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ORIGINAL ARTICLE

The association between intraoperative anesthesia methods used during gastric cancer surgery and long-term mortality: A retrospective observational study using a Japanese claims database

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Abstract

Purpose Various basic and clinical studies have investigated the association between the types of anesthetic agents and prognosis. However, the results have varied among studies and remain controversial. In the present study, we aimed to investigate whether the risk of all-cause mortality differs between inhaled or intravenous anesthetics in patients with gastric cancer undergoing gastrectomy.

Methods Using a Japanese nationwide insurance claims database, we analyzed patients who underwent gastrectomy under general anesthesia for gastric cancer between January 2005 and September 2019. Postoperative outcomes were compared between two groups: those who received inhaled anesthetics (Sevoflurane, Isoflurane, or Desflurane) and those who received intravenous anesthetics (propofol), using a multivariable Cox proportional hazards model. The primary outcome was overall survival.

Results Among 2671 eligible patients, 2105 were in the inhaled anesthetic group, and 566 were in the intravenous anesthetic group. The median (interquartile range) age was 58 (51–63) years, and 1979 (74.1%) were men. The median follow-up period was 795 days. We identified 56 (2.7%) and 16 (2.8%) deaths during the follow-up period in the inhaled and intravenous anesthetic use groups, respectively. There was no difference in postoperative overall survival between the two groups (hazard ratio, 0.97; 95% confidence interval, 0.56–1.70; $P = 0.93$).

Conclusions We found no significant difference in the postoperative risks of overall survival between inhaled and intravenous anesthesia in patients with gastric cancer undergoing gastrectomy.

Keywords Anesthesia · Gastric cancer · Gastrectomy · Mortality

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Introduction

Gastric cancer is a significant health problem because it is globally the fifth most common cancer and the third most common cause of cancer death [1, 2]. The primary treatment for non-early operable gastric cancer is surgery [2]. General anesthesia is essential for surgical procedures, and there are two main anesthetic methods for maintaining general anesthesia: inhalational and intravenous.

Recently, an association between perioperative anesthetics and postoperative outcomes has been discussed. A review article suggests that certain anesthetics act as a prognostic factor based on retrospective human studies [3]. Preclinical studies indicated that propofol decreased the invasion ability of human cancer cells [4] or that propofol inhibited hypoxia-inducible factor (HIF)-1 activation and downstream gene expression induced by lipopolysaccharide (LPS) and suppressed HIF-1-dependent glucose metabolic reprogramming [5]. A systematic review of animal experiments revealed that volatile anesthetics increase the number and risk of metastases [6]. A recent systematic review and meta-analysis showed that all-cause mortality and recurrence-free survival, regardless of cancer type or stages, favored total intravenous anesthesia (TIVA) compared with inhalational anesthesia [7]. However, the subgroup analysis among different cancer types did not show any remarkable difference in mortality between the groups. The paper concluded that clinical studies are further needed in each cancer type to substantiate the role of anesthesia in cancer surgery prognosis [7]. Information on the association between anesthetics used during surgery and the postoperative prognosis of gastric cancer remains limited.

We hypothesized that there would be an increased postoperative all-cause mortality on gastrectomy for patients with gastric cancer in the inhaled anesthetic group compared with the intravenous group. The present study aims to clarify the association between all-cause mortality and anesthetics used for gastric cancer patients during gastrectomy.

Methods

Informed consent was waived because of the anonymous nature of the data. The present study was approved by the Institutional Review Board at the Kyoto University Graduate School and the faculty of medicine (Approval number: R0807) on 8 September 2016. This manuscript complies with the applicable Strengthening the reporting of observational studies in epidemiology (STROBE) guidelines [8].

