Propofol-based Total Intravenous Anesthesia Is Associated with Better Survival Than Desflurane Anesthesia in Colon Cancer Surgery

Zhi-Fu Wu, M.D., Meei-Shyuan Lee, D.P.H., Chih-Shung Wong, M.D., Ph.D., Chueng-He Lu, M.D., Yuan-Shiou Huang, M.D., Kuen-Tze Lin, M.D., Yu-Sheng Lou, M.S., Chin Lin, Ph.D., Yue-Cune Chang, Ph.D., Hou-Chuan Lai, M.D.

ABSTRACT

Background: Previous research has shown different effects of anesthetics on cancer cell growth. Here, the authors investigated the association between type of anesthetic and patient survival after elective colon cancer surgery.

Methods: A retrospective cohort study included patients who received elective colon cancer surgery between January 2005 and December 2014. Patients were grouped according to anesthesia received: propofol or desflurane. After exclusion of those who received combined propofol anesthesia with inhalation anesthesia or epidural anesthesia, survival curves were constructed from the date of surgery to death. After propensity matching, univariable and multivariable Cox regression models were used to compare hazard ratios for death. Subgroup analyses were performed for tumor–node–metastasis staging and postoperative metastasis.

Results: A total of 706 patients (307 deaths, 43.5%) with desflurane anesthesia and 657 (88 deaths, 13.4%) with propofol anesthesia were eligible for analysis. After propensity matching, 579 patients remained in each group (189 deaths, 32.6%, in the desflurane group *vs.* 87, 15.0%, in the propofol group). In the matched analyses, the propofol-treated group had a better survival, irrespective of lower tumor–node–metastasis stage (hazard ratio, 0.22; 95% CI, 0.11 to 0.42; $P < 0.001$) or higher tumor–node–metastasis stage (hazard ratio, 0.42; 95% CI, 0.32 to 0.55; $P < 0.001$) and presence of metastases (hazard ratio, 0.67; 95% CI, 0.51 to 0.86; $P = 0.002$) or absence of metastases (hazard ratio, 0.08; 95% CI, 0.01 to 0.62; $P = 0.016$). Simple propensity score adjustment produced similar findings.

Conclusions: Propofol anesthesia for colon cancer surgery is associated with better survival irrespective of tumor–node–metastasis stage. **(Anesthesiology 2018; XXX:00-00)**

SURGICAL resection is the mainstay of therapy for potentially curable colon cancer.[1] Paradoxically, surgery itself may cause the dissemination of tumor cells into the peripheral circulation and result in tumor proliferation or metastasis.[2] In addition, surgical stress leads to metabolic and neuroendocrine changes, which may cause significant depression of cell-mediated immunity and the eventual implantation of circulating tumor cells.[3] This combination of potential tumor seeding and an impaired immune response increases the susceptibility of patients receiving cancer surgery to the development of metastasis and is associated with worse long-term outcomes. The possibility that anesthetic drugs can affect the process of cancer recurrence has attracted interest.[3]

Growing evidence from animal and human cancer cell line studies reveals that various anesthetics can influence the immune system in different ways.[4–9] Studies have shown that inhalation agents may alter immune processes; for instance, inhalation agents appear to increase the incidence of lung and breast cancer metastases in mice and humans.[8–11] Inhalation agents are also proinflammatory.[12] By contrast, propofol appears to suppress tumor growth and reduce the risk of metastases in mice and humans because of its antiinflammatory and antioxidative activities.[6,11–14]

What We Already Know about This Topic

- Propofol may better preserve host defenses against cancer
- Whether cancer recurrence is less likely with propofol than volatile anesthesia remains unknown

What This Article Tells Us That Is New

- The authors conducted a propensity-matched retrospective analysis of 1,158 patients who had colon cancer surgery
- Patients anesthetized with propofol had better overall survival

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The reduction in mortality associated with epidural anesthesia/analgesia during colon cancer surgery has been investigated,[1,15] but few studies have compared propofol- *versus* desflurane-based anesthesia. Therefore, we conducted a retrospective study to assess whether the choice of anesthetic, desflurane anesthesia *versus* propofol anesthesia is associated with long-term survival, postoperative recurrence, and postoperative metastasis after colon cancer surgery.

Materials and Methods

Study Design

This was a retrospective cohort study.

Setting

This study was conducted at the Tri-Service General Hospital (Taipei, Taiwan, Republic of China).

Participants and Data Sources

The ethics committee of the Tri-Service General Hospital approved this retrospective study and waived the need for informed consent on March 9, 2017 (Tri-Service General Hospital Institutional Review Board No. 1-106-05-034). Relevant information was retrieved from the medical records and the electronic database of Tri-Service General Hospital. From January 2005 to December 2014, 1,432 patients with an American Society of Anesthesiologists (ASA) score of I to III who had undergone elective colon cancer open surgery for tumor–node–metastasis stage I to IV colon cancer under propofol anesthesia (propofol group, n = 657) or desflurane anesthesia (desflurane group, n = 706) were considered for inclusion. The type of anesthesia was determined according to the anesthesiologist's preference. No isoflurane, sevoflurane, or spinal anesthesia was used in these patients. Sixty-nine patients were excluded from the analysis. The exclusion criteria were combined propofol anesthesia with inhalation or epidural anesthesia; incomplete data; or age less than 20 yr (fig. 1).

