0.945	23.6 (3.2)	23.8 (3.6)	0.521	0.047
ASA physical status			0.839			0.513	0.031
I	28 (7.4%)	77 (8.4%)		28 (7.5%)	30 (8.0%)		
II	278 (73.7%)	667 (73.1%)		276 (73.6%)	271 (72.3%)		
III	71 (18.8%)	169 (18.5%)		71 (18.9%)	74 (19.7%)		
Comorbidities							
Diabetes	36 (9.6%)	85 (9.3%)	0.966	36 (9.6%)	33 (8.8%)	0.801	0.028
Hypertension	77 (20.5%)	194 (21.2%)	0.816	77 (20.5%)	81 (21.6%)	0.788	0.026
Cardiac disease	50 (13.3%)	91 (10.0%)	0.1	49 (13.1%)	44 (11.7%)	0.658	0.04
Cerebral disease	18 (4.8%)	35 (3.8%)	0.529	18 (4.8%)	18 (4.8%)	1	0
Smoker	120 (31.9%)	248 (27.2%)	0.099	119 (31.7%)	110 (29.3%)	0.526	0.052
Alcohol consumption	77 (20.5%)	156 (17.1%)	0.174	77 (20.5%)	82 (21.9%)	0.721	0.033
Family history	84 (22.3%)	216 (23.7%)	0.663	84 (22.4%)	92 (24.5%)	0.546	0.05
Anesthesia							
Anesthesia duration (min)	180 [150-215]	180 [150-210]	0.83	180 [150-215]	180 [150-210]	0.422	0.049
Blood transfusion	30 (8.0%)	110 (12.0%)	0.042	30 (8.0%)	36 (9.6%)	0.519	0.057
Sufentanyl	361 (96.0%)	859 (94.1%)	0.208	360 (96.0%)	360 (96.0%)	1	0
NSAIDS	314 (83.5%)	701 (76.8%)	0.009*	313 (83.5%)	310 (82.7%)	0.846	0.021
Surgical factors							
Laparoscopic surgery	30 (8.0%)	90 (9.9%)	0.342	30 (8.0%)	23 (6.1%)	0.393	0.073
Tumor localization			0.418			0.826	0.021
Left hemicolon	204 (54.3%)	471 (51.6%)		204 (54.4%)	200 (53.3%)		
Right hemicolon	172 (45.7%)	442 (48.4%)		171 (45.6%)	175 (46.7%)		
Increased CEA value	145 (38.6%)	345 (37.8%)	0.843	145 (38.7%)	144 (38.4%)	1	0.005
Increased CA19-9 value	68 (18.1%)	145 (15.95)	0.376	68 (18.1%)	67 (17.9%)	1	0.007
Vascular infiltration	26 (6.9%)	56 (6.1%)	0.691	26 (6.9%)	24 (6.4%)	0.884	0.021
Nerve infiltration	55 (14.6%)	97 (10.6%)	0.054	54 (14.4%)	62 (16.5%)	0.48	0.059
TNM stage			0.923			0.602	0.074
I	24 (6.4%)	58 (6.4%)		24 (6.4%)	24 (6.4%)		
II	209 (55.6%)	497 (54.4%)		209 (55.7%)	222 (59.2%)		
III	143 (38.0%)	358 (39.2%)		142 (37.9%)	129 (34.4%)		
Adjuvant therapy	249 (66.2%)	653 (71.5%)	0.069	248 (66.1%)	246 (65.6%)	0.939	0.011

Data shown as mean (standard deviation, SD), median (inter-quartile range, IQR), or n (portion, %).
Abbreviations: NSAIDs, Non-Steroidal Anti-Inflammatory Drugs; SMD: Standardized Mean Differences; TNM: Tumour-Node-Metastasis; .-: not applicable; *P<0.05 used for significance

or sevoflurane-based anesthesia on 5-year overall survival and recurrence-free survival in colon cancer patients. The risk factors were age, anesthesia duration, open surgery, CEA and CA199 values, vascular infiltration, nerve invasion, and TNM stage and adjuvant therapy.