We conducted the retrospective observational study using a Japanese nationwide insurance claims database provided by JMDC Inc (Tokyo, Japan). As of September 2021, the total number of patients in the database was 13 million. The claims data include information from 2005 on patient enrollment, medical facilities, diagnoses, procedures, drugs and materials, annual health checkups, and the costs for each visit. The database includes the following information: patient characteristics (age and sex); diagnostic codes using the International Classification of Diseases 10th revision (ICD-10); claims of inpatient, outpatient, and pharmacy, including drugs, diagnostic tests, and procedures with Japanese standardized procedure codes. In this database, we can identify prescribed drugs by Anatomical Therapeutic Chemical (ATC) codes. The database can track patient data in chronological order, whichever hospital the patient has visited or has been hospitalized [9]. Most people in the database were 65 years of age or younger because most people retire from their jobs and leave company insurance plans at 65 years in Japan. In addition, the database included no people equal to or older than 75 because people automatically enter the public health insurance plan for older people at the age of 75.

In this study, we identified patients aged ≥ 20 admitted for gastric cancer according to ICD 10 codes C16.0–C16.9 and underwent gastrectomy under general anesthesia from 1 January 2005 to 30 September 2019. We used original Japanese-specific standardized procedure codes to identify surgery, anesthesia, and radiation therapy (online supplementary Table 1). The exclusion criteria are patients with end-stage cancer of any origin, patients who received systemic corticosteroids or immunosuppressants, underwent radiation therapy or chemotherapy within 180 days before the surgery, received inhalational anesthesia and propofol > 500 mg, or received neither inhalation anesthesia nor propofol > 500 mg during surgery. These judgments were made according to the ATC codes of each patient (online supplementary Table 2).

Patients were classified in the inhalational anesthesia group when they received Sevoflurane, Isoflurane, or Desflurane during surgery without receiving propofol > 500 mg. Patients receiving propofol > 500 mg without inhalational anesthesia were classified into the intravenous anesthesia group. We set a cut-off of propofol ≤ 500 mg because the largest vial contains 500 mg of propofol, and it may be used for induction only rather than maintenance if the amount of propofol is small.

The primary outcome was overall survival. Patients were followed up from the surgery date to the date of death, the last visit, five years after inclusion, or 30 September 2019, which came first. In addition, because of the nature of this database, patient follow-up was censored if they left the company and health insurance plan.

The characteristics of the study population were summarized with medians and interquartile ranges (IQR) for

continuous variables and numbers and proportions for categorical variables. Mann–Whitney *U* test was used for continuous variables, and Pearson's chi-square test for categorical variables. The probability of overall survival was assessed using the Kaplan–Meier method and the log-rank test. A multivariable Cox proportional hazards analysis was performed to estimate the adjusted hazard ratio (HR) and 95% confidence interval (CI). We included the following covariates in the model: age, sex, Charlson Comorbidity Index (CCI) [10], use of laparoscopic surgery, use of epidural anesthesia, and the number of hospital beds (< 500 or ≥ 500), which means the volume of each hospital. On the other hand, we did not include the following variables in the model because they may have been conducted after surgery: use of intensive care unit, use of mechanical ventilation, use of blood transfusion, and postoperative chemotherapy. We picked up patients who claimed these codes on the day or months of surgery (online supplementary Table 1). All analyses were performed using SAS 9.4 for Windows (SAS Institute Inc; Cary, NC). All statistical tests were two-sided, and *P* values of < 0.05 were considered statistically significant.

Results

Of 3968 patients who met the inclusion criteria, 1297 were excluded, and 2671 were analyzed (Fig. 1). Among them, 566 patients received intravenous anesthesia, and 2105 received inhalational anesthesia. The median follow-up period (IQR) was 795 (334–1494) days.