No premedication was given before anesthesia induction. Routine monitoring, including noninvasive blood pressure, electrocardiography (lead II), pulse oximetry, end-tidal carbon dioxide, radial arterial line monitoring, and a central venous catheter were used for each patient. Anesthesia was induced with fentanyl, propofol, and rocuronium in all patients. The patient was then intubated and maintained with either propofol or desflurane, as well as the analgesic fentanyl.

In the propofol group, anesthesia was maintained using target-controlled infusion (Fresenius Orchestra Primea; Fresenius Kabi AG, Germany) with propofol at an effect-site concentration 3 to 4 $\mu g \cdot ml^{-1}$ and an oxygen flow of $0.3\,l \cdot min^{-1}$ with fractional inspired oxygen tension 100%. In the desflurane group, anesthesia was maintained with 8 to 12% desflurane under a 100% oxygen flow of $300\,ml \cdot min^{-1}$ in a closed system. Repetitive bolus injections of cisatracurium and fentanyl were given as necessary throughout the operation.[16–18]

Maintenance of the effect-site concentration using target-controlled infusion with propofol or desflurane was adjusted upward and downward by 0.2 to 0.5 $\mu g \cdot ml^{-1}$, or 0.5 to 2%, when necessary according to the hemodynamics. The end-tidal carbon dioxide was maintained at 35 to 45 mmHg by adjusting the ventilation rate and maximum airway pressure. Patients were sent to the postanesthetic care unit or intensive care unit for further care and assessed by the anesthesiologist after surgery.[16–18]

Variables

The retrospectively collected patient data included anesthetic technique; time since the earliest included patient (which serves as a surrogate of calendar year); sex; age at the time of surgery; tumor–node–metastasis stage of the primary tumor; preoperative functional status, such as metabolic equivalents (patients were grouped according to whether their metabolic equivalents were greater than or equal to 4 or less than 4 because the perioperative cardiac and long-term risks increased in patients with a capacity of less than 4 metabolic equivalents during most normal daily activities)[19]; use of adjuvant chemotherapy; use of patient-controlled epidural analgesia (patient-controlled epidural analgesia was used to maintain a numerical rating scale score of 4 [where 0 = no pain and 10 = greatest pain] when coughing or moving in the 3 days after surgery); use of postoperative nonsteroidal antiinflammatory drugs (NSAIDs); tumor side (left side included distal transverse, splenic flexure, descending, and sigmoid colon; right side included cecum, ascending, hepatic flexure, and proximal transverse colon)[20]; grade of surgical complications using the Clavien–Dindo classification; presence of postoperative recurrence; and presence of postoperative metastasis. Preoperative morbidity was assessed using the ASA physical status scores of I (least morbidity) to V (highest), as recorded by the anesthesiologist preoperatively. Ten-year survival in patients with multiple comorbidities was predicted using the Charlson Comorbidity Index of 0 (least comorbidity) to 37 (most). The grade of surgical complication was scaled from 0 (no) to V (most) according to the Clavien–Dindo classification. These variables were chosen as potential confounders as they have either been shown, or posited, to affect the outcome.

Study Sample Size

The study sample included only patients 20 yr or older who received elective colon cancer open surgery between January 2005 and December 2014. All available patients were included (657 in the propofol group and 706 in the desflurane group). To achieve a power of 80% and a two-tailed type I error rate of $\alpha = 0.05$, 213 patients were needed in each unmatched group (assuming a mortality rate of 24% with desflurane anesthesia and 13.5% with propofol anesthesia), and 465 patients were needed in each matched group (assuming a mortality rate of 22.8% with desflurane anesthesia and 15.6% with propofol anesthesia).[3]

Statistical Methods

The primary endpoint was overall survival, which was compared between the groups that had received propofol or

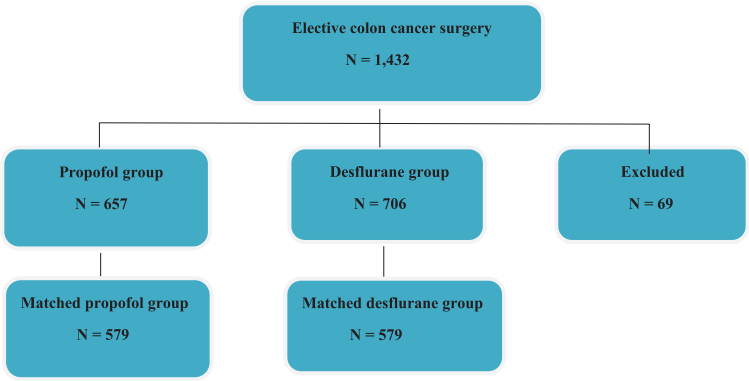

Fig. 1. Flow diagram detailing the selection of patients included in the retrospective analysis. Sixty-nine patients were excluded due to combined propofol anesthesia with inhalation anesthesia or epidural anesthesia, incomplete data, or age less than 20 yr.

