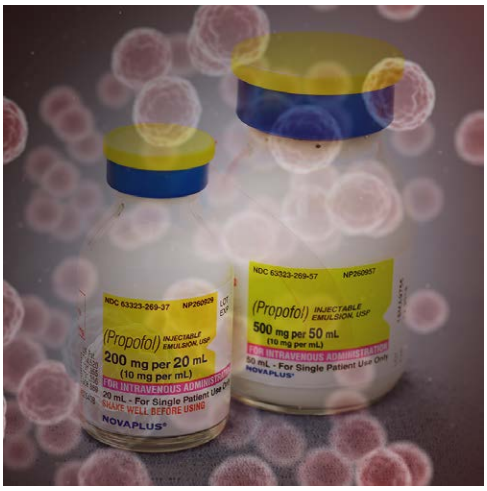
Anesthetic Drugs and Cancer Progression

Fact or Fiction

Juan P. Cata, M.D., Anil K. Sood, M.D., Holger K. Eltzschig, M.D., Ph.D.

THERE has been growing interest in understanding whether perioperative events such as short-term exposure to a general anesthesia could have a deleterious effect on the oncologic outcomes of cancer surgery by promoting growth and progression of the so-called minimally residual disease. Specifically, it has been hypothesized that the use of volatile anesthetics could be associated with minimally residual disease proliferation, whereas propofol could promote apoptosis and have antimetastatic effects.[1] In this issue of Anesthesiology, Makito *et al.*[2] report the results of a retrospective study evaluating the association between overall or recurrence-free survival after cancer surgery and the use of propofol-based total intravenous anesthesia *versus* volatile anesthetic-based general anesthesia. This cohort study included cancer patients who underwent esophagectomy, gastrectomy, hepatectomy, cholecystectomy, pancreatectomy, colectomy, and rectal cancer surgery.[2] Makito *et al.* have to be commended for conducting this thorough and large-scale retrospective study that included 196,303 oncologic surgery patients in their analysis. Briefly, they showed that the use of propofol-based anesthesia in comparison with volatile-based general anesthesia was not associated with significant improvements in recurrence-free (hazard ratio, 1.00; 95% CI, 0.96 to 1.05; $P = 0.94$) or overall survival (hazard ratio, 1.01; 95% CI, 0.79 to 1.21; $P = 0.77$) after adjusting and matching patients for several factors known to impact cancer recurrence.[3] The authors also conducted an instrumental variable analyses that indicated a small difference in recurrence-free survival (hazard ratio, 0.92; 95% CI, 0.87 to 0.98; $P = 0.01$) but not in overall survival (hazard ratio, 1.02; 95% CI, 0.95 to 1.09; $P = 0.65$).



"…the practice of using propofol-based [*versus* volatile anesthetic–based] anesthesia during oncologic surgery with the goal to reduce cancer recurrence or metastatic disease is no longer supported by the available evidence."

These findings are in sharp contrast to those from a previous study conducted by Wigmore *et al.*[4] Although both studies were retrospective, the most striking differences are the sample sizes and the source of data. The retrospective study by Makito *et al.* evaluated 196,303 patients, whereas that by Wigmore evaluated 11,395 patients. Makito *et al.* used a national administrative registry, whereas Wigmore *et al.* reported results from a single institution. Findings from single-center studies are known to suffer from external validity. In addition, Makito *et al.*'s work is in line with a *post hoc* analysis of a recent international randomized, controlled trial indicating that the use of sevoflurane did not impact breast cancer progression.[5] It has been recently suggested that the modulatory effects of general anesthesia on the stress response associated with relatively small surgical procedures such as mastectomies may not matter.[5] In fact, Makito *et al.*'s results suggest that the general anesthesia technique used in more extensive cancer surgeries is also irrelevant to modify factors (*i.e.*, immunity) that influence oncological outcomes.

One of the main strengths of Makito *et al.*'s study is the large number of patients included in the analysis. This study currently represents the largest retrospective analysis investigating the impact of propofol-based anesthesia *versus* volatile-based general anesthesia on oncological outcomes using data from the Japanese Diagnosis Procedure

Image: Adobe Stock/J. P. Rathmell.

This editorial accompanies the article on p. 764.

Accepted for publication July 15, 2020. Published online first on August 17, 2020. From the Department of Anesthesiology and Perioperative Medicine (J.P.C.) and the Department of Gynecologic Oncology and Reproductive Medicine (A.K.S.), The University of Texas – MD Anderson Cancer Center, Houston, Texas; and the Department of Anesthesiology, McGovern Medical School at UTHealth, Houston, Texas (H.K.E.).

 Anesthesiology 2020; 133:698–9. DOI: 10.1097/ALN.0000000000003510

Combination database. Although the information contained in that database is standardized, potential weaknesses include the possibility of sampling bias and limited accuracy of information. Makito *et al.* used a variety of strategies in their statistical analysis to limit confounding and biases. Another strength of the study is that the authors adjusted for multiple factors that are known to affect cancer progression and survival, including the administration of neoadjuvant and adjuvant therapies, perioperative blood transfusions, functional status (Barthel's index) and postoperative complications. Unfortunately, previous studies had limited information or could not adjust for those important factors, which highlights the superior quality of the study by Makito *et al.*[2]

Cancer growth and progression is a complex and highly orchestrated process. The objective of administering adjuvant therapies (*i.e.*, chemotherapy or radiation) is to eliminate or at least control the growth of the minimally residual disease; however, it is poorly understood whether the cellular events triggered during surgery and anesthesia in cancer cells are blunted or exaggerated by adjuvant therapies which can confound the effect of anesthetics on survival outcomes. The *in vitro* cellular effects of anesthetics on various steps of the metastasis process have been well documented. Unfortunately, well-designed experimental studies indicate that such effects are difficult to reproduce *in vivo* under experimental conditions that resemble major cancer surgery in humans.[6] Perhaps one way to bridge the gap between laboratory *in vitro* studies and clinical research is the use of humanized mice models. In such models, tumors grow in mice implanted with human hematopoietic stem cells. Then, these cells will colonize the bone marrow and differentiate into the multiple cell lineages that constitute the human immune system. Using humanized mice models, researchers would have the opportunity to test any potential impact of the combination of surgery and anesthetics on cancer progression.[7] To date, there is no evidence from randomized clinical trials indicating that propofol-based anesthesia is superior to volatile-based anesthesia in terms of oncological outcomes.

In summary, current evidence suggests that volatile anesthetics do not affect cancer-related outcomes in a negative fashion or impact the survival of surgical cancer patients. In other words, the practice of using propofol-based anesthesia during oncologic surgery with the goal to reduce cancer recurrence or metastatic disease is no longer supported by the available evidence. Therefore, anesthesiologists should not be using propofol-based anesthesia to improve oncologic outcomes.

Research Support

Supported by grant Nos. R01DK122796, R01DK109574, R01HL133900 from the National Institutes of Health (Bethesda, Maryland; to Dr. Eltzschig).

Competing Interests

Dr. Sood reports the following competing interests: Merck (Kenilworth, New Jersey, scientific advisory board), Kiyatec (Greenville, South Carolina, consulting), M-Trap (Oak Ridge, Tennessee, research grant), and BioPath (Bellaire, Texas, shareholder). The other authors declare no competing interests.