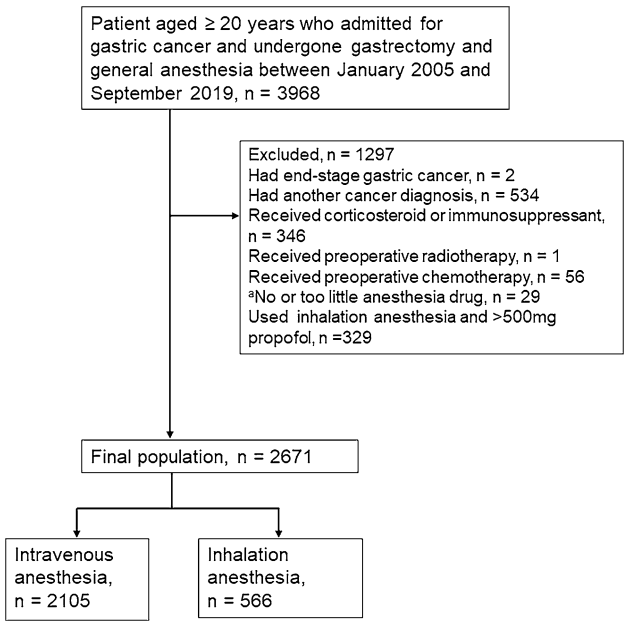

Fig. 1 Flowchart of the study. [a]Patients were excluded if they did not receive inhalation anesthesia, and propofol used was ≤ 500 mg

Patient characteristics

Patient characteristics are presented in Table 1. The median (IQR) age was 58 (51–63) years, and 1979 (74.1%) were men. Comorbidities were almost similar between the two groups. The intravenous anesthesia group included fewer men and more epidural anesthesia

Table 1 Patient characteristics of the two groups

	Intravenous group (*n* = 566)	Inhalation group (*n* = 2105)	*P* value
Age (year)	57 (50, 63)	59 (52, 63)	0.03
Age group (year)			
< 60	334 (59)	1160 (55)	0.10
60–69	197 (35)	796 (38)	0.19
≥ 70	35 (6.2)	149 (7.1)	0.46
Sex (M)	374 (66)	1605 (76)	< 0.001
CCI			
2	134 (24)	453 (22)	0.27
3	261 (46)	893 (42)	0.12
4	106 (19)	456 (22)	0.13
≥ 5	65 (12)	303 (14)	0.08
Comorbidities			
Myocardial infarction	3 (0.5)	25 (1.2)	0.17
Chronic heart failure	34 (6.0)	158 (7.5)	0.22
Diabetes w/o complications	48 (8.5)	175 (8.3)	0.90
Diabetes with complications	17 (3.0)	94 (4.5)	0.12
Cerebrovascular disease	31 (5.5)	148 (7.0)	0.19
Chronic lung disease	73 (13)	285 (14)	0.69
Rheumatic disease	8 (1.4)	19 (0.9)	0.28
Epidural anesthesia	477 (84)	1597 (76)	< .0001
Opioid use	566 (100)	2099 (99)	0.20
Procedures			
Laparoscopic surgery	323 (57)	1173 (56)	0.57
Total gastrectomy	130 (23)	467 (22)	0.69
Intensive care unit use	60 (11)	256 (12)	0.31
Mechanical ventilation	6 (1.1)	8 (0.4)	0.05
Transfusion	33 (5.8)	87 (4.1)	0.08
Post-operative chemotherapy			
5-FU	115 (20)	402 (19)	0.51
Imatinib	8 (1.4)	15 (0.7)	0.11
Others	21 (3.7)	89 (4.2)	0.58
Number of hospital beds, ≥ 500	340 (60)	1163 (55)	0.04

Values are presented as median (interquartile range) or *n* (%)

IQR interquartile range, *CCI* Charlson comorbidity index, *FU* fluorouracil

than the inhalation anesthesia group. Opioid use and procedural characteristics, including laparoscopic surgery and total gastrectomy, were similar between the two groups. Mechanical ventilation was less frequent in the inhalation anesthesia group than in the intravenous anesthesia group; however, the absolute number of patients was small. Also, postoperative chemotherapy, except for imatinib, was similarly conducted (Table 1).

Multivariable Cox proportional hazard analysis

The Kaplan–Meier curves are shown in Fig. 2. During the follow-up, 16 (2.8%) and 56 (2.7%) died in the intravenous and inhalational anesthesia groups. Both in unadjusted and adjusted analyses, overall survival was not significantly different between the two groups (unadjusted HR: 1.00, 95%CI: 0.58–1.75; adjusted HR: 0.97, 95% CI: 0.56–1.70, *P* value: 0.93) (Table 2).

