Volatile anesthesia versus propofol-based total intravenous anesthesia
A retrospective analysis of charts of patients who underwent elective digestive tract cancer curative surgeries

Ying Zhang, MD, Fang Wang, MD, Hui Zhang, MD, Yulong Wei, MD, Yanan Deng, MD, Dezhi Wang, MD*

Abstract
The surgical stress responses, surgeries, and anesthetics used during surgeries have effects on post-surgery complications and metastasis. Volatile and/or intravenous anesthetics are generally used for cancer curative surgeries. Therefore, appropriate selection of anesthetics should be considered for better clinical outcomes. The objectives of the study were to compare postoperative complications, the overall survival, and recurrence-free survival of patients who had received volatile anesthesia against those of patients who had received propofol-based total intravenous anesthesia for digestive tract cancer curative surgeries. Patients had received propofol-based total intravenous anesthesia (PA cohort, n = 120) or volatile anesthesia (VA cohort, n = 185) for elective digestive tract cancer curative surgeries. Patients with age > 50 years (P = .0399), body mass index ≥ 25 kg/m² (P = .0423), cancer stage III (P = .0041), and cancer stage IV (P = .0189) were operated through volatile anesthesia. Females (P = .0346), disabled patients (P = .0479), patients with Charlson Comorbidity Index 2 (P = .0449), patients with cancer stage 0 or I (P = .0141), and patients with cancer stage II (P = .0289) were operated through propofol-based total intravenous anesthesia. Postoperative complication(s) between patients of both cohorts were statistically same (P = .9217). After 3-years of the follow-up period, a total of 81 (44%) patients from the VA cohort and 63 (52%) patients from the PA cohort survived irrespective of any kind of disease(s) (P = .9918). Also, a total of 53 (29%) patients from the VA cohort and 42 (35%) patients from the PA cohort survived without progression of cancer (P = .9981) after 3-years. Age > 50 years (P = .0491), Charlson Comorbidity Index ≥ 3 (P = .0481), and cancer stage > II (P = .0412) were independent parameters for death of patients suffering from digestive tract cancer due to any reason(s) during 3-years of the follow-up period after surgeries. The selection of anesthetic agents for cancer curative surgeries does not affect survival during 3-years of follow-up and postoperative complication(s) of patients suffering from digestive tract cancer (Level of Evidence: III; Technical Efficacy Stage: 4).

Abbreviations: CI = confidence interval, PA cohort = patients had received propofol-based total intravenous anesthesia for digestive tract cancer curative surgeries, SD = standard deviation, VA cohort = patients had received volatile anesthesia for digestive tract cancer curative surgeries. χ²-test = chi-square test of independence.

Keywords: cancer curative surgery, digestive tract cancer, postoperative complication, propofol, survival, volatile anesthesia

1. Introduction
Cancer is a major cause of death worldwide and cancer associated death is occurred due to metastasis. Curative surgeries are generally done for the removal of solid tumors. Also, advancement in surgical techniques can lead to decrease postoperative death. Volatile and/or intravenous anesthetic agents are generally used for the maintenance of anesthesia in cancer surgeries. These agents enhance the activity of cancer cells by suppression of the immune system, modulating stress response to surgeries, and cancer cell signalling. However, propofol has demonstrated antitumor effects during oncological surgeries and has improved survival and recurrence-free survivals. Clinical studies have demonstrated conflicting effects of anesthetic agent(s) on peri-and post-operative parameters.

The authors have no funding and conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

Department of Anesthesiology, Honghui Hospital, Xi’an Jiaotong University, Xi’an, Shaanxi Province, China.

*Correspondence: Dezhi Wang, Department of Anesthesiology, Honghui Hospital, Xi’an Jiaotong University, Xi’an 710064, Shaanxi Province, China (e-mail: dezhi.wang12@gmail.com).

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Although advances in cancer treatment, curative surgeries are the first-line treatment for digestive tract cancers. The surgical stress responses, surgeries, and anesthetics used during surgeries have effects on post-surgery complications and metastasis. Therefore, appropriate selection of anesthetics should be considered for better clinical outcomes.