Correspondence

Address correspondence to Dr. Cata: jcata@mdanderson.org

References

1. Sessler DI, Riedel B: Anesthesia and cancer recurrence: Context for divergent study outcomes. Anesthesiology 2019; 130:3–5
2. Makito K, Matsui H, Fushimi K, Yasunaga H: Volatile *versus* total intravenous anesthesia for cancer prognosis in patients having digestive cancer surgery: A nationwide retrospective cohort study. Anesthesiology 2020; 133:764–73
3. Matsuda S, Fujimori K, Kuwabara K, Ishikawa KB, Fushimi K: Diagnosis procedure combination as an infrastructure for the clinical study. Asian Pacific Journal of Disease Management 2011; 5: 81–7
4. Wigmore TJ, Mohammed K, Jhanji S: Long-term survival for patients undergoing volatile *versus* IV anesthesia for cancer surgery: A retrospective analysis. Anesthesiology 2016; 124:69–79
5. Sessler DI, Pei L, Huang Y, Fleischmann E, Marhofer P, Kurz A, Mayers DB, Meyer-Treschan TA, Grady M, Tan EY, Ayad S, Mascha EJ, Buggy DJ; Breast Cancer Recurrence Collaboration: Recurrence of breast cancer after regional or general anaesthesia: A randomised controlled trial. Lancet 2019; 394:1807–15
6. Afsharimani B, Doornebal CW, Cabot PJ, Hollmann MW, Parat MO: Comparison and analysis of the animal models used to study the effect of morphine on tumour growth and metastasis. Br J Pharmacol 2015; 172:251–9
7. Shultz LD, Ishikawa F, Greiner DL: Humanized mice in translational biomedical research. Nat Rev Immunol 2007; 7:118–30

ANESTHESIOLOGY

Volatile *versus* Total Intravenous Anesthesia for Cancer Prognosis in Patients Having Digestive Cancer Surgery

A Nationwide Retrospective Cohort Study

Kanako Makito, M.D., M.P.H., Hiroki Matsui, M.P.H., Kiyohide Fushimi, M.D., Ph.D., Hideo Yasunaga, M.D., Ph.D.

ANESTHESIOLOGY 2020; XXX:00–00

EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Experimental and clinical studies suggest that intravenous anesthesia may reduce cancer recurrence after potentially curative surgery

What This Article Tells Us That Is New

- Among more than 190,000 patients who had cancer surgery, overall and recurrence-free survival were comparable in patients who had propofol-based total intravenous and volatile anesthesia
- Selection of anesthetic approach should be based on factors other than putative effects on cancer recurrence

ABSTRACT

Background: Previous experimental and clinical studies have shown that anesthetic agents have varying effects on cancer prognosis; however, the results were inconsistent among these studies. The authors compared overall and recurrence-free survival in patients given volatile or intravenous anesthesia for digestive tract cancer surgery.

Methods: The authors selected patients who had elective esophagectomy, gastrectomy, hepatectomy, cholecystectomy, pancreatectomy, colectomy, and rectal cancer surgery from July 2010 to March 2018 using the Japanese Diagnosis Procedure Combination database. Patients were divided into a volatile anesthesia group (desflurane, sevoflurane, or isoflurane with/without nitrous oxide) and a propofol-based total intravenous anesthesia group. The authors hypothesized that total intravenous anesthesia is associated with greater overall and recurrence-free survival than volatile anesthesia. Subgroup analyses were performed for each type of surgery.

Results: The authors identified 196,303 eligible patients (166,966 patients in the volatile anesthesia group and 29,337 patients in the propofol-based total intravenous anesthesia group). The numbers (proportions) of death in the volatile anesthesia and total intravenous anesthesia groups were 17,319 (10.4%) and 3,339 (11.4%), respectively. There were no significant differences between the two groups in overall survival (hazard ratio, 1.02; 95% CI, 0.98 to 1.07; $P = 0.28$) or recurrence-free survival (hazard ratio, 0.99; 95% CI, 0.96 to 1.03; $P = 0.59$), whereas instrumental variable analyses showed a slight difference in recurrence-free survival (hazard ratio, 0.92; 95% CI, 0.87 to 0.98; $P = 0.01$). Subgroup analyses showed no significant difference in overall or recurrence-free survival between the groups in any type of surgery.

Conclusions: Overall and recurrence-free survival were similar between volatile and intravenous anesthesia in patients having digestive tract surgery. Selection of the anesthetic approach for these patients should be based on other factors.

(ANESTHESIOLOGY 2020; XXX:00–00)

Volatile and intravenous anesthetic agents are commonly used for maintenance of anesthesia. Laboratory and animal studies have suggested that volatile anesthetic drugs are more likely to enhance the activity of cancer cells through suppression of immune cell function, modulation of the neuroendocrine stress response to surgery, and cancer cell signaling.[1–3] In contrast, intravenous anesthetic agents (*e.g.*, propofol) have antiinflammatory and antioxidative effects that may protect against perioperative immune suppression. Previous experimental studies have demonstrated antitumor effects by direct regulation of key ribonucleic acid pathways and signaling in cancer cells in patients with gastric cancer, non–small cell lung cancer, breast cancer, and endometrial and esophageal squamous cell carcinoma.[4–9]

Several studies have compared overall survival or recurrence-free survival of patients with cancer who had volatile anesthesia *versus* total intravenous anesthesia. A meta-analysis of 10 studies (nine retrospective studies and one small randomized controlled trial) involving patients having breast, esophageal, gastric, colon, rectal, or non–small cell lung cancer surgery showed that total intravenous anesthesia was not associated with improved recurrence-free survival, but was associated with improved overall survival, compared to volatile anesthesia.[10] However, all studies in

Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are available in both the HTML and PDF versions of this article. Links to the digital files are provided in the HTML text of this article on the Journal's Web site (www.anesthesiology.org).

Submitted for publication January 9, 2020. Accepted for publication May 29, 2020. From the Department of Clinical Epidemiology and Health Economics, School of Public Health, The University of Tokyo (K.M., H.M., H.Y.); and the Department of Health Policy and Informatics, Graduate School of Medicine, Tokyo Medical and Dental University (K.F.), Tokyo, Japan.

<zdoi;. DOI: 10.1097/ALN.0000000000003440>

the meta-analysis were limited because of their small sample sizes and possibility of residual confounders.

We therefore conducted a large-scale study to compare overall survival and recurrence-free survival between volatile anesthesia and total intravenous anesthesia using a national inpatient database in Japan. The objective of the study was to evaluate the association of volatile anesthesia *versus* total intravenous anesthesia with cancer prognosis among patients having digestive cancer surgery. We hypothesized that total intravenous anesthesia is associated with a greater overall survival and recurrence-free survival than is volatile anesthesia.

Materials and Methods

Data Source

Patient data were extracted from the Japanese Diagnosis Procedure Combination database, the details of which have been previously described.[11] Briefly, the database includes administrative claims data and the following detailed patient data: age; sex; body mass index (BMI); diagnoses and comorbidities at admission; complications after admission recorded with text data in the Japanese language and encoded by *International Classification of Diseases and Related Health Problems, 10th Revision* (ICD-10) codes; medical procedures encoded by Japanese original codes; tumor node metastasis classification of malignant tumors and cancer stage; medications; activities of daily living at admission (converted to Barthel Index); and discharge status. According to a previous validation study of the database, the recorded diagnoses of several common diseases (including malignant tumors, cardiac diseases, stroke, and renal diseases) have moderate sensitivity and high specificity, whereas the recorded procedures and drugs have high sensitivity and specificity.[11] The database includes administrative data on 7 million inpatients per year, accounting for approximately 50% of all acute care inpatients in Japan. More than 1,000 hospitals participate in the database voluntarily, and approximately 300 hospitals also provide outpatient data.