Discussion

Using a Japanese nationwide insurance claims database, we investigated the association between overall survival after gastrectomy and anesthetics used during surgery. The type of anesthetic agents used during surgery was not associated with postoperative overall survival in patients with gastric cancer.

In previous in vitro study on renal cancer, it has been suggested that isoflurane may promote the amplification of HIF-1α, which plays a crucial role in the central features of oncogenesis, including angiogenesis, invasion, metastasis, and anti-apoptosis [11]. In addition, HIF-1α overexpression is associated with increased mortality in patients with gastric cancer [12]. Propofol has been shown to suppress transcription factor activity of the androgen receptor, which is essential for prostate cancer growth [13]. One study also reported that propofol inhibits the growth and metastasis of gastric cancer cells and promotes apoptosis [14]. However, these findings are based on in vitro study, and clinical studies are imperative to validate the relationship.

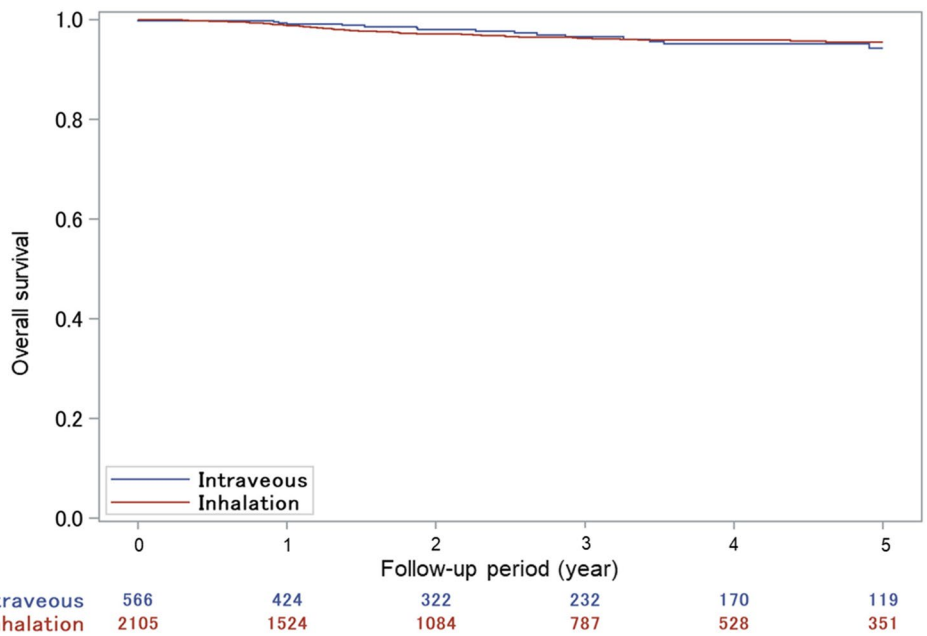

Fig. 2 Kaplan–Meier curves for the overall survival. During the follow-up, 16 (2.8%) and 56 (2.7%) died in the intravenous anesthesia and inhalation anesthesia groups, respectively. The median follow-up period (interquartile range) was 795 (334–1494) days

Table 2 Overall survival of the two groups

	n (%)	Unadjusted HR (95% CI)	Adjusted HR[a] (95% CI)	*P* value
Intravenous (*n* = 566)	16 (2.8)	Reference	Reference	Reference
Inhalation (*n* = 2105)	56 (2.7)	1.00 (0.58–1.75)	0.97 (0.56–1.70)	0.93

[a]These models were adjusted with the following covariates: age, sex, Charlson comorbidity index, epidural anesthesia, laparoscopic surgery, and the number of hospital beds (≥ 500)