desflurane as the main anesthetic agent. Disease-free survival was also evaluated. Survival time was defined as the interval between the date of surgery and the date of death, or March 31, 2017, for those who were censored. All data are presented as mean ± SD or number (percentage).

Patient characteristics and death rates were compared between the groups treated with the different anesthetics using Student's *t* test or the chi-square test. Survival and type of anesthesia were depicted visually. To deal with the differences in baseline characteristics between the two groups, we created propensity scores by linear (simple logistic regression) algorithm. Interaction terms did not improve model fit. A greedy nearest-neighbor matching procedure, with calipers set at 0.25 SD of the logit of the propensity score, was used to create matched pairs (579 pairs). When calipers set at 0.2 SD, the results were almost identical (578 pairs).

The standardized differences for the abovementioned variables (except the postoperative recurrence and metastasis) between groups in the matched sample were calculated. The Cox proportional-hazards model was used to conduct all survival analyses without and with adjustment for confounders. To evaluate the effects of tumor–node–metastasis stage and metastasis on survival between the two groups, two interaction terms were assessed. Because significant interactions with the type of anesthesia (propofol or desflurane) were found, subgroup analyses for tumor–node–metastasis stage and postoperative metastasis followed. Two adjustment approaches were applied, namely propensity score modeling and using matched pairs only, to avoid potential confounding effects.[21,22] The proportional-hazards assumption was not violated in our analyses based on weighted residuals.[23] R (version 3.4.3, available at https://cran.r-project.org/src/base/R-3/R-3.4.3.tar.gz, accessed February 8, 2014) was used for statistical analyses. Two-tailed *P* values less than 0.05 were considered significant.

Results

The patient and treatment characteristics are shown in table 1. Time since the earliest included patient was significantly shorter in the desflurane group (5.7 ± 2.3 yr) than in the propofol group (6.1 ± 2.4 yr; $P = 0.001$). The desflurane group was significantly older (67 ± 12 yr) than the propofol group (65 ± 11 yr; $P = 0.022$). The Charlson Comorbidity Index score was significantly higher in the desflurane group (5.3 ± 1.8) than in the propofol group (4.7 ± 1.7; $P < 0.001$). The desflurane group had significantly more patients with an ASA score of III ($P = 0.014$) and preoperative functional status less than 4 metabolic equivalents ($P = 0.014$) than the propofol group. The tumor–node–metastasis stage differed significantly between the desflurane and propofol groups ($P < 0.001$). Patients in the propofol group were more prone to have tumor–node–metastasis stage I or III cancer, and patients in the desflurane group were more prone to have tumor–node–metastasis stage II or IV cancer.

A greater percentage of patients in the desflurane group (9.1%) exhibited postoperative recurrence compared with the propofol group (5.8%; $P = 0.021$). The presence of postoperative metastasis was significantly higher in the desflurane group (42.5%) than in the propofol group (16.7%) during follow-up ($P < 0.001$). The overall mortality rate was significantly higher in the desflurane group (43.5%) than in the propofol group (13.4%) during follow-up ($P < 0.001$). The median follow-up time was 3.7 yr for the propofol group and 3.2 yr for the desflurane group. No significant differences were found between groups in sex, adjuvant chemotherapy, use of patient-controlled epidural analgesia, use of postoperative NSAIDs, tumor side, or grade of surgical complications.

Because of the significant differences in baseline characteristics between the two groups, we used a series of algorithms to create a propensity score. We chose the propensity score from the logistic regression without interaction terms because of its predictability in cross-validation tests (data not shown). After matching, 579 pairs were formed. All standardized mean differences were less than 0.1 (table 1).

