



Carbon dioxide gas-induced pneumothorax versus one-lung ventilation in minimally invasive esophagectomy: a multicenter propensity score matching cohort study

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Background: Carbon dioxide gas-induced pneumoperitoneum might be the reason for the shorter postoperative survival of patients with malignant tumors. Whether CO₂ gas-induced pneumothorax has unfavorable impacts on the surgical and oncological outcomes of minimally invasive esophagectomy remains unclear.

Methods: Between 2010 and 2016, a total of 998 patients with squamous cell carcinoma of the esophagus who received video-assisted surgery were registered from three large-volume medical centers. The overall survival (OS) and disease-free survival (DFS) were compared after using propensity score-matched and inverse probability-weighted methods. In addition, the tumor-relapse state was evaluated, and the relapse pattern was compared.

Results: A total of 422 and 576 minimally invasive esophagectomies with intraoperative one-lung ventilation and CO₂-induced pneumothorax were enrolled, respectively. The 5-year OS and DFS were similar between the CO₂-induced pneumothorax (64.2% and 64.7%) and one-lung ventilation (65.3% and 62.4%) groups following propensity matching. The inverse probability weighting revealed similarly equal survival results in the two groups. The 5-year relapse rates were 35.1% and 30.6% in the one-lung ventilation and CO₂-induced pneumothorax groups, respectively. Moreover, the relapse patterns were not significantly different between the two groups.

Conclusion: The results of this study suggested that the use of intraoperative one-lung ventilation and CO₂-induced pneumothorax have similar oncological outcomes; therefore, the two methods are both viable options in esophagectomy.

Keywords: artificial pneumothorax, carbon dioxide, esophageal cancer, surgery

Introduction

Compared with open esophagectomy, minimally invasive approaches are preferable for operable esophageal cancer patients due to their short-term surgical benefits^[1] and comparable long-term outcomes^[2]. Carbon dioxide gas-induced pneumothorax (CO₂ pneumothorax) and one-lung ventilation

are two major methods to maintain lung collapse and therefore ensure successful procedures in the chest cavity. Intraoperative CO₂ pneumothorax is similar to artificial pneumoperitoneum but with lower gas pressures of 6–12 mmHg^[3]. Although CO₂ pneumothorax and one-lung ventilation can both provide equal surgical visualization during surgery for esophageal cancer, the influx of CO₂ might be one of the factors affecting

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tumor cell spillage and metastasis. In the LACC (Laparoscopic Approach to Cervical Cancer) trial, CO₂-induced pneumoperitoneum may have been the reason for the shorter overall survival (OS) resulting from minimally invasive radical hysterectomy^[4]. Previous studies suggested that insufflation of CO₂ could result in tumor cell metastasis^[5] and may induce tumor spillage into the peritoneal cavity^[6]. Therefore, it is hypothesized that CO₂ gas-induced pneumothorax might have unfavorable impacts on the oncological outcomes of minimally invasive esophagectomy.

Additionally, the order of surgical procedures is different in CO₂ pneumothorax compared with the one-lung ventilation setting. Using CO₂ pneumothorax, the esophagus with a cutting margin and circumferential resection margin is usually left temporarily in the chest for later removal in cervical or abdominal procedures; however, the isolated esophagus can be removed from the chest cavity immediately when using the one-lung ventilation technique. Studies have suggested that the rate of positive esophageal cancer is 8.6–83.1%^[7] in circumferential resection margins. When applying CO₂ pneumothorax, the extended exposure of esophageal samples might result in tumor cell dissemination in the pleural cavity and therefore trigger tumor relapse inside the chest, which has unfavorable effects on prognosis.

In this initial study, data from three high-volume medical centers from southeast China were analyzed to compare the oncological impacts of CO₂ pneumothorax versus one-lung ventilation. OS and DFS were compared by using propensity score matching and inverse probability of treatment propensity score weighting. Additionally, the tumor-relapse state and pattern were evaluated.