The objectives of the retrospective study were to compare post-operative complications, recurrence-free survival, and overall survival during follow-up of 3-years of patients who had received volatile anesthesia (isoflurane, sevoflurane, or desflurane) against those of patients who had received propofol-based total intravenous anesthesia for elective digestive tract cancer curative surgeries.

2. Materials and Methods

2.1. Ethics approval and consent to participate

The study was a retrospective review of charts of patients who underwent elective digestive tract cancer curative surgeries. Therefore, approval of the protocol, registration in the Chinese trial registry, and patient’s consent was waived by the Honghui hospital review board. The study adheres to the law of China and the V2008 Declarations of Helsinki.

2.2. Inclusion criteria

Patients who received either volatile anesthesia or propofol-based total intravenous anesthesia for digestive tract cancer curative surgeries were included in the analysis.

2.3. Exclusion criteria

Patients who had received combined anesthesia were excluded from analysis.

2.4. Clinical information

Demographical and clinical characteristic before surgeries, preoperative, perioperative, and postoperative parameters for curative cancer surgeries, recurrence-free survival, and overall survival of patients during follow-up of 3-years were collected for analysis.

2.5. Cohorts

A total of 185 patients had received volatile anesthesia (isoflurane, sevoflurane, or desflurane) for digestive tract cancer curative surgeries (VA cohort) and 120 patients had received propofol-based total intravenous anesthesia for digestive tract cancer curative surgeries (PA cohort).

2.6. Anesthesia induction and maintenance

No medication was given before anesthesia induction. Routine monitoring was performed. In the VA cohort, fentanyl and rocuronium were induced. Then patients were intubated and maintained with volatile anesthesia (isoflurane, sevoflurane, or desflurane) with oxygen flow. In the PA cohort, anesthesia was maintained using target-controlled infusion with an effective concentration of propofol with oxygen flow. Bolus injections of cisatracurium and fentanyl were given if required.

2.7. Demographical and clinical characters

Age, gender, body mass index, cancer stage, Barthel Index, and Charlson Comorbidity Index of patients before surgeries were collected.

2.7.1. Barthel Index

It includes 10 items of mobility and self-care functions. It is ranged from 0 to 100. Fewer the score the higher disability. A score of 95 or more is considered normal or no disability.

2.7.2. Charlson Comorbidity Index

It is used to measure the comorbidities of hospitalized patients. Higher the score, higher comorbidities.

2.7.3. Survivals

2.7.3.1. Recurrence-free survival

After the cure of patients, the time for further development of cancer (metastasis).

2.7.3.2. Overall survival

The time from detection of cancer to death.

2.7.3.3. Postoperative complication

Any complication after surgery.

2.8. Statistical analysis

The sample size was calculated based on assumption that after 3-years of follow-up at least 30% of patients were survived, for 0.05 type-I error and 0.1 type-II error, the sample size (minimum patients required in each cohort) was 110. InStat, 3.01, GraphPad Software, San Diego, CA, USA was used for statistical analysis purpose. Unpaired t test was used for none variables parameters and the Fisher exact test (when the size of compared classes was 2), or the chi-square test of independence (χ²-test; when the size of compared classes was more than 2) for variables parameters were performed for purposes of statistical analysis. Univariate following multivariate analysis were performed for evaluation of independent parameters for the death of patients. All results were considered significant if a P value was less than .05.

3. Results

3.1. Study population

From September 15, 2017 to January 1, 2018, a total of 322 patients more than 18 years of age underwent digestive tract cancer curative surgeries at the department of surgery of the Honghui Hospital, Xi’an, Shaanxi, China, and the referring hospitals. A total of 305 patients received either volatile anesthesia or propofol-based total intravenous anesthesia. A total of 17 patients had received combined anesthesia. Therefore, clinical information of a total of 305 patients was collected from the patients’ medical records of the hospitals. The flow diagram of the retrospective study is presented in Figure 1.