Patients who received propofol exhibited better overall survival than those who received desflurane (86.6 *vs.* 56.5%, respectively); the crude hazard ratio was 0.27 (95% CI, 0.22 to 0.35; $P < 0.001$). Patients who received propofol exhibited better disease-free survival than those who received

Table 1. Patient and Treatment Characteristics for Overall Group and Matched Group after Propensity Scoring

	Overall Patients			Matched Patients			
Variables	Propofol (n = 657)	Desflurane (n = 706)	*P* Value	Propofol (n = 579)	Desflurane (n = 579)	*P* Value	SMD
Time since the earliest included patient (yr)	6.1 ± 2.4	5.7 ± 2.3	0.001	5.9 ± 2.3	5.7 ± 2.2	0.210	0.074
Age (yr)	65 ± 11	67 ± 12	0.022	66 ± 11	66 ± 12	0.439	0.045
Charlson Comorbidity Index score	4.7 ± 1.7	5.3 ± 1.8	< 0.001	4.8 ± 1.7	5.0 ± 1.7	0.095	0.098
Sex, male	377 (57)	389 (55)	0.396	329 (57)	321 (55)	0.636	0.028
ASA score			0.014			0.322	0.058
II	497 (76)	492 (70)		429 (74)	414 (72)		
III	160 (24)	214 (30)		150 (26)	165 (28)		
TNM stage of primary tumor			< 0.001			0.438	0.097
I	251 (38)	229 (32)		222 (38)	221 (38)		
II	130 (20)	195 (28)		120 (21)	131 (23)		
III	211 (32)	181 (26)		173 (30)	152 (26)		
IV	65 (10)	101 (14)		64 (11)	75 (13)		
Functional status			0.014			0.322	0.058
< 4 MET	160 (24)	214 (30)		150 (26)	165 (28)		
≥ 4 MET	497 (76)	492 (70)		429 (74)	414 (72)		
Adjuvant chemotherapy	345 (53)	375 (53)	0.823	299 (52)	300 (52)	0.953	0.003
PCEA	154 (23)	173 (25)	0.646	135 (23)	145 (25)	0.493	0.040
Postoperative NSAIDs	530 (81)	542 (77)	0.079	460 (79)	449 (78)	0.431	0.046
Tumor side			0.876			0.768	0.017
Left	349 (53)	378 (54)		310 (54)	315 (54)		
Right	308 (47)	328 (46)		269 (46)	264 (46)		
Grade of surgical complications			0.953			0.906	0.050
0	617 (94)	663 (94)		543 (94)	543 (94)		
I	3 (0.5)	3 (0.4)		3 (0.5)	3 (0.5)		
II	34 (5)	35 (5)		31 (5)	29 (5.0)		
III	3 (0.5)	5 (0.7)		2 (0.3)	4 (0.7)		
Postoperative recurrence	38 (6)	64 (9)	0.021	N/A	N/A		
Postoperative metastasis	110 (17)	300 (43)	< 0.001	N/A	N/A		
All-cause mortality	88 (13)	307 (44)	< 0.001	N/A	N/A		

Data shown as mean ± SD or n (%). Grade of surgical complications: Clavien-Dindo classification.

ASA = American Society of Anesthesiologists; MET = metabolic equivalents; N/A = not applicable; NSAID = nonsteroidal antiinflammatory drugs; PCEA = patient-controlled epidural analgesia; SMD = standardized mean differences; TNM = tumor–node–metastasis.

desflurane anesthesia (overall survival 99.8 *vs.* 96.7%, respectively). Survival curves by Cox model for the two types of anesthesia are shown in figure 2, A and B. Adjustment for time since the earliest included patient, sex, age, ASA score, tumor–node–metastasis stage, Charlson Comorbidity Index score, preoperative functional status, adjuvant chemotherapy, patient-controlled epidural analgesia, postoperative NSAIDs, tumor side, grade of surgical complications, and the presence of postoperative recurrence did not change the finding substantially (hazard ratio, 0.36; 95% CI, 0.28 to 0.47; $P < 0.001$).

The overall mortality risk associated with the use of propofol and desflurane during colon cancer surgery is shown in table 2. Overall survival from the date of surgery grouped according to anesthesia type and other variables was compared separately in a univariable Cox model and subsequently in a multivariable Cox regression. Other variables that significantly increased the risk of death after the multivariable analysis were younger age, higher ASA score, higher tumor–node–metastasis stage (except stage IV), higher Charlson Comorbidity Index score, poor preoperative functional status, and use of postoperative NSAIDs (table 2).

Subgroup Analyses for Tumor–Node–Metastasis Stage and Presence of Postoperative Metastasis

Because of the significant interaction effect between the type of anesthesia and tumor–node–metastasis stage ($P = 0.001$) and postoperative metastasis ($P = 0.013$) on survival, all analyses were stratified by these two variables.

Patients who received propofol exhibited better survival than those who received desflurane, regardless of whether they had a lower or higher tumor–node–metastasis stage. For a lower tumor–node–metastasis stage (I and II), the crude hazard ratio was 0.10 (95% CI, 0.06 to 0.19; $P < 0.001$), the propensity score–adjusted hazard ratio was 0.17 (95% CI, 0.09 to 0.31; $P < 0.001$), and the propensity score–matched hazard ratio was 0.22 (95% CI, 0.11 to 0.42; $P < 0.001$). For a higher tumor–node–metastasis stage (III and IV), the crude hazard ratio was 0.32 (95% CI, 0.25 to 0.42; $P < 0.001$), the propensity score–adjusted hazard ratio was 0.48 (95% CI, 0.37