The requirement for informed consent was waived because the study was based on a secondary analysis of anonymous administrative data. This study was approved by the Institutional Review Board at The University of Tokyo (Institutional Review Board number 3501).

Patient Selection

From the database, we obtained the records of patients who had elective esophagectomy, gastrectomy, hepatectomy, cholecystectomy, pancreatectomy, colectomy, or rectal cancer surgery from July 1, 2010 to March 31, 2018 at 218 hospitals that provided outpatient data. The inclusion criteria were an age of greater than or equal to 18 yr at the time of the first surgery with volatile anesthesia or total intravenous anesthesia. We excluded patients who had anesthesia multiple times during the study period, those who were diagnosed with a benign tumor or a malignant potential tumor, those who had spinal anesthesia, and those in whom nitrous oxide was used without volatile anesthesia. A malignant potential tumor is a tumor that is reported to be associated with a risk of malignancy, including intraductal papillary mucinous neoplasm, mucinous cystic neoplasm, and Crohn's disease.

Exposure

The exposure variable was having volatile anesthesia or total intravenous anesthesia. The patients were divided into two groups: (1) those who had volatile anesthesia using desflurane, sevoflurane, or isoflurane with/without nitrous oxide and (2) those who had propofol-based total intravenous anesthesia.

Confounding Variables and Outcomes

We extracted information on baseline characteristics including age at the time of the first elective surgery, sex, BMI, length of stay, smoking status (current/past smoker or nonsmoker), admission date of cancer recurrence, date of death, comorbidities at admission, complications after admission, type of surgery (esophagectomy, gastrectomy, hepatectomy, cholecystectomy, pancreatectomy, colectomy, or rectal cancer surgery), year of surgery, cancer stage, use of epidural anesthesia, use of morphine, use of oxycodone, preoperative chemotherapy, preoperative radiotherapy, postoperative chemotherapy, postoperative radiotherapy, preoperative renal replacement therapy, intraoperative blood transfusion, type of hospital (academic or nonacademic), Barthel Index at admission, and hospital volume. The patients were categorized into four age groups (younger than 59, 60 to 69, 70 to 79, and 80 yr or older) because more than 65% of the patients were aged 60 to 79 yr. The BMI was divided into five categories based on the World Health organization classifications of underweight (less than 18.5 kg/m^2), normal weight (18.5 to 24.9 kg/m^2), overweight (25.0 to 29.9 kg/m^2), and obese (30.0 kg/m^2 or more). The tumor, node, metastasis cancer stages were determined by postoperative pathology and divided into 0 or I, II, III, and IV.

The Barthel Index is frequently used to measure performance in activities of daily living, with scores ranging from 0 to 100 points (higher scores indicate less disability). This index includes 10 items of mobility and self-care functions. We divided the Barthel Index into two groups (0 to 95 and 100) because more than 90% of the patients had a Barthel Index of 100.

For comorbidities at admission, each ICD-10 code for a comorbidity was converted into a Charlson Comorbidity Index score, which is widely used as a validated measure to predict in-hospital morbidity and mortality for each patient.[12] All patients were diagnosed with cancer; therefore, the lowest Charlson Comorbidity Index score was 2.

Hospital volume was defined as the average number of surgeries performed at each hospital annually and was

divided into three groups containing almost equal numbers of patients.

Perioperative complications were defined as the occurrence of the following diseases during the first perioperative period: cerebral infarction or hemorrhage (ICD-10 codes I60 to I64), acute coronary events (I21, I22, and I252), heart failure (I50), pulmonary embolism (I26), acute and subacute hepatic failure (K720), acute renal failure (N17), sepsis (A40 and A41), wound infection (T793 and T814), pneumonia (J12 to J18 and J69), and urinary tract infection (N390, T835, and N30). We also searched for anastomotic leakage using Japanese text.

The primary outcomes were recurrence-free survival and overall survival.

Statistical Analysis

No statistical power calculation was conducted before the study because the sample size in our study was based on secondary use of administrative claims data and a fixed available sample.

The patient characteristics and type of surgery in each group are described using number and proportion for categorical variables and mean with SD for continuous variables. Standardized differences were used to compare the distribution of baseline covariates between treatment groups in observational studies. Small differences in the absolute standardized differences (less than 0.10) suggest balanced baseline characteristics between patients in the volatile anesthesia and total intravenous anesthesia groups.[13]

Kaplan–Meier survival analysis was used to compare overall survival and recurrence-free survival between the two groups. Cox proportional hazard regression models were used to compare the relationship between total intravenous anesthesia and overall survival or recurrence-free survival with adjustment for the following baseline variables: age, sex, BMI, smoking status, Charlson Comorbidity Index score, cancer stage, preoperative adjuvant therapy, postoperative adjuvant therapy, preoperative renal replacement therapy, preoperative or intraoperative blood transfusion, preoperative use of morphine or oxycodone, type of hospital (academic or nonacademic), hospital volume, Barthel Index at admission, and at least one postoperative complication. We used the Schoenfeld residuals test and complementary log plots to assess the proportional hazards assumption. The proportional hazards assumption was not violated in any of our analyses. Some data regarding the BMI, cancer stage, and Barthel Index at admission were missing. We used a complete case analysis for these missing values. Follow-up was censored on March 31, 2018 or the last outpatient record.

Observational studies have the potential for residual confounders due to measured and unmeasured baseline characteristics, which can lead to incorrect associations between the type of anesthesia and outcomes. One strategy to address this limitation is the use of an instrumental variable analysis designed to adjust for unmeasured confounding between two groups, allowing the achievement of a pseudo-randomized controlled trial.[14] An instrumental variable analysis requires the following assumptions: (1) the instrumental variable is independent of the unmeasured confounding; (2) the instrumental variable is strongly associated with the treatment; and (3) the instrumental variable is associated with the outcome only indirectly through its effect on the treatment. The type of anesthesia performed mainly depends on the physician's preference; therefore, we used the proportion of total intravenous anesthesia use at each hospital as an instrumental variable. The proportion of total intravenous anesthesia use was defined as the number of patients who had total intravenous anesthesia divided by the number of all patients in each hospital. We conducted two-stage residual inclusions for the instrumental variable analyses to compare recurrence-free survival or overall survival between the volatile anesthesia and total intravenous anesthesia groups. We fit a first stage logistic model that predicts treatment assignment (volatile anesthesia and total intravenous anesthesia) with the instrumental variable and the aforementioned variables to estimate the probability of having total intravenous anesthesia. Next, the second stage model was fitted by regressing these outcomes on the performance of total intravenous anesthesia in a Cox regression model, along with the residuals from the first-stage model and the other variables.

We confirmed that the proportion of total intravenous anesthesia use at each hospital was not a weak instrument using a partial F test, with an F statistic of more than 10.[15]

Two additional approaches were performed as sensitivity analyses. First, we used Cox regression analyses after propensity score matching. We estimated the propensity score using a logistic regression model for the receipt of total intravenous anesthesia, incorporating the baseline characteristics of the aforementioned variables without postoperative adjuvant therapy and at least one postoperative complication. We set a caliper at 0.2 SD of the estimated logit of the propensity score and performed one-to-one propensity score matching of patients between the types of anesthesia using the nearest neighbor method without replacement. We estimated the balance in the propensity score–matched cohort using standardized differences. Second, we performed an instrumental variable analysis using the proportion of total intravenous anesthesia at each of 47 prefectures as another instrumental variable.