3.2. Demographical and clinical characters

All patients had Charlson Comorbidity Index ≥ 2. There were no significant differences for mean age, smoking habits, mean body mass index, mean Barthel Index, numbers of patients with Charlson Comorbidity Index ≥ 3, numbers of patients who had received preoperative adjuvant therapy, numbers of patients who had received preoperative renal replacement therapy, type of surgery, and postoperative blood transfusion between patients of both cohorts (P > .0500 for all, χ²-test, Fisher test, or t test).

Higher numbers of patients with age more than 50 years had received volatile anesthesia (P = .0399, Fisher test). Female patients were operated mostly through propofol-based total intravenous anesthesia (P = .0346, Fisher test). Patients who were overweight (body mass index ≥ 25 kg/m²) were operated mostly through volatile anesthesia (P = .0423, Fisher test). Disable patients (Barthel Index < 95) were operated on mostly through propofol-based total intravenous anesthesia (P = .0479, Fisher test). Patients with Charlson Comorbidity Index 2 were...
operated mostly through propofol-based total intravenous anesthesia \((P = .0449, \text{Fisher test})\). Cancer stage 0 or I \((P = .0141, \text{Fisher test})\) and II \((P = .0289, \text{Fisher test})\) were operated mostly through propofol-based total intravenous anesthesia. Cancer stage III \((P = .0041, \text{Fisher test})\) and IV \((P = .0189, \text{Fisher test})\) were operated mostly through volatile anesthesia. Higher numbers of patients had received postoperative adjuvant therapy who were operated through propofol-based total intravenous anesthesia. Higher numbers of patients had received postoperative adjuvant therapy who were operated through propofol-based total intravenous anesthesia \((P = .0321, \text{Fisher test})\). Patients of the VA cohort have received epidural anesthesia \((P = .0323, \text{Fisher test})\) and preoperative opioid(s) \((P = .0415, \text{Fisher test})\). The details of demographical and clinical characters before surgeries, preoperative, perioperative, and postoperative parameters of curative surgeries are reported in Table 1. All patients were sent to the post-anesthesia care unit or surgical intensive care unit at least for 1 day. The reason for more epidural anesthesia and opioid in the VA cohort were the demographical and clinical characters of patients.

3.3. Survival

After 3-years of the follow-up period, a total of 81 (44\%) patients from the VA cohort and 63 (52\%) patients from the PA cohort survived irrespective of any kind of disease(s). There was no significant difference between overall survived patients between both cohorts \((P = .9918, t \text{ test})\). Also, the overall survival curves of both patients were not crossed during 3-years of follow-up. The overall survival curves of patients are reported in Figure 2.

After 3-years of the follow-up period, a total of 53 (29\%) patients from the VA cohort and 42 (35\%) patients from the PA cohort survived without progression of cancer. There was no significant difference between overall survived patients between both cohorts \((P = .9981, t \text{ test})\). Also, progression-free survival curves of both patients were not crossed during 3-years of follow-up. The progression-free survival curves of patients are reported in Figure 3.

3.4. Association of parameters for the death of patients

Older patients, patients with Charlson Comorbidity Index ≥ 3, and patients with cancer stage >II had the risk of death due to any reason but the type of anesthesia (volatile or propofol-based total intravenous) was not associated with the death of patients during 3-years of the follow-up period (Table 2).

3.5. Postoperative complication(s)

There were no significant differences for postoperative complication(s) within the hospital and 3-years of follow-up between patients of both cohorts.

4. Discussion

The current study found that type of anesthesia did not affect the death of patients during the 3-years follow-up period. The results of the death during follow-up of the current study were consistent with retrospective cohort studies\(^1\) and a retrospective cohort study on breast cancer surgeries\(^14\) but not consistent with a meta-analysis\(^1\) retrospective analyses,\(^10,11,15\) and in vitro study on breast cancer women.\(^16\) The reason for the contradictory results of the current study with a meta-analysis\(^1\) is that besides esophageal cancer surgeries, a meta-analysis\(^1\) was
included studies on curative surgeries regarding breast cancer and non-small cell lung cancer. The reason for the contradictory results of the current study with a retrospective analysis [10] is that a retrospective analysis [10] was performed with curative surgeries on esophageal cancer. In contrast, the current study was performed on curative surgeries with all types of gastric cancer. Propofol has only protective effects on esophageal squamous cell carcinoma. [16] The reasons for contradictory results of the current study with retrospective analyses [11,15] are that retrospective analyses [11,15] were included colonoscopies under