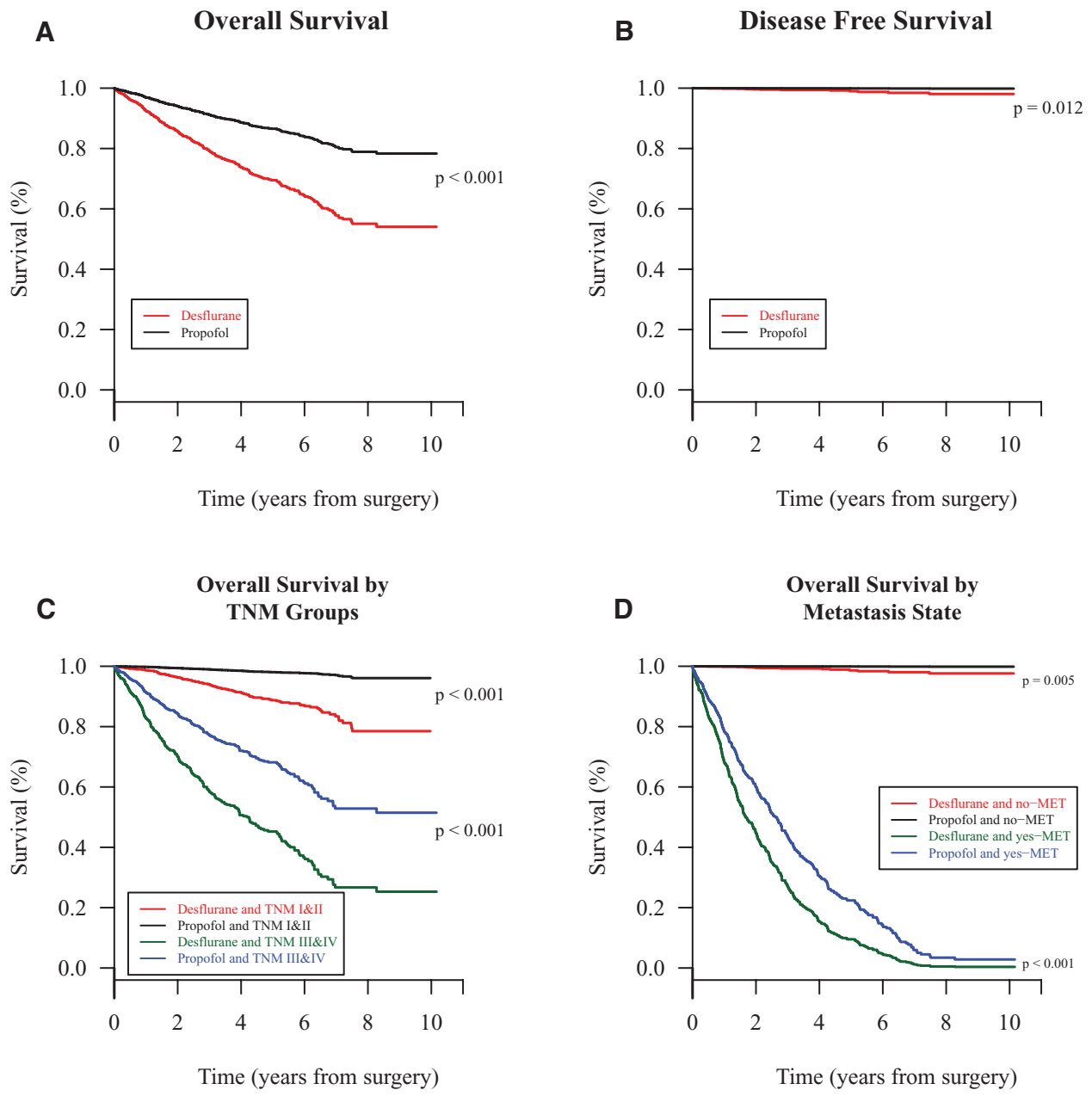

Fig. 2. (*A*) Overall survival curves from the date of surgery by anesthesia type. (*B*) Disease-free survival curves from the date of surgery by anesthesia type. (*C*) Overall survival curves from the date of surgery by tumor–node–metastasis stage of primary tumor. (*D*) Overall survival curves from the date of surgery by presence (or not) of metastasis. MET = metastasis; TNM = tumor–node–metastasis.

to 0.64; $P < 0.001$), and the propensity score–matched hazard ratio was 0.42 (95% CI, 0.32 to 0.55; $P < 0.001$; table 3).