HR hazard ratio, *CI* confidence interval

There are many clinical studies on the association between the type of anesthetics and postoperative prognosis. A large cohort study including 7,000 patients with various types of cancer has reported differences in postoperative survival between inhalation anesthesia and TIVA [15]. Although the study described that overall survival was significantly higher in the TIVA group, there was no association between anesthetics and prognosis for gastrointestinal cancer. Regarding gastric cancer, clinical studies have conflicting results. One study reported a better overall survival with TIVA than with desflurane anesthesia [16]. Another represented no significant difference between TIVA and inhalation anesthesia for postoperative outcomes in gastric cancer patients [17]. Thus, the relevance of anesthetics to patients' prognosis for gastric cancer surgery remains controversial.

In recent years, analysis using big data has been attracting attention. In a large cohort study using the Japanese Diagnosis Procedure Combination database (DPC database), there was no significant difference in postoperative prognosis for digestive cancers depending on the type of anesthetic [18]. The present study used a Japanese nationwide insurance claims database (JMDC claims). JMDC claims allow tracking of mortality outcomes even if patients transfer to different hospitals. Therefore, JMDC claims have a higher traceability than other databases [19]. Moreover, JMDC claims also include data from non-DPC hospitals, thus comprising a more diverse range of healthcare organizations. To our best knowledge, the present study is the first large cohort study using the JMDC claims that investigated overall survival after gastrectomy for gastric cancer according to the type of anesthetic agents used during surgery.

The present study has several limitations. First, due to the nature of retrospective observational studies and administrative claims data, we could not include clinical information such as performance status and cancer stage in our data set. However, we tried to minimize the selection and confounding biases by excluding the end-stage cancer patients and patients who had received preoperative radiotherapy or chemotherapy from the study population. We also adjusted data with confounders, including CCI that reflects general conditions. Second, we could not track patients in the database when the patients retired from employment. Therefore, most of the patients in the present study were under the age of 70, which lowered the external validity of the present study. Third, due to the nature of the database, information on intra-operative fluid administration, blood transfusion, duration of surgery, preoperative frailty status, body mass index, smoking history, and alcohol consumption is not available.

In conclusion, the present study using JMDC claims showed no significant difference in overall survival after curative gastrectomy between intravenous and volatile anesthesia.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00540-023-03288-z.

Author contributions Conceptualization: [Tomoko Kagawa, Kiyoyasu Kurahashi, Tomotsugu Seki, Isao Nahara, Chikashi Takeda, Hiroshi Yonekura, Koji Kawakami]; Methodology: [Tomoko Kagawa, Kiyoyasu Kurahashi, Tomotsugu Seki, Yohei Kawasaki, Isao Nahara, Chikashi Takeda, Hiroshi Yonekura, Shiro Tanaka, Koji Kawakami]; Formal analysis and investigation: [Tomoko Kagawa, Tomotsugu Seki]; Writing—original draft preparation: [Tomoko Kagawa, Tomotsugu Seki]; Writing—review and editing: [Tomoko Kagawa, Kiyoyasu Kurahashi, Tomotsugu Seki]; Funding acquisition: [Kiyoyasu Kurahashi, Koji Kawakami]; Resources: [Kiyoyasu Kurahashi, Koji Kawakami]; Supervision: [Kiyoyasu Kurahashi].

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Data availability Data distribution is prohibited due to the contract with the data provider (JMDC Inc.).

Declarations

Conflict of interest Koji Kawakami received advisory fees from Shin Nippon Biomedical Laboratories, Ltd, Japan; JMDC Inc., Japan; LEBER Inc., and CICS, Japan; research funds from Eisai, Kyowa Kirin, and Real World Data, Co, Ltd, Japan; and held stock of Real World Data, Co, Ltd, Japan. Kiyoyasu Kurahashi receives advisory fees from Masimo Corporation Japan, Japan, and research funds from the International University of Health and Welfare, Japan, Maruishi Pharmaceutical Co. Ltd., MSD K.K., Japan, and Japan Blood Products Organization, Japan. Other authors have no direct or indirect conflicts of interest.

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