Tumor survival depends on the balance between the cancer metastatic potential and the host defense [18]. Surgical stress or tissue damage reduces the activity of NK, T and B lymphocytes in the postoperative period, which possibly decreases the host immunity [19]. Clinical studies found that propofol promoted NK cell cytotoxicity, and potentiated the expression of CD28 on peripheral T-helper cells, increased the ratio of IFN-α/IL-4, which was a key step in antitumor immune response [20]. By contrast, volatile anesthetics were associated with systemically impaired immune function by inducing T-lymphocyte apoptosis, attenuating natural killer cell activity, and enhanced levels of tumorigenic markers TGF-β, VEGF, and HIF-1α, which can increase the malignancy potential of cancer cells [21-24]. Similarly, there may be a clinically important effect that the survival rates after colon cancer surgery were better for patients who received propofol-based anesthesia than for those who received

Table 2: Association between anesthetics and 5-year overall survival in patients with colon cancer surgery after Cox regression analyses with propensity score matching.

	Univariable Cox model		Multivariable Cox model	
	HR (95% CI)	***P-value***	**HR (95% CI)**	***P-value***
Anesthetics				
Propofol	1 (ref)		1 (ref)	
Sevoflurane	0.91 (0.71-1.17)	0.467	0.86 (0.66-1.11)	0.236
Age (yr)	1.32 (1.18-1.48)	0	1.27 (1.10-1.46)	0.001
Sex				
Male	1 (ref)		_	
Female	1.07 (0.85-1.34)	0.549	_	
BMI (kgm^{-2})	0.98 (0.95-1.01)	0.176	_	
ASA physical status				
I	1 (ref)		1 (ref)	
II	1.35 (0.83-2.18)	0.225	0.72 (0.41-1.25)	0.245
III	1.91 (1.14-3.20)	0.014	0.62 (0.32-1.20)	0.155
Diabetes	1.25 (0.87-1.78)	0.229	_	
Hypertension	1.15 (0.88-1.50)	0.309	_	
Cardiac disease	0.88 (0.60-1.28)	0.506	_	
Cerebral disease	1.67 (1.05-2.66)	0.031	_	
Smoker	0.98 (0.76-1.26)	0.888	_	
Alcohol consumption	1.06 (0.80-1.42)	0.683	_	
Family history	0.94 (0.72-1.23)	0.645	_	
Anesthesia duration (h)	1.23 (1.08-1.40)	0.001	1.26 (1.10-1.45)	0.001
Blood transfusion	1.63 (1.19-2.22)	0.002	1.17 (0.84-1.62)	0.36
Laparoscopic surgery	0.35 (0.19-0.62)	0	0.29 (0.16-0.53)	0
Sufentanyl	1.17 (0.69-2.01)	0.558	0.96 (0.54-1.70)	0.893
NSAIDS	0.83 (0.64-1.09)	0.178	1.00 (0.76-1.32)	0.998
Increased CEA value	2.03 (1.62-2.54)	0	1.52 (1.19-1.94)	0.001
Increased CA19-9 value	2.07 (1.60-2.67)	0	1.42 (1.07-1.88)	0.014
Nerve infiltration	2.47 (1.88-3.26)	0	1.62 (1.21-2.17)	0.001
Vascular infiltration	2.75 (1.96-3.87)	0	1.92 (1.34-2.75)	0
Tumor localization				
Left hemicolon	1 (ref)		1 (ref)	
Right hemicolon	1.24 (0.99-1.55)	0.063	1.15 (0.91-1.46)	0.228
TNM stage				
I	1 (ref)		1 (ref)	
II	3.24 (1.20-8.80)	0.021	3.14 (1.14-8.63)	0.026
III	10.18 (3.78-27.39)	0	10.11 (3.66-27.93)	0
Adjuvant therapy	0.94 (0.74-1.20)	0.626	0.55 (0.42-0.73)	0

Propensity score matching analyses were adjusted by factors including age, ASA physical status, anesthesia duration, blood transfusion, laparoscopic surgery, sufentanyl, NSAIDS, CEA and CA19-9 values, nerve or vascular infiltration, tumor localization, TNM stage, and adjuvant chemotherapy or radiation therapy

Abbreviations: CI: Confidence Interval; HR: Hazard Ratio; NSAIDs: Non-Steroidal Anti Inflammatory Drugs; TNM: Tumour-Node-Metastasis; -: not applicable; *P<0.05 used for significance

sevoflurane-based anesthesia [12].