Patients who received propofol also had a better survival than those who received desflurane, regardless of the presence or absence of postoperative metastasis. For patients with postoperative metastasis, the crude hazard ratio was 0.67 (95% CI, 0.52 to 0.85; $P = 0.001$), the propensity score–adjusted hazard ratio was 0.64 (95% CI, 0.50 to 0.81; $P < 0.001$), and the propensity score–matched hazard ratio was 0.67 (95% CI, 0.51 to 0.86; $P = 0.002$). For patients with no postoperative metastasis, the crude hazard ratio was 0.05 (95% CI, 0.01 to 0.39; $P = 0.004$), the propensity score–adjusted hazard ratio was 0.06 (95% CI, 0.01 to 0.42; $P = 0.005$), and the propensity score–matched hazard ratio was 0.08 (95% CI, 0.01 to 0.62; $P = 0.016$; table 3).

In summary, the present study demonstrated better outcomes for propofol anesthesia, regardless of whether the tumor–node–metastasis stage was lower or higher (fig. 2C), and whether postoperative metastases were present or absent (fig. 2D).

Discussion

Compared with desflurane, propofol anesthesia for colon cancer surgery was associated with better overall survival, less

Table 2. Cox Regression Proportional Hazard Survival: Univariable and Multivariable Models for Overall Patients

Variables	Univariable HR (95% CI)	*P* Value	Multivariable HR (95% CI)	*P* Value
Anesthesia				
Desflurane	1		1	
Propofol	0.27 (0.22–0.35)	< 0.001	0.36 (0.28–0.47)	< 0.001
Sex				
Male	1		1	
Female	0.98 (0.81–1.20)	0.879	0.83 (0.67–1.02)	0.083
Time since earliest included patient (yr)	0.93 (0.88–0.97)	0.001	1.08 (1.03–1.13)	0.003
Age (yr)	1.03 (1.02–1.04)	< 0.001	0.95 (0.94–0.97)	< 0.001
ASA score				
II	1		1	
III	2.01 (1.64–2.46)	< 0.001	2.47 (1.61–3.80)	< 0.001
TNM stage of primary tumor				
I	1		1	
II	8.92 (5.27–15.1)	< 0.001	4.56 (2.64–7.89)	< 0.001
III	10.23 (6.09–17.3)	< 0.001	5.90 (3.39–10.29)	< 0.001
IV	46.86 (27.8–78.8)	< 0.001	1.12 (0.54–2.33)	0.754
Charlson Comorbidity Index functional status	2.07 (1.95–2.19)	< 0.001	2.95 (2.57–3.38)	< 0.001
< 4 MET	1		1	
≥ 4 MET	0.50 (0.41–0.61)	< 0.001	0.40 (0.26–0.62)	< 0.001
Adjuvant chemotherapy				
No	1		1	
Yes	1.91 (1.54–2.36)	< 0.001	1.03 (0.81–1.32)	0.793
PCEA				
No	1		1	
Yes	0.82 (0.65–1.04)	0.105	1.00 (0.78–1.28)	0.984
Postoperative NSAID				
No	1		1	
Yes	0.53 (0.43–0.66)	< 0.001	1.95 (1.29–2.94)	0.002
Tumor side				
Left	1		1	
Right	1.19 (0.98–1.45)	0.087	1.03 (0.83–1.27)	0.781
Grade of surgical complications				
0	1		1	
I	2.19 (0.70–6.81)	0.178	0.82 (0.26–2.57)	0.727
II	1.45 (0.98–2.14)	0.065	0.85 (0.57–1.27)	0.432
III	2.29 (0.85–6.14)	0.099	1.20 (0.42–3.39)	0.735
Postoperative recurrence				
No	1		1	
Yes	2.54 (1.95–3.32)	< 0.001	0.81 (0.60–1.09)	0.161
Postoperative metastasis				
No	1			
Yes	104.36 (63.13–172.53)	< 0.001		

All results of adjusted HR were adjusted by anesthesia, sex, time since the earliest included patient, age, ASA score, TNM stage, Charlson Comorbidity Index score, functional status, adjuvant chemotherapy, PCEA, postoperative NSAIDs, tumor side, grade of surgical complications, and postoperative recurrence. Grade of surgical complications: Clavien-Dindo classification.

ASA = American Society of Anesthesiologists; HR = hazard ratio; MET = metabolic equivalents; NSAID = nonsteroidal antiinflammatory drugs; PCEA = patient-controlled epidural analgesia; TNM = tumor–node–metastasis.

local (anastomotic, nodal, or mesenteric) recurrence, and less postoperative metastasis. Subgroup analyses showed significantly better survival in patients given propofol anesthesia, regardless of having a lower or higher tumor–node–metastasis stage and presence or absence of postoperative metastasis. Similarly, Enlund *et al.* found that propofol-based anesthesia was associated with better survival after colon cancer surgery compared with sevoflurane anesthesia.[12] In addition, younger age, higher ASA score, higher tumor–node–metastasis stage (except stage IV), higher Charlson Comorbidity Index score, poor preoperative functional status, and use of postoperative NSAIDs were significant predictors of death after surgery in our colon cancer patients. *In vitro* and animal data support an important effect of anesthetic selection on cancer growth and survival. Furthermore, some previous retrospective analyses suggest that there may be a clinically important effect in humans. Our results also suggest a potential effect in humans, although the magnitude of the effect we observed