| Characteristics | Cohorts | Comparisons |
|----------------|---------|-------------|
| **Anesthesia method** | Isoflurane, sevoflurane, or desflurane | Propofol-based total intravenous |
| Numbers of patients | 185 | 120 |
| Age (yr) | | | |
| =50 | 61 (33) | 54 (45) | .0399 (Fisher test) 0.6651–0.9941 N/A |
| >50 | 124 (67)* | 66 (55) | |
| Minimum | 44 | 44 | .2531 (t test) -1.430 to 4.3230 303 |
| Maximum | 68 | 68 | |
| Mean ± SD | 55.22 ± 11.15 | 56.81 ± 12.85 | |
| Gender | | | |
| Male | 111 (60) | 57 (48) | .0346 (Fisher test) 1.0131–1.4771 N/A |
| Female | 74 (40) | 63 (52)* | |
| Smoking habit | | | |
| No smoker | 126 (68) | 67 (56) | .0888 (χ²-test) N/A 2 |
| Previous smoker | 44 (24) | 38 (32) | |
| Current smoker | 15 (8) | 15 (12) | |
| Body mass index (kg/m²) | | | |
| =25 | 103 (55) | 81 (68) | .0423 (Fisher test) 0.6921–0.9871 N/A |
| Mean ± SD | 25.12 ± 2.85 | 24.81 ± 2.15 | .3094 (t test) -0.9092 to 0.2892 303 |
| Barthel Index | | | |
| =95 | 40 (22) | 15 (13) | .0479 (Fisher test) 1.0341–1.5211 N/A |
| Mean ± SD | 145 (78) | 105 (88)* | .0811 (t test) -7.1517 to 40.4142 303 |
| Charlson Comorbidity Index | | | |
| 2 | 93 (50) | 75 (63)* | .0449 (Fisher test) 0.6891–0.9861 N/A |
| 3 | 75 (41) | 37 (31) | .0903 (Fisher test) 0.9831–1.4051 N/A |
| =4 | 17 (9) | 8 (6) | .5243 (Fisher test) 0.9561–1.6111 N/A |
| Cancer stage | | | |
| 0 or I | 122 (66) | 95 (79)* | .0141 (Fisher test) 0.6581–0.9371 N/A |
| II | 30 (16) | 21 (17)* | .0289 (Fisher test) 0.5771–0.9981 N/A |
| III | 18 (10)* | 2 (2) | .0041 (Fisher test) 1.2881–1.8311 N/A |
| IV | 15 (8)* | 2 (2) | .0191 (Fisher test) 1.2261–1.8231 N/A |
| Preoperative adjuvant therapy | 15 (8) | 11 (9) | |
| Postoperative adjuvant therapy | 67 (36) | 59 (49)* | .0321 (Fisher test) 0.6641–0.9801 N/A |
| Preoperative renal replacement therapy | 3 (2) | 1 (1) | .9999 (Fisher test) 0.6991–2.1991 N/A |
| Type of surgery | | | |
| Gastrectomy | 48 (26) | 38 (32) | .6929 (χ²-test) N/A 6 |
| Colectomy | 42 (23) | 33 (27) | |
| Hepatectomy | 31 (17) | 18 (15) | |
| Rectal cancer surgery | 22 (12) | 12 (10) | |
| Pancreatctomy | 19 (10) | 10 (8) | |
| Choledoctectomy | 15 (8) | 6 (5) | |
| Esophagectomty | 8 (4) | 3 (3) | |
| Epidural anesthesia use (s) | 47 (25)* | 18 (15) | .0323 (Fisher test) 1.0441–1.5141 N/A |
| Preoperative opioid (s) | 44 (24)* | 17 (14) | .0415 (Fisher test) 1.0331–1.5081 N/A |
| Postoperative blood transfusion | 3 (2) | 1 (1) | .9999 (Fisher test) 0.6991–2.1991 N/A |
| Postoperative complication (s) | | | |
| Wound infection | 8 (4) | 6 (5) | .9217 (χ²-test) N/A 7 |
| Urinary tract infection | 2 (1) | 2 (2) | |
| Sepsis | 3 (2) | 2 (2) | |
| Cardiovascular problem (s) | 4 (2) | 1 (1) | |
| Pneumonia | 5 (3) | 2 (2) | |
| Anastomotic leakage | 1 (1) | 1 (1) | |
| Cerebrovascular problem (s) | 3 (2) | 1 (1) | |
| Nephrotic abnormalities | 14 (8) | 13 (11) | |