Methods

Patient cohort

Between 2010 and 2016, patients with a primary diagnosis of pathologically confirmed esophageal squamous cell carcinoma (ESCC) were retrospectively reviewed from three high-volume (> 400 esophagectomies per year) clinical centers in southeast China (names of medical centers are omitted temporarily due to the double-blind peer review policy). The esophagectomies were performed by experienced surgical teams.

The inclusive criteria were: (1) patients with pathologically diagnosed ESCC; (2) the surgical procedure was minimally invasive McKeown esophagectomy with extended 2-field lymph node dissection. Patients were excluded if: (1) they received neoadjuvant therapies; (2) patients had synchronous or metachronous second malignant cancer. The work has been reported in line with the STROCSS criteria^[8].

Covariates

General characteristics, including case ID, name, age, sex, body mass index (BMI), cancer history, pathological stage, margin state, adjuvant therapies, use of CO₂ pneumothorax or one-lung ventilation, and follow-up, were retrospectively collected. The tumors and harvested lymph nodes were restaged according to the 7th edition of the American Joint Committee on Cancer (AJCC) staging system.

HIGHLIGHTS

- The study performed a large, multicenter analysis using propensity score matching and inverse probability of treatment weight models.
- The long-term effects of carbon dioxide pneumothorax and traditional one-lung ventilation methods were similar in minimally invasive esophagectomy.
- The application of carbon dioxide pneumothorax ventilation methods is not correlated with esophageal squamous cell carcinoma relapse or different relapse patterns.
- Carbon dioxide gas-induced pneumothorax has no unfavorable impacts on the surgical and oncological outcomes of minimally invasive esophagectomy.

Objectives

The primary objective of this study was to compare the OS and DFS of surgically managed ESCC patients who underwent CO₂ pneumothorax or one-lung ventilation. A secondary objective was to determine the impacts of CO₂ pneumothorax and one-lung ventilation methods on tumor relapse both inside and outside the pleural cavity.

CO₂ pneumothorax and one-lung ventilation techniques

All patients were operated under general anesthesia with combined inhalation and intravenous methods. During one-lung ventilation, a double-lumen endotracheal tube was inserted, and the correct position was assured by auscultation and fiberoptic bronchoscopy before and after the patient was in the lateral decubitus position. Mechanical ventilation with a tidal volume (TV) of 6–8 ml/kg and respiratory rate of 12–14 bpm was used during one-lung ventilation. The FiO₂% and respiratory rate were adjusted to maintain normocapnia (partial arterial carbon dioxide pressure between 35 and 45 mmHg) and oxygen saturation (over 90%).

When using CO₂ pneumothorax, a single-lumen endotracheal tube was inserted. The CO₂ insufflation (CO₂ pressure = 6–8 mmHg)-induced artificial pneumothorax allowed two-lung ventilation during surgery and provided good exposure as well. The ventilation parameters were similar to those in the one-lung ventilation setting: a TV of 6–8 ml/kg and a respiratory rate of 12–14 bpm. The FiO₂ and respiratory rate were adjusted to maintain normocapnia and oxygen saturation.

Follow-ups

Patients were followed every 3 months postoperatively for the first 2 years and then every 6 months for 3–5 years. Additionally, annual follow-up visits were conducted 5 years postoperatively. The OS was calculated from the date of first diagnosis to the date of death or the last follow-up. The time from R0 resection to disease recurrence or death was considered DFS. Patients who lost to follow-up or who survived until the last follow-up were regarded as censored.

Statistical analysis

Distributions of patient characteristics and perioperative surgical outcomes in the one-lung ventilation or CO₂ pneumothorax groups were calculated using Pearson's chi-square (χ^2) or Fisher's exact test for categorical data and the Wilcoxon test for continuous data. All tests were two-sided, and values of $P < 0.05$ were considered statistically significant.

Table 1
Patient characteristics in CO₂ pneumothorax and one-lung ventilation groups both before and after inverse probability matching.