Subgroup analyses were performed for the type of cancer surgery. We evaluated the association between total intravenous anesthesia and the primary outcomes using Cox regression analyses. A two-tailed P value of less than 0.05 was considered statistically significant. All analyses were performed using Stata/MP 16.0 (StataCorp, USA).

A Priori versus Post Hoc Analyses

As *a priori* analyses, we planned to perform Cox regression analyses and instrumental variable analyses using the

proportion of total intravenous anesthesia use at each hospital as an instrumental variable in all patients to evaluate the association between the type of anesthesia and outcomes. As a *post hoc* sensitivity analysis, we performed Cox regression analyses in propensity score–matched patients and instrumental variable analyses using the proportion of total intravenous anesthesia in each of 47 prefectures as another instrumental variable.

Results

We selected 255,330 patients who had cancer surgery during the study period. We then excluded 52,209 patients who had anesthesia multiple times during the study period, 5,905 patients diagnosed with a benign tumor or a malignant potential tumor, 227 patients who had spinal anesthesia, and 686 patients who received nitrous oxide without volatile anesthesia. In total, 196,303 patients who met the inclusion criteria were divided into those who had volatile anesthesia using desflurane, sevoflurane, or isoflurane with/without nitrous oxide (volatile anesthesia group, n = 166,966) and those who had propofol-based total intravenous anesthesia (total intravenous anesthesia group, n = 29,337; fig. 1).

Table 1 shows the baseline characteristics of the patients, hospitals, and procedures for the overall study cohort and each of the two groups. Overall, 63,678 (32.4%) patients had colectomy and 61,056 (31.1%) had gastrectomy. The standardized differences for all variables suggested no differences between the volatile anesthesia and total intravenous anesthesia groups with the exception of male sex, academic hospital, year of surgery, and high hospital volume. The BMI data were missing for 1,856 (0.9%) patients, the cancer stage was missing for 39,342 (20.0%) patients, and the Barthel Index at admission was missing for 5,795 (3.0%) patients.

The median postoperative follow-up period was 639 days (interquartile range, 234 to 1,301 days) in the volatile anesthesia group and 768 days (interquartile range, 286 to 1,525 days) in the total intravenous anesthesia group.

The overall mortality rates in the volatile anesthesia and total intravenous anesthesia groups were 10.4% and 11.4%, respectively. The proportions of recurrence or death in the volatile anesthesia and total intravenous anesthesia groups were 18.3% and 18.8%, respectively.

The results of the Kaplan–Meier analysis are shown in figure 2 (overall survival) and figure 3 (recurrence-free survival). The 1-yr overall survival was 89.8% in the volatile anesthesia group and 90.0% in the total intravenous anesthesia group. The 1-yr recurrence-free survival was 80.8% in the volatile anesthesia group and 81.9% in the total intravenous anesthesia group.

Figure 4 shows the association between total intravenous anesthesia and overall survival or recurrence-free survival by Cox regression analyses. We found no significant difference in overall survival (hazard ratio, 1.02; 95% CI, 0.98 to 1.07; $P = 0.28$) or recurrence-free survival (hazard ratio, 0.99; 95% CI, 0.96 to 1.03; $P = 0.59$) between the volatile anesthesia and total intravenous anesthesia groups. Variables that were significantly associated with worse overall survival and recurrence-free survival were an age of older than 60 yr, male sex, underweight (BMI of less than 18.5 kg/m^2), Charlson Comorbidity Index score of 3 or 4, cancer stage, preoperative adjuvant therapy, postoperative adjuvant therapy, preoperative renal replacement therapy, smoking, preoperative or intraoperative blood transfusion, preoperative use of morphine or oxycodone, academic hospital, Barthel Index, and at least one postoperative complication.

Figure 5 shows the association between total intravenous anesthesia and overall survival or recurrence-free survival by instrumental variable analyses. The F statistic was 27,416 ($P < 0.001$), suggesting that the instrumental variable was strongly associated with the treatment assignment (volatile anesthesia or total intravenous anesthesia). Compared with volatile anesthesia, total intravenous anesthesia was not significantly associated with better overall survival (hazard ratio, 1.02; 95% CI, 0.95 to 1.09; $P = 0.65$), but was significantly associated with better

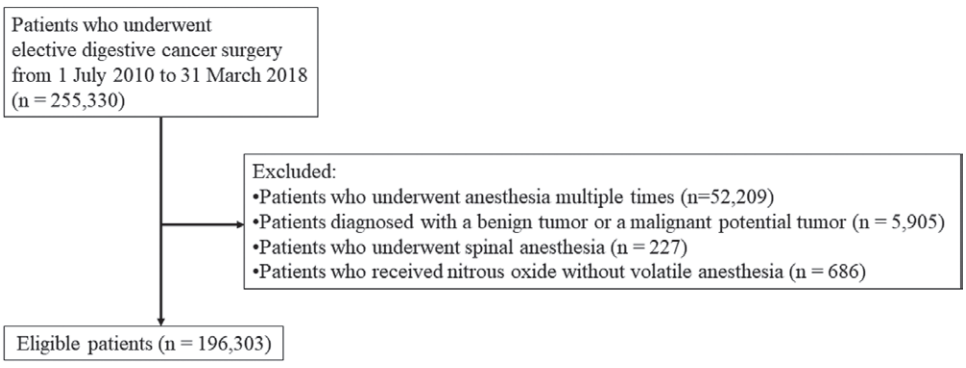


Fig. 1. Flow chart of patient selection.