None variables parameters are depicted frequency (percentages) and variable parameters are depicted mean standard deviation (SD). Unpaired t test was performed for none variables parameters and the Fisher exact test, or the χ²-square test of independence was performed for variables parameters. All results were considered significant if a P value was less than .05.

Q = confidence interval, df = degree of freedom, N/A = not applicable, χ²-test = χ²-test of independence.

*Significantly different value.
propofol-based anesthesia which were performed in the early stage of colon cancer and included colonoscopies under volatile anesthesia which were performed on older, sicker patients with worse conditions. However, the current study had no significant differences for mean age value, Charlson Comorbidity Index ≥ 3, mean Barthel Index value, and numbers of patients who had received preoperative adjuvant therapy between patients who received propofol and those who received intravenous anesthesia. Also, looking at the retrospective analysis,[11] which showed the effects of propofol-based total intravenous anesthesia and inhalation were different, and which the current study used to calculate N, it had a larger number of patients (706 vs 657). It used propensity matching to minimize selection bias. Even after matching, its numbers of patients (579 vs 579) were much bigger than those of the current study (185 vs 120). In vitro nature and breast cancer women, the population of study [6] is reasons for contradictory results with the current study. The selection of anesthetic agents for cancer curative surgeries does not affect the survival of patients suffering from digestive tract cancer during follow-up of 3 years.

The anesthesia management (volatile or propofol based) applied in the sub-patient groups of the study (over 50 years old, female, obese, disabled patients) showed a significant difference in terms of distribution. This prevents the correct interpretation of the outputs. However, the current study only reported univariate following multivariate analysis to state the hypothesis clearly. Available published literature (for examples retrospective cohort studies[3–4,13] and retrospective analyses[10,11,15]) had performed propensity score matching analysis. Because N was already too small in the current study, it seemed hard to correct (using matching or other methods) the heterogeneity or appropriate standardization.

The current study evaluated follow-up of only 3-years. However, retrospective cohort study[3] had follow-up of 1-year, retrospective cohort study[4] had follow-up of 8-years, retrospective cohort study[10] had follow-up of 11-years, retrospective cohort study[15] had a follow-up of 90 months, retrospective cohort study[11] had a follow-up of 10-years, and retrospective cohort study[13] had a follow-up of 8-years. Types of anesthesia had effects on the survival of patients after gastric cancer surgeries but they last for 1–3 years.[3] A long follow-up period is not beneficial for the evaluation of the effects of type of anesthesia on survival after digestive tract cancer surgeries.

The current study found that age, Charlson Comorbidity Index and cancer stage were associated with the death of patients. The results of associated parameters for the death of the current study were consistent with those of a retrospective analysis[15] and another available study.[17] Older age, higher Charlson Comorbidity Index and higher cancer stage were independent parameters of death of patients suffering from digestive tract cancer.

The current study found that postoperative complication(s) between both cohorts were statistically the same. The results of postoperative complication(s) of the current study were consistent with those of retrospective studies[4,10] and in vitro studies.[5] A higher sample size of a retrospective study,[4] a