Our retrospective study of cancer survival did not demonstrate significant difference between propofol and sevoflurane anesthesia. This may be due to the following reasons. First, 1.5 mg/kg to 2.5 mg/kg of 1% propofol was used for the sevoflurane group to induce a loss of consciousness, and the effect of single-dose propofol would have dissipated within 10 min or less as anesthesia was maintained with sevoflurane [25]. Although no further propofol was administered, the initial injection of propofol may have influenced results in the inhalation group. And then, sufentanyl was used for anesthetic induction in both groups, especially, sufentanyl was given in all patients to blunt intraoperative stress response and provide postoperative analgesia, which might serve as a major confounder, making it difficult to differentiate the properties of two anesthetics on

Table 3: Association between anesthetics and 5-year recurrence-free survival in patients with colon cancer surgery after Cox regression analyses with propensity score matching.

	Univariable Cox model		Multivariable Cox model	
	HR (95% CI)	***P-value***	**HR (95% CI)**	***P-value***
Anesthetics				
Propofol	1 (ref)		1 (ref)	
Sevoflurane	0.96 (0.77-1.19)	0.7	0.86 (0.69-1.08)	0.184
Age (yr)	1.21 (1.10-1.33)	0	1.17 (1.04-1.33)	0.012
Sex				
Male	1 (ref)		_	
Female	1.06(0.87-1.30)	0.557	_	
BMI (kgm^{-2})	0.98 (0.95-1.01)	0.168		
ASA physical status				
I	1 (ref)		1 (ref)	
II	1.24 (0.83-1.86)	0.288	0.75 (0.41-1.21)	0.24
III	1.59 (1.02-2.46)	0.039	0.67 (0.38-1.18)	0.163
Diabetes	1.31 (0.96-1.79)	0.088	_	
Hypertension	1.23 (0.98-1.55)	0.077	_	
Cardiac disease	0.88 (0.63-1.23)	0.46	_	
Cerebral disease	1.69 (1.12-2.56)	0.012	_	
Smoker	1.07 (0.86-1.33)	0.557	_	
Alcohol consumption	1.09 (0.85-1.40)	0.515	_	
Family history	0.89 (0.70-1.14)	0.353	_	
Anesthesia duration (h)	1.23 (1.10-1.38)	0	1.24 (1.08-1.41)	0.002
Blood transfusion	1.44 (1.08-1.92)	0.014	1.17 (0.86-1.58)	0.322
Laparoscopic surgery	0.49 (0.32-0.76)	0.001	0.40 (0.26-0.63)	0
Sufentanyl	1.45 (0.87-2.44)	0.156	1.33 (0.77-2.28)	0.305
NSAIDS	0.84 (0.67-1.05)	0.131	1.00 (0.79-1.28)	0.971
Increased CEA value	1.71 (1.41-2.09)	0	1.35 (1.09-1.67)	0.006
Increased CA19-9 value	1.77 (1.40-2.24)	0	1.26 (0.97-1.64)	0.077
Nerve infiltration	3.11 (2.47-3.92)	0	2.23 (1.74-2.85)	0
Vascular infiltration	2.85 (2.11-3.84)	0	1.83 (1.33-2.51)	0
Tumor localization				
Left hemicolon	1 (ref)		1 (ref)	
Right hemicolon	1.12 (0.92-1.36)	0.271	1.1 (0.90-1.37)	0.312
TNM stage				
I	1 (ref)		1 (ref)	
II	2.40 (1.20-5.12)	0.024	2.29 (1.05-4.96)	0.036
III	8.10 (3.82-17.18)	0	7.87 (3.61-17.17)	0
Adjuvant therapy	1.11 (0.89-1.39)	0.348	0.51 (0.47-0.77)	0

Propensity score matching analyses were adjusted by factors including age, ASA physical status, anesthesia duration, blood transfusion, laparoscopic surgery, sufentanyl, NSAIDS, CEA and CA19-9 values, nerve or vascular infiltration, tumor localization, TNM stage, and adjuvant chemotherapy or radiation therapy