Table 1. Baseline Characteristics of Patients, Hospitals, and Procedures

	Total (n = 196,303)		Volatile Anesthesia (n = 166,966)		Total Intravenous Anesthesia (n = 29,337)		Absolute Standardized Difference
Age, yr							
≤ 59	32,806	(16.7)	27,256	(16.3)	5,550	(18.9)	0.067
60–69	59,502	(30.3)	50,477	(30.2)	9,025	(30.8)	0.013
70–79	70,514	(35.9)	60,546	(36.3)	9,968	(34.0)	0.045
≥ 80	33,481	(17.1)	28,687	(17.2)	4,794	(16.3)	0.028
Sex, male	122,254	(62.3)	105,345	(63.1)	16,909	(57.6)	0.114
Body mass index, kg/m^2							
< 18.5	22,503	(11.5)	19,014	(11.4)	3,489	(11.9)	0.015
18.5–24.9	130,076	(66.3)	110,510	(66.2)	19,566	(66.7)	0.008
25.0–29.9	36,545	(18.6)	31,145	(18.7)	5,400	(18.4)	0.008
30.0–34.9	4,585	(2.3)	3,982	(2.4)	603	(2.1)	0.029
≥ 35.0	738	(0.4)	652	(0.4)	86	(0.3)	0.021
Missing	1,856	(0.9)	1,663	(1.0)	193	(0.7)	
Charlson comorbidity index							
2	143,545	(73.1)	121,402	(72.7)	22,143	(75.5)	0.066
3	12,664	(6.5)	10,884	(6.5)	1,780	(6.1)	0.022
≥ 4	40,094	(20.4)	34,680	(20.8)	5,414	(18.5)	0.059
Cancer stage							
0 or I	55,440	(28.2)	47,089	(28.2)	8,351	(28.5)	0.015
II	42,002	(21.4)	35,973	(21.5)	6,029	(20.6)	0.027
III	42,195	(21.5)	35,770	(21.4)	6,425	(21.9)	0.016
IV	17,324	(8.8)	14,814	(8.9)	2,510	(8.6)	0.009
Missing	39,342	(20.0)	33,320	(20.0)	6,022	(20.5)	
Preoperative adjuvant therapy	10,528	(5.4)	9,205	(5.5)	1,323	(4.5)	0.051
Postoperative adjuvant therapy	67,508	(34.4)	57,000	(34.1)	10,508	(35.8)	0.037
Preoperative renal replacement therapy	1,627	(0.8)	1,473	(0.9)	154	(0.5)	0.039
Type of surgery							
Esophagectomy	8,859	(4.5)	7,212	(4.3)	1,647	(5.6)	0.072
Gastrectomy	61,056	(31.1)	51,701	(31.0)	9,355	(31.9)	0.010
Hepatectomy	18,095	(9.2)	15,976	(9.6)	2,119	(7.2)	0.086
Cholecystectomy	4,064	(2.1)	3,534	(2.1)	530	(1.8)	0.017
Pancreatectomy	16,045	(8.2)	13,972	(8.4)	2,073	(7.1)	0.043
Colectomy	63,678	(32.4)	53,886	(32.3)	9,792	(33.4)	0.028
Rectal cancer surgery	24,506	(12.5)	20,685	(12.4)	3,821	(13.0)	0.026
Year of surgery							
2010 (July–December)	14,378	(7.3)	11,549	(6.9)	2,829	(9.6)	0.104
2011 (January–December)	25,039	(12.8)	20,330	(12.2)	4,709	(16.1)	0.114
2012 (January–December)	24,109	(12.3)	19,943	(11.9)	4,166	(14.2)	0.048
2013 (January–December)	23,678	(12.1)	19,811	(11.9)	3,867	(13.2)	0.013
2014 (January–December)	24,194	(12.3)	20,697	(12.4)	3,497	(11.9)	0.010
2015 (January–December)	25,395	(12.9)	22,020	(13.2)	3,375	(11.5)	0.045
2016 (January–December)	26,172	(13.3)	23,057	(13.8)	3,115	(10.6)	0.087
2017 (January–December)	27,355	(13.9)	24,166	(14.5)	3,189	(10.9)	0.100
2018 (January–March)	5,983	(3.0)	5,393	(3.2)	590	(2.0)	0.069
Epidural anesthesia	141,896	(72.3)	120,751	(72.3)	21,145	(72.1)	0.042
Smoking	92,023	(46.9)	79,191	(47.4)	12,832	(43.7)	0.073
Pre- or postoperative blood transfusion	31,669	(16.1)	27,520	(16.5)	4,149	(14.1)	0.058
Preoperative morphine or oxycodone	961	(0.5)	816	(0.5)	145	(0.5)	0.002
Academic hospital	55,462	(28.3)	49,968	(29.9)	5,494	(18.7)	0.209
Hospital volume							
Low (< 125)	64,711	(33.0)	54,665	(32.7)	10,046	(34.2)	0.020
Medium (125–245)	65,509	(33.4)	54,414	(32.6)	11,095	(37.8)	0.092
High (> 245)	66,083	(33.7)	57,887	(34.7)	8,196	(27.9)	0.115
Barthel Index							
100	177,094	(90.2)	150,849	(90.3)	26,245	(89.5)	0.021
0–95	13,414	(6.8)	11,578	(6.9)	1836	(6.3)	0.021
Missing	5,795	(3.0)	4,539	(2.7)	1,256	(4.3)	
Complication after operation							
At least one complication	15,280	(7.8)	15,280	(9.2)	677	(2.3)	0.025
Cerebral infarction or hemorrhage	582	(0.3)	504	(0.3)	78	(0.3)	0.005
Acute coronary events	196	(0.1)	172	(0.1)	24	(0.1)	0.008
Heart failure	2,593	(1.3)	2,321	(1.4)	272	(0.9)	0.034
Pulmonary embolism	372	(0.2)	337	(0.2)	35	(0.1)	0.019
Acute hepatic failure	157	(0.1)	140	(0.1)	17	(0.1)	0.005
Acute renal disease	466	(0.2)	403	(0.2)	63	(0.2)	0.007
Sepsis	1,780	(0.9)	1,559	(0.9)	221	(0.8)	0.019
Wound infection	5,320	(2.7)	4,503	(2.7)	817	(2.8)	0.008
Pneumonia	3,790	(1.9)	3,288	(2.0)	502	(1.7)	0.018
Urinary tract infection	1,165	(0.6)	970	(0.6)	195	(0.7)	0.012
Anastomotic leakage	96	(0.0)	81	(0.0)	15	(0.1)	0.002

Data are presented as n (%).

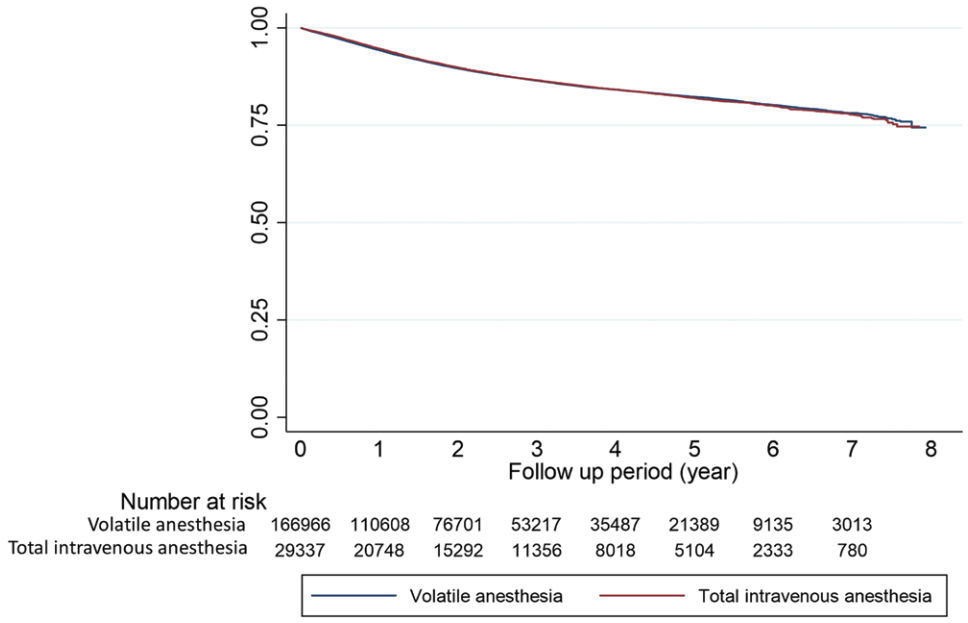


Fig. 2. Kaplan–Meier analysis of overall survival.