### Table 2

| Parameters | Odds ratio | 95% CI          | P value |
|------------|------------|-----------------|---------|
| Age (=50 yr vs >50 yr*) | 1.0151 | 0.9851–1.0451 | .0912   |
| Gender (male vs female) | 0.9521 | 0.9521–1.0521 | .0491   |
| Body mass index (=20 vs >25 kg/m²) | 0.9511 | 0.8021–1.0112 | .0652   |
| Barthel Index (=95 vs >95) | 0.9511 | 0.9511–1.0011 | .0011   |
| Charlson Comorbidity Index (2 vs =3*) | 1.1212 | 0.9523–1.3121 | .0481   |
| Cancer stage (=II vs >II*) | 1.1122 | 0.9521–1.3212 | .0481   |
| Anesthesia (volatile vs propofol-based total intravenous) | 0.7521 | 0.6021–0.9512 | .0481   |
| Postoperative adjuvant therapy (yes vs no) | 0.8521 | 0.7521–0.9512 | .0481   |
| Epidural anesthesia (yes vs no) | 0.9521 | 0.8021–1.1122 | .0481   |
| Preoperative opioid(s) (yes vs no) | 0.8521 | 0.7521–0.9512 | .0481   |

Multivariate analyses. An odds ratio of more than 1 and a P value less than .05 was considered significant. Overall survived patients (n = 95) were considered as reference. CI = confidence interval. *Significant parameters for death due to any reason (s).
more homogeneous population, and a much larger number of patients who underwent esophageal cancer surgery included in a retrospective study, and in vitro nature of the study are responsible for contradictory results with the current study. The current study was human study, has a small size, and underwent all types of gastric cancer curative surgeries. Unlike propofol, inhaled anesthetic had organ protective effects but these effects are short-term. Different postoperative analgesia approaches result in different effects on the stress response. This affects the primary outcome but these effects are also short-term. The anesthetic agents have fewer effects on postoperative complication(s) of patients suffering from digestive tract cancer.

The data of different studies on digestive tract cancer curative surgeries are reported in Table 3. For the independent parameters, for example, age, an odds ratio of 1.0151 is given, which is supposed to be statistically significant with a P value of .0491 (an odds ratio of more than 1 and a P value less than .05 were considered significant), but the confidence interval (0.9851–1.1212) “intersects” the value 1 and thus cannot be significant by definition. The possible justification for the same is an odds ratio can also be less than 1 and still parameter be significant. Similarly, Charlson Comorbidity Index and cancer stage were independent parameters of death of patients suffering from digestive tract cancer. The selection of anesthetic agents for surgeries does not affect the condition of patients. Although the results of this study are consistent with other retrospective studies, the study lacks features differentiated from the other studies based on digestive tract cancer surgeries. The study did not consider the surgeon or anesthesiologist factor in postoperative complications. The study did not conduct subgroup analysis for sevoflurane, desflurane, or isoflurane. Intraoperative complications were not investigated. Intraoperative complications will certainly have an impact on the survey. Lack of explanations for selection bias (demographic results, surgeons and anesthesiologist impact, etc). Death related analysis should also be focused on actual cancer-related deaths, analyzed and reported. However, it is difficult to judge actual cancer related death because in most of cases the patients died due to confound factors.

5. Conclusions

The selection of anesthetic agents for surgeries does not affect the survival of patients suffering from digestive tract cancer. Older age, higher Charlson Comorbidity Index and higher cancer stage were independent parameters of death of patients suffering from digestive tract cancer. The anesthetic agent has fewer effects on postoperative complication(s) of patients suffering from digestive tract cancer. The retrospective single-center cohort study is of exceptional value, novelty, and interest to readers because had clinical implications for the management of gastric cancer. However, the small sample size and the retrospective single-center design as well as the heterogeneous study population limit the conclusions that can be drawn from this study.
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Author contributions
Data curation: Yanan Deng, Yulong Wei.
Formal analysis: Yulong Wei.
Investigation: Fang Wang, Hui Zhang, Yanan Deng.
Methodology: Dezhi Wang, Hui Zhang, Yanan Deng, Yulong Wei.
Project administration: Ying Zhang.
Resources: Hui Zhang, Yanan Deng, Ying Zhang, Yulong Wei.
Software: Fang Wang, Ying Zhang.
Supervision: Ying Zhang.
Validation: Dezhi Wang, Hui Zhang, Fang Wang.
Writing – original draft: Dezhi Wang.
Writing – review & editing: Dezhi Wang.

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