Table 3. Subgroup Analyses for TNM Stage and Presence of Postoperative Metastasis

Stratified Variable	Anesthesia	Crude HR (95% CI)	*P* Value	*P* Value (interaction)	PS-adjusted HR (95% CI)	*P* Value	PS-matched HR (95% CI)	*P* Value
Metastasis				0.013				
No	Desflurane	1.00			1.00		1.00	
	Propofol	0.05 (0.01–0.39)	0.004		0.06 (0.01–0.42)	0.005	0.08 (0.01–0.62)	0.016
Yes	Desflurane	1.00			1.00		1.00	
	Propofol	0.67 (0.52–0.85)	0.001		0.64 (0.50–0.81)	< 0.001	0.67 (0.51–0.86)	0.002
TNM stage				0.001				
I and II	Desflurane	1.00			1.00		1.00	
	Propofol	0.10 (0.06–0.19)	< 0.001		0.17 (0.09–0.31)	< 0.001	0.22 (0.11–0.42)	< 0.001
III and IV	Desflurane	1.00			1.00		1.00	
	Propofol	0.32 (0.25–0.42)	< 0.001		0.48 (0.37–0.64)	< 0.001	0.42 (0.32–0.55)	< 0.001

HR = hazard ratio; PS = propensity score; TNM = tumor–node–metastasis.

is considerably larger than in previous studies. It seems biologically implausible that something as complicated as cancer can be reduced by more than a factor-of-two simply by anesthetic selection. Almost surely our results overestimate the true treatment effect, which is common in retrospective studies. Nonetheless, our results are at least consistent in direction and indicate that further work, especially randomized trials, should be pursued.

Surgical resection of a tumor can cause the release of cancer cells into the circulation,[24] promote angiogenesis, and stimulate inflammation.[1,3,12] The distribution of micrometastases to sites distant to the tumor may occur at the time of surgery.[25] In addition, the immune system, which protects against the proliferation of cancer cells, is suppressed at the time of surgery.[1,3,12] Growing evidence from studies of animal and human cancer cell lines show that various anesthetics may affect the immune system in different ways,[4–9] and may influence the cancer patient's survival or risk of recurrence.[6,8–11] Briefly, inhalation agents have been suggested to act as tumor promoters, whereas the intravenously administered hypnotic agent propofol exerts an anticancer effect.[3,11,12]

For both the total patient group and the propensity-matched groups, multivariable analysis showed an association between propofol anesthesia and long-term survival in colon cancer patients. Using a human colon carcinoma cell line, Miao *et al.*[26] reported that propofol restrained the invasive activity of cancer cells. Previous research has demonstrated that propofol inhibits colon carcinoma cell migration *via* γ-aminobutyric acid receptors,[26,27] and human neutrophil activation through the selective and competitive blockade of formyl peptide receptor 1, which improves the prognosis of patients with colon cancer.[28,29]

Previous research has also shown that inhalation agents have deleterious effects on the upregulation of hypoxia-inducible factor and stimulate angiogenesis.[30,31] Upregulation of hypoxia-inducible factor is associated with poor prognosis in a clinical cancer study.[32] By contrast, propofol was reported to reduce hypoxia-inducible factor-1α expression in prostate cancer cells.[30] A recent study suggested that inhalation agents may increase insulin-like growth factor expression.[3] Overexpression of insulin-like growth factor contributes to cell cycle progression and inhibition of cellular apoptosis, and has been noted in many cancers, including colon cancer.[3,33] Taken together, these cancer cell line reports suggest that administration of inhalation anesthetics may promote colon cancer cell growth, and that an alternative agent (propofol) has the opposite (beneficial) effect.

A large retrospective analysis found a 30% lower death rate with the use of propofol anesthesia than with the use of inhalation anesthetics in patients receiving surgical treatment for a solid tumor.[3] Similarly, Enlund *et al.*[12] reported a 25% lower death rate with propofol anesthesia than with sevoflurane in patients receiving colon cancer surgery. Here, we found a 65% lower death rate with propofol anesthesia than with desflurane anesthesia in patients receiving colon cancer surgery.

We also found that propofol anesthesia was related to a lower incidence of local recurrence and distant metastasis compared with desflurane anesthesia. Similarly, Lee *et al.*[11] reported that propofol anesthesia, but not volatile anesthesia, reduced the cancer recurrence rate of mastectomy at the first 5-yr follow-up. In addition, Kim concluded that volatile anesthesia may promote cancer cell growth, whereas propofol seems to provide protection from cancer cell growth after oncology surgery.[34] By contrast, Müller-Edenborn *et al.*[35] reported that sevoflurane or desflurane inhibits colorectal cancer cell migration *via* downregulation of matrix metallopeptidase-9. Therefore, further investigations are needed to understand the effects of the type of anesthesia on the rates of recurrence and metastasis after colon cancer surgery.