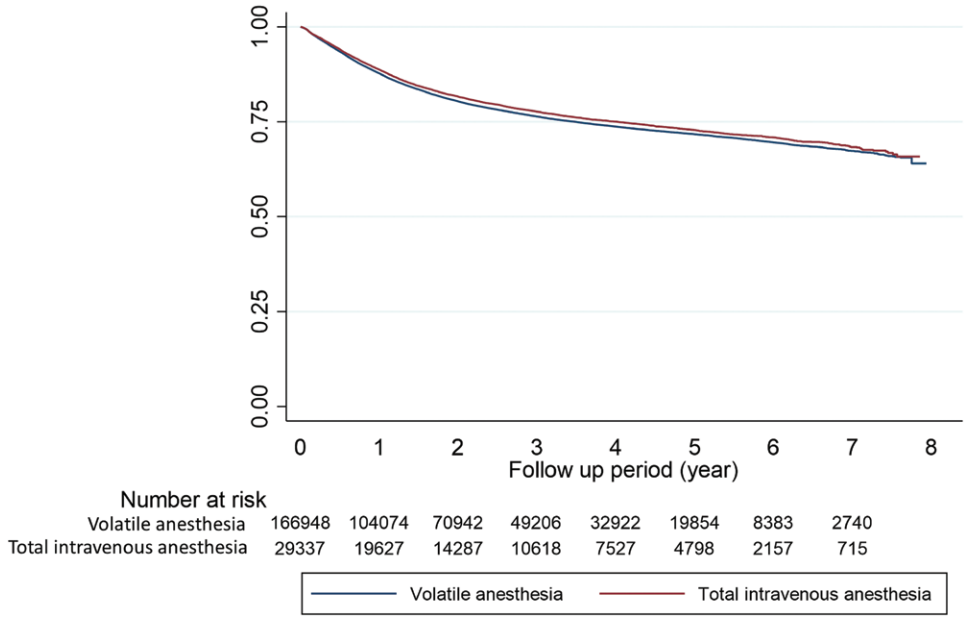


Fig. 3. Kaplan–Meier analysis of recurrence-free survival.

recurrence-free survival (hazard ratio, 0.92; 95% CI, 0.87 to 0.98; $P = 0.01$).

Table 2 shows the results of the subgroup analyses for each type of cancer surgery. There was no significant difference in overall survival or recurrence-free survival between the volatile anesthesia and total intravenous anesthesia groups in any type of surgery.

Supplemental Digital Content, table 1 (http://links.lww.com/ALN/C420) shows the patients' characteristics after propensity score matching. The distribution was well-balanced

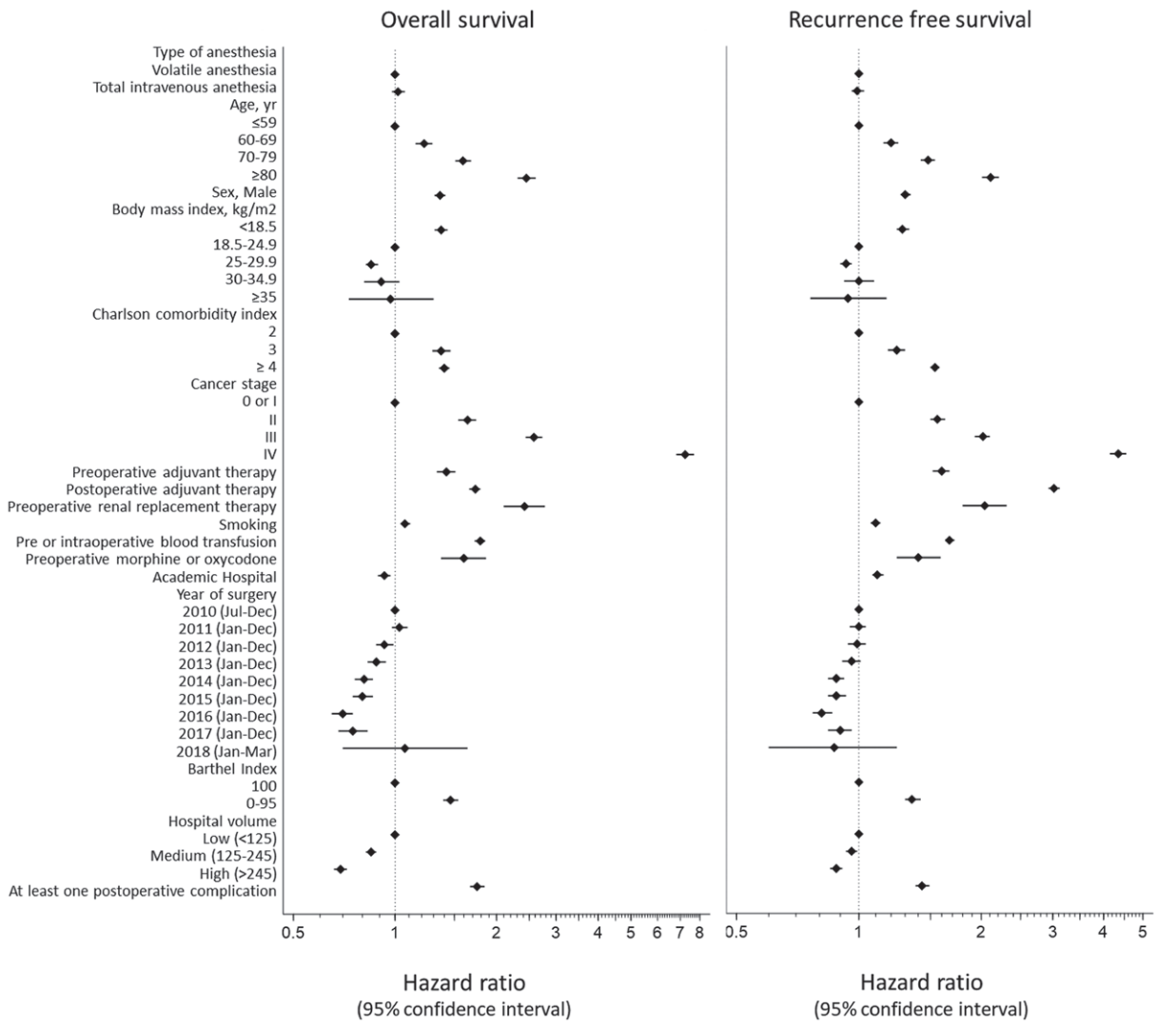


Fig. 4. Results of Cox regression analyses for recurrence-free survival and overall survival.

between the volatile anesthesia and total intravenous anesthesia groups. Supplemental Digital Content, table 2 (http://links.lww.com/ALN/C421) shows that total intravenous anesthesia was not significantly associated with improved overall survival (hazard ratio, 1.01; 95% CI, 0.79 to 1.21; $P = 0.77$) or recurrence-free survival (hazard ratio, 1.00; 95% CI, 0.96 to 1.05; $P = 0.94$) in the propensity score-matched cohort.

The results of the instrumental variable analyses using the proportion of total intravenous anesthesia in each of 47 prefectures as another instrumental variable were similar to those in the main analyses; total intravenous anesthesia was significantly associated with improved recurrence-free survival, but not significantly associated with improved overall survival, compared with volatile anesthesia (Supplemental Digital Content, table 3, http://links.lww.com/ALN/C422).

Discussion

This study showed no significant association between total intravenous anesthesia and better overall survival in patients who had elective cancer surgery including esophagectomy, gastrectomy, hepatectomy, cholecystectomy, pancreatectomy, colectomy, and rectal cancer surgery. We also found that total intravenous anesthesia was not significantly associated with better recurrence-free survival by the Cox regression analysis, but that it was significantly associated with better recurrence-free survival by the instrumental variable analysis. This difference in these results may reflect the control for unmeasured confounders by the instrumental variable analysis. However, the adjusted hazard ratio (95% CI) of total intravenous anesthesia for recurrence-free survival was 0.92 (0.87 to 0.98); therefore, the influence of total intravenous anesthesia on reducing cancer recurrence was small, if any.