Abbreviations: CI: Confidence Interval; HR: Hazard Ratio; NSAIDs: Non-Steroidal Anti-Inflammatory Drugs; TNM: Tumour-Node-Metastasis; -: not applicable; *P<0.05 used for significance

immune responses [26,27]. The continuous infusion of remifentanil in both groups could be another important reason for our results. Assuming the immunosuppression was caused by the opioid [25,28], the use of sufentanyl and remifentanil may further complicated the explanation for results. At last, the time and cumulative dose of exposure to propofol/sevoflurane was less in colon cancer surgery could be another reason for our negative outcome. The clinical concentration of propofol is 50 to 500 times lower than the free propofol concentration employed in the cell culture experiments [7], which is an important reason for no influence of anesthetics on 5-year survival in this clinical study.

In this study, we found that the risk of recurrence or death is increased by following factors, such as age, anesthesia duration, TNM stage, open surgery, CEA and CA19-9 values, vascular

Table 4: Association between anesthetics and 5-year survival in patients undergoing colon cancer surgery.

Variables	Anesthetics	Crude HR (95% CI)	*P-value*	PS-adjusted HR(95% CI)	*P-value*	PS-matched HR(95% CI)	*P-value*
Overall survival	Propofol	1 (ref)	0.467	1 (ref)	0.283	1 (ref)	0.513
	Sevoflurane	0.91 (0.71-1.17)		0.87 (0.67-1.12)		0.91 (0.67-1.22)	
Recurrence-free survival	Propofol	1 (ref)	0.7	1 (ref)	0.348	1 (ref)	0.293
	Sevoflurane	0.96 (0.77-1.19)		0.90 (0.72-1.12)		0.87 (0.68-1.13)	

Abbreviations: CI: Confidence Interval; HR: Hazard Ratio; PS: Propensity Score; *P<0.05 used for significance

infiltration, nerve invasion, and adjuvant therapy. Factors affecting cancer prognosis are very diverse and complex. They may not differ simply because of the anesthetic used [29]. Studies showed that the risk of poor survival increases significantly with increasing age [30], ASA physical status [31] and poor preoperative functional status. Long anesthesia time and open surgery [32] seems to be related to postoperative mortality. The development of cancer is dependent on a variety of factors including the tumor microenvironment, cancer type and TNM stage [33], and genetic background. A previous review showed that colorectal cancer survival is highly dependent on the stage at diagnosis and that the 5-year survival varies from 90% for localized stage cancers and 70% for regional cancer to 10% for distant metastatic [34]. Thus, higher TNM stage, vascular infiltration and nerve invasion were associated with poor survival after surgery, as has been observed previously. In addition, blood transfusions might promote perioperative cancer cell growth [35,36], and neoadjuvant chemotherapy has prolonged the prognosis of tumor [37].

There are limitations to our study. First, due to its retrospective nature, patients were not randomly allocated, and selection bias may exist along with a possible lack of generalizability of the results. The size of the study population was small. As this was performed as a retrospective cohort study, we did not calculate a sample size. In this single-centre study, a total of 1,826 patient cases were searched from July 01st, 2009 to July 31st, only 376 received sevoflurane anesthesia, thus 375 patients remained in each group after propensity score matching, which further decrease statistics power. Second, we cannot dynamically detect the level of tumor markers in blood and objectively establish their correlation with oncologic outcomes. Finally, we cannot compare the anti-tumor effect of the individual anesthetic in clinic, because the interactions of different anesthetics may complicate the explanation for results, thus this study aimed to compare the distinct of propofol/sevoflurane-based anesthesia rather than attributing to individual anesthetic. In the retrospective cohort study, there were no differences in 5-year overall survival and recurrence-free survival between propofol-based intravenous anesthesia and sevoflurane-based inhalational anesthesia for use in colon cancer surgery.

In conclusion, our study showed no better benefit for propofol-based intravenous anesthesia, in comparison with sevoflurane-based inhalational anesthesia, in terms of 5-year overall survival and recurrence-free survival after colon cancer surgery. Large-sample sized, prospective multicentre studies with 5-year follow-up are necessary to clarify this association of anesthetics and oncologic outcomes.

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