A recent study reported poor prognosis of younger patients with colorectal cancer.[36] Similarly, we found better survival in older patients. This observation may reflect our transfer of older patients to the intensive care units postoperatively; that is, these high-risk patients might have benefited from more detailed preoperative evaluation and care in the intensive care unit with intensive circulatory monitoring with the aim of optimizing oxygen-transport capacity.[37] However, another study reported no difference in survival

according to age,[38] and other studies have shown that the risk of death increases significantly with increasing age.[1,3,12] Therefore, further investigation is needed to determine whether age has an effect on survival in these patients.

We found that a higher ASA score was associated with poor survival after colon cancer surgery, which is in agreement with findings of previous studies.[3,12] As in previous studies,[12,39] we also found that a higher tumor–node–metastasis stage was associated with poor survival after colon cancer surgery. Similarly, a previous review showed that colorectal cancer survival is highly dependent on the stage at diagnosis and that the 5-yr survival rate varies from 90% for localized stage cancers and 70% for regional cancer to 10% for distant metastatic cancer.[40] As in a recent study,[41] we found that a higher Charlson Comorbidity Index score was associated with poor survival after colon cancer surgery. We also found that poor preoperative functional capacity was associated with poor survival after colon cancer surgery, which is similar to the results of a previous study reporting that functional status seems to be related to postoperative complications, including mortality.[42]

In this study, we first found that use of postoperative NSAIDs (IV tenoxicam 20 mg · day^{-1} for 3 days) was associated with poor survival after colon cancer surgery. By contrast, a meta-analysis showed that NSAID use (oral dosage of aspirin from 75 to greater than 300 mg daily) after diagnosis, but not prediagnosis, improved colorectal cancer survival.[43] To our knowledge, no study has reported on the relationship between postoperative administration of short-term and low-dose tenoxicam and survival after colon cancer surgery. In our clinical practice, we do not give NSAIDs to older patients (older than 80 yr) or patient-controlled epidural analgesia users, and this may have been a confounding factor. Therefore, further investigation is needed to determine whether the use of postoperative NSAIDs affects survival.

This study has some limitations. First, the study used a retrospective design and patients were not randomly allocated. Therefore, characteristics such as age, ASA score, and tumor–node–metastasis stage differed between groups, and these might have been confounding factors and have been addressed in data analyses. However, we still cannot avoid the possibility of residual confounding due to unmeasured confounders. Second, information about blood transfusion was incomplete in our medical records. A previous study has shown that blood transfusions might promote perioperative cancer cell growth.[44] However, in our clinical practice, the rate of perioperative blood transfusion is very low (less than 1%). Third, we used the tumor–node–metastasis classification, as opposed to the American Joint Committee on Cancer staging system, because we had incomplete data about the American Joint Committee on Cancer staging. Vogelaar *et al.* also used the tumor–node–metastasis classification for colon cancer staging.[1] Fourth, most propofol-based techniques and early detection of colon cancer by colonoscopy were used in the latter period of the study. Therefore, patients in the desflurane group were older, sicker, and generally in a worse stage of the disease. However, we conducted the propensity-score matching to deal with this issue. Postoperative recurrence and metastases did not suit propensity-score matching because most were observed several months to years after colon cancer surgery, but not perioperatively; we did not conduct propensity-score matching to postoperative recurrence and metastases. Fifth, tumor–node–metastasis staging and postoperative metastasis provide overlapping information (*e.g.*, stage IV includes metastasis); we retained only the tumor–node–metastasis stages in the multivariable model to avoid multicollinearity. Our findings showed possible qualitative confounding (age, tumor–node–metastasis stage IV, use of postoperative NSAIDs) in both of the multivariable models (overall and matched patients). Fortunately, no substantial changes in the relationship between the exposures of interest (anesthetic approaches) and mortality were found. Sixth, we did not refine the histologic subtypes of colon cancers because of incomplete data; however, more than 60% of patients had adenocarcinoma in this study, which is consistent with the finding in a previous study.[45] Antiinflammatory strategies might prevent adenocarcinoma metastasis,[46] but there were no significant differences in postoperative NSAIDs use, patient-controlled epidural analgesia use, or postoperative inflammation status based on the Clavien–Dindo classification between groups in this study.

In conclusion, propofol anesthesia for colon cancer surgery was associated with better survival irrespective of tumor–node–metastasis stage. Prospective trials are warranted to evaluate the effects of propofol anesthesia on colon cancer outcomes.

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Competing Interests

The authors declare no competing interests.

Correspondence

Address correspondence to Dr. Lai: Department of Anesthesiology, Tri-Service General Hospital and National Defense Medical Center, #325, Section 2, Chenggung Road, Neihu 114, Taipei, Taiwan, Republic of China. m99ane@gmail.com.

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