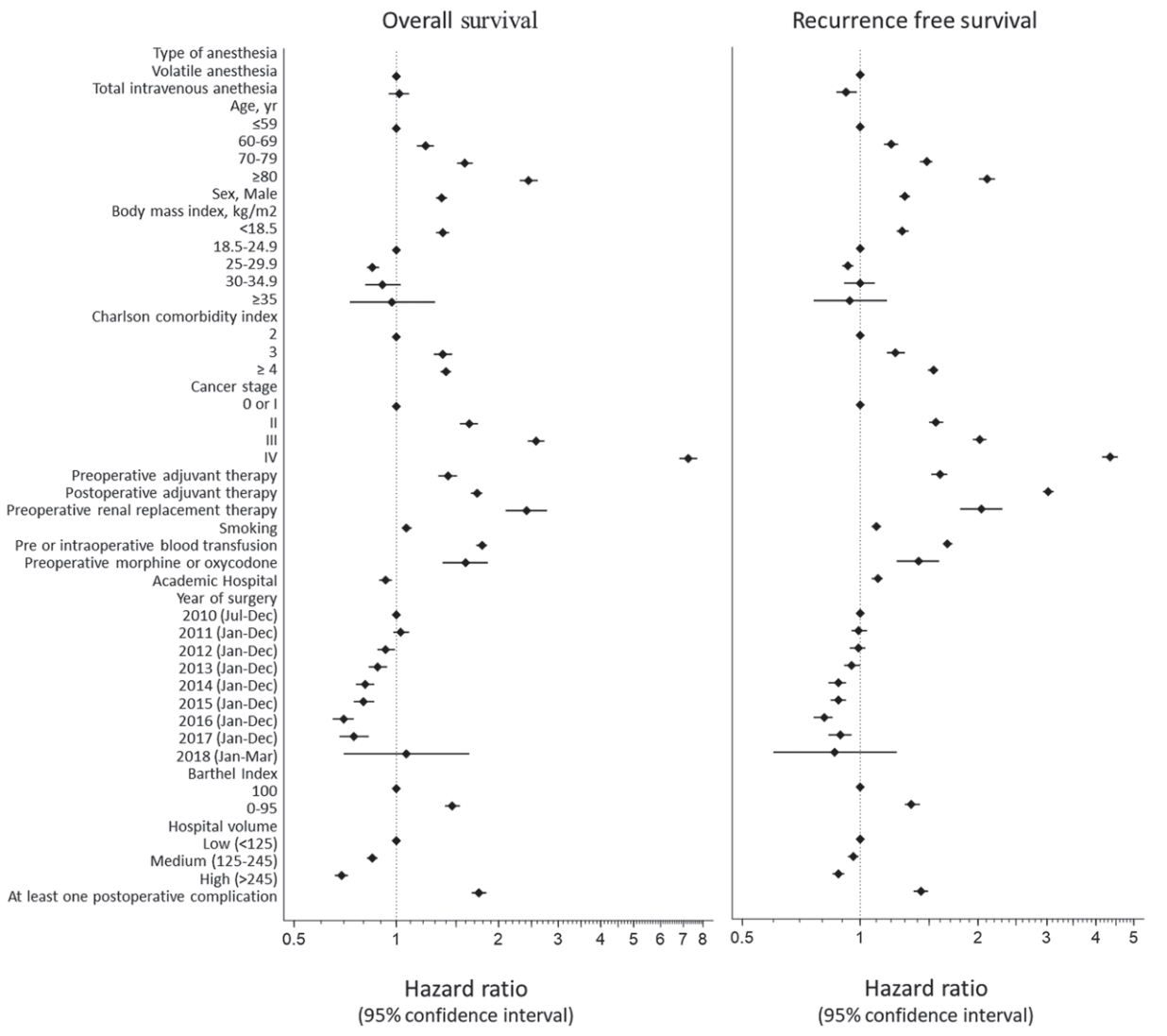


Fig. 5. Results of instrumental variable analyses for recurrence-free survival and overall survival, in which the instrumental variable was defined as the proportion of total intravenous anesthesia at each hospital.

Table 2. Subgroup Analyses for Each Type of Surgery: Association of Volatile Anesthesia with Recurrence-free Survival and Overall Survival by Cox Regression

	Recurrence-free Survival			Overall Survival		
	Hazard Ratio	95% CI	*P* Value	Hazard Ratio	95% CI	*P* Value
Esophagectomy	1.02	0.92–1.13	0.699	1.11	0.97–1.27	0.133
Gastrectomy	0.96	0.89–1.03	0.240	0.97	0.89–1.06	0.553
Hepatectomy	1.07	0.96–1.18	0.210	1.00	0.86–1.17	0.977
Cholecystectomy	0.85	0.70–1.04	0.110	0.83	0.65–1.05	0.120
Pancreatectomy	0.96	0.88–1.05	0.350	0.99	0.89–1.11	0.910
Colectomy	0.99	0.93–1.06	0.810	1.02	0.93–1.11	0.680
Rectal cancer surgery	0.92	0.83–1.02	0.110	1.04	0.91–1.19	0.580

Many previous experimental studies have revealed a premetastatic effect of volatile anesthesia and a beneficial effect of propofol for various cancer cells. Laboratory studies of prostate or renal cancer cells have shown that isoflurane induces modulation of hypoxia-inducible factor 1-alpha (HIF-1α) or vascular endothelial growth factor, which may affect cancer recurrence after surgery.[1,16] One study of ovarian cancer cells demonstrated increased expression of genes related to metastasis after exposure to sevoflurane, desflurane, and isoflurane, while another study suggested that sevoflurane promoted metastatic potential and chemoresistance in renal carcinoma but not in non–small cell lung cancer.[17,18] In contrast, laboratory studies of propofol have shown antitumor effects in various cancers. A previous study of gastric cancer cells showed that propofol inhibited cell proliferation, invasion, and migration and promoted apoptosis.[19] Another study of non–small cell lung cancer showed that propofol disrupted upregulation of HIF-1α in a dose-dependent manner and therefore reduced the migration and invasion of cancer cells.[20]

Clinical studies have shown conflicting results regarding whether total intravenous anesthesia may have a beneficial effect on cancer prognosis compared with volatile anesthesia. A previous meta-analysis of overall mortality (including three randomized clinical trials and five observational studies) suggested that total intravenous anesthesia might lead to decreased mortality compared with volatile anesthesia.[21] This result may be attributable to one large study that showed higher overall mortality in the volatile anesthesia group than total intravenous anesthesia group. However, this study did not adjust for potential confounders including the cancer stage and preoperative comorbidities.[22] Observational studies have shown inconsistent results. Total intravenous anesthesia was not associated with overall survival or recurrence-free survival in patients having breast cancer surgery.[23] Two other studies showed inconsistent results in terms of overall survival between propofol and sevoflurane in patients having gastric or rectal cancer surgery.[24,25]

Our findings showed little association between the type of anesthesia and cancer prognosis. The advantage of our study is the larger sample size than those in previous studies and the use of instrumental variable analyses to control for unmeasured confounders. Another advantage of the present study was the inclusion of various types of cancer in digestive organs.

In instrumental variable analyses, all individuals in the study population are assumed to be compliers. This is called the "monotonicity assumption."[26,27] In the present study, compliers were those who were likely to receive total intravenous anesthesia in hospitals with a high preference for total intravenous anesthesia, whereas they were unlikely to receive total intravenous anesthesia in hospitals with a low preference for total intravenous anesthesia. Complex decision processes with multiple factors may violate the monotonicity assumption when using the physician's preference as an instrument.[26,27] However, in the present study, the proportion of total intravenous anesthesia use at each hospital as an instrumental variable may not violate the monotonicity assumption because the decision regarding the use of total intravenous anesthesia must be based only on anesthesiologists' preferences, not on patients' willingness; that is, most patients are considered to be compliers.

The current study had several limitations. First, retrospective observational studies are associated with the potential for residual confounding. We therefore performed propensity score–matched analyses, which were designed to balance variables between the two groups and thus reduce the potential measured confounding effect of each variable. In addition, instrumental variable analyses may help to account for unmeasured confounders such as laboratory data and surgical invasiveness. Second, we could identify only patients who died in a hospital in which the patients had cancer surgery; patients who died at home or in another institution could not be followed. Finally, the postoperative follow-up period was short (median of just over 2 yr); a study with a longer follow-up period of more than 5 yr is warranted.

In conclusion, the present study showed no significant difference in overall survival and little difference, if any, in recurrence-free survival between total intravenous anesthesia and volatile anesthesia.

Research Support

This work was supported by grants from the Ministry of Health, Labor and Welfare (Tokyo, Japan; 19AA2007 and H30-Policy-Designated-004) and the Ministry of Education, Culture, Sports, Science and Technology (Tokyo, Japan; 17H04141).

Competing Interests

The authors declare no competing interests.

Correspondence

Address correspondence to Dr. Makito: Department of Clinical Epidemiology and Health Economics, School of Public Health, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan. canakana87@m.u-tokyo.ac.jp.

References

1. Benzonana LL, Perry NJ, Watts HR, Yang B, Perry IA, Coombes C, Takata M, Ma D: Isoflurane, a commonly used volatile anesthetic, enhances renal cancer growth and malignant potential via the hypoxia-inducible factor cellular signaling pathway *in vitro*. Anesthesiology 2013; 119:593–605
2. Buckley A, McQuaid S, Johnson P, Buggy DJ: Effect of anaesthetic technique on the natural killer cell anti-tumour activity of serum from women undergoing breast

cancer surgery: A pilot study. Br J Anaesth 2014; 113 Suppl 1:i56–62
3. Desmond F, McCormack J, Mulligan N, Stokes M, Buggy DJ: Effect of anaesthetic technique on immune cell infiltration in breast cancer: A follow-up pilot analysis of a prospective, randomised, investigator-masked study. Anticancer Res 2015; 35:1311–9
4. Jiang S, Liu Y, Huang L, Zhang F, Kang R: Effects of propofol on cancer development and chemotherapy: Potential mechanisms. Eur J Pharmacol 2018; 831:46–51
5. Kim R: Anesthetic technique and cancer recurrence in oncologic surgery: Unraveling the puzzle. Cancer Metastasis Rev 2017; 36:159–77
6. Jaura AI, Flood G, Gallagher HC, Buggy DJ: Differential effects of serum from patients administered distinct anaesthetic techniques on apoptosis in breast cancer cells *in vitro*: A pilot study. Br J Anaesth 2014; 113 Suppl 1:i63–7
7. Baki ED, Aldemir M, Kokulu S, Koca HB, Ela Y, Sıvacı RG, Öztürk NK, Emmiler M, Adalı F, Uzel H: Comparison of the effects of desflurane and propofol anesthesia on the inflammatory response and s100β protein during coronary artery bypass grafting. Inflammation 2013; 36:1327–33
8. Liu S, Gu X, Zhu L, Wu G, Zhou H, Song Y, Wu C: Effects of propofol and sevoflurane on perioperative immune response in patients undergoing laparoscopic radical hysterectomy for cervical cancer. Medicine (Baltimore) 2016; 95:e5479
9. Liu TC: Influence of propofol, isoflurane and enflurance on levels of serum interleukin-8 and interleukin-10 in cancer patients. Asian Pac J Cancer Prev 2014; 15:6703–7
10. Yap A, Lopez-Olivo MA, Dubowitz J, Hiller J, Riedel B; Global Onco-Anesthesia Research Collaboration Group: Correction to: Anesthetic technique and cancer outcomes: A meta-analysis of total intravenous *versus* volatile anesthesia. Can J Anaesth 2019; 66:1007–8
11. Yamana H, Moriwaki M, Horiguchi H, Kodan M, Fushimi K, Yasunaga H: Validity of diagnoses, procedures, and laboratory data in Japanese administrative data. J Epidemiol 2017; 27:476–82
12. Quan H, Li B, Couris CM, Fushimi K, Graham P, Hider P, Januel JM, Sundararajan V: Updating and validating the Charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. Am J Epidemiol 2011; 173:676–82
13. Austin PC: Using the standardized difference to compare the prevalence of a binary variable between two groups in observational research. Commun Stat Simul Comput 2009; 38:1228-34
14. Newhouse JP, McClellan M: Econometrics in outcomes research: The use of instrumental variables. Annu Rev Public Health 1998; 19:17–34
15. Staiger D, Stock JH: Instrumental variables regression with weak instruments. Econometrica 1997; 65:557
16. Huang H, Benzonana LL, Zhao H, Watts HR, Perry NJ, Bevan C, Brown R, Ma D: Prostate cancer cell malignancy via modulation of HIF-1α pathway with isoflurane and propofol alone and in combination. Br J Cancer 2014; 111:1338–49
17. Ciechanowicz S, Zhao H, Chen Q, Cui J, Mi E, Mi E, Lian Q, Ma D: Differential effects of sevoflurane on the metastatic potential and chemosensitivity of non-small-cell lung adenocarcinoma and renal cell carcinoma *in vitro*. Br J Anaesth 2018; 120:368–75
18. Iwasaki M, Zhao H, Jaffer T, Unwith S, Benzonana L, Lian Q, Sakamoto A, Ma D: Volatile anaesthetics enhance the metastasis related cellular signalling including CXCR2 of ovarian cancer cells. Oncotarget 2016; 7:26042–56
19. Yang C, Gao J, Yan N, Wu B, Ren Y, Li H, Liang J: Propofol inhibits the growth and survival of gastric cancer cells *in vitro* through the upregulation of ING3. Oncol Rep 2017; 37:587–93
20. Yang N, Liang Y, Yang P, Ji F: Propofol suppresses LPS-induced nuclear accumulation of HIF-1α and tumor aggressiveness in non-small cell lung cancer. Oncol Rep 2017; 37:2611–9
21. Soltanizadeh S, Degett TH, Gögenur I: Outcomes of cancer surgery after inhalational and intravenous anesthesia: A systematic review. J Clin Anesth 2017; 42:19–25
22. Wigmore TJ, Mohammed K, Jhanji S: Long-term survival for patients undergoing volatile *versus* IV anesthesia for cancer surgery: A retrospective analysis. Anesthesiology 2016; 124:69–79
23. Yoo S, Lee HB, Han W, Noh DY, Park SK, Kim WH, Kim JT: Total intravenous anesthesia *versus* inhalation anesthesia for breast cancer surgery: A retrospective cohort study. Anesthesiology 2019; 130:31–40
24. Zheng X, Wang Y, Dong L, Zhao S, Wang L, Chen H, Xu Y, Wang G: Effects of propofol-based total intravenous anesthesia on gastric cancer: A retrospective study. Onco Targets Ther 2018; 11:1141–8
25. Enlund M, Berglund A, Andreasson K, Cicek C, Enlund A, Bergkvist L: The choice of anaesthetic–sevoflurane or propofol–and outcome from cancer surgery: A retrospective analysis. Ups J Med Sci 2014; 119:251–61
26. Lousdal ML: An introduction to instrumental variable assumptions, validation and estimation. Emerg Themes Epidemiol 2018; 15:1
27. Swanson SA, Miller M, Robins JM, Hernán MA: Definition and evaluation of the monotonicity condition for preference-based instruments. Epidemiology 2015; 26:414–20