Characteristics	Before matching		P	After matching		P
	One-lung ventilation (N= 422)	CO ₂ pneumothorax (N= 576)		One-lung ventilation (N= 1008)	CO ₂ pneumothorax (N= 995)	
Age (mean ± SD ^a)	60.4 ± 8.2	61.3 ± 8.7	0.077	61.0 ± 8.1	61.0 ± 8.6	0.959
Gender (M/F)	311 (73.7)/111 (26.3)	422 (73.3)/154 (26.7)	0.936	755 (74.9)/253 (25.1)	729 (73.3)/266 (26.7)	0.628
pT stages			< 0.001			0.995
Tis	15 (3.6)	137 (23.8)		162 (16.1)	152 (15.3)	
T1	94 (22.3)	57 (9.9)		151 (15.0)	149 (15.0)	
T2	67 (15.9)	134 (23.3)		204 (20.2)	202 (20.3)	
T3	243 (57.6)	240 (41.7)		482 (47.8)	481 (48.3)	
T4a	3 (0.7)	8 (1.4)		9 (0.9)	11 (1.1)	
pN stages			0.128			0.968
N0	225 (53.3)	97 (42.0)		591 (58.6)	566 (56.9)	
N1	115 (27.3)	89 (38.5)		254 (25.2)	262 (26.3)	
N2	68 (16.1)	44 (19.0)		138 (13.7)	142 (14.2)	
N3	14 (3.3)	11 (1.9)		25 (2.5)	25 (2.5)	
Smoking (Yes/No)	194 (46.0)/228 (54.0)	238 (41.3)/338 (58.7)	0.161	448 (44.4)/560 (55.6)	428 (43.0)/567 (57.0)	0.700
Alcohol (Yes/No)	126 (29.9)/296 (70.1)	135 (23.4)/441 (76.6)	0.027	249 (24.7)/759 (75.3)	251 (25.2)/744 (74.8)	0.867
R0 resection (Yes/No)	4 (0.9)/418 (99.1)	3 (0.5)/573 (99.5)	0.465	6 (0.6)/1002 (99.4)	3 (0.3)/992 (99.7)	0.507
Adjuvant therapies (Yes/No)	86 (20.4)/336 (79.6)	132 (22.9)/444 (77.1)	0.459	215 (21.3)/793 (78.7)	220 (22.1)/775 (77.9)	0.677

^aSD, standard deviation.

The survival result of a pilot cohort of 626 patients (208 in one-lung ventilation and 418 in CO₂ pneumothorax groups) show that 5-year OS rates were 65.7% and 56.3% in CO₂ pneumothorax and one-lung ventilation groups. The sample size calculation was then performed by ‘pwr’ package in R software using the ‘two proportions’ method. The significant level (α) and power were set as 0.05 and 0.8, respectively. As a result, the number of patients required in each group should be 421.

Two models, propensity score and inverse probability of treatment weight (IPTW), were constructed to balance patient characteristics. The 1:1 propensity score matching was performed by using the ‘MatchIt’ package in R software. The propensity score was calculated using the logistic regression model and the ‘nearest’ method. Based on the propensity score, we used IPTW, which was calculated as $1/(\text{propensity score})$ in the CO₂ pneumothorax group and $1/(1-\text{propensity score})$ in the one-lung ventilation group. The difference between groups is further evaluated by standardized mean difference (SMD) both before and after IPTW. The cohort with SMD less than 10% and *P*-value over 0.05 is regarded as well-adjusted.

Candidate variables included all variables considered to be correlated with the prognosis of ESCC, or significantly different in variance estimations among patients who underwent one-lung ventilation or CO₂ pneumothorax (with a threshold of $P < 0.10$) by univariable analysis. Finally, the covariates included in the propensity score matching were age, sex, smoking status, alcohol consumption status, pT stage, pN stage, and adjuvant therapy.

Results

Patient characteristics

According to the inclusion and exclusion criteria, 998 ESCC patients were treated with minimally invasive McKeown esophagectomy, of whom 576 (57.7%) underwent CO₂

pneumothorax and 422 (42.3%) underwent one-lung ventilation. The distribution of cases was 375 (37.6%), 196 (19.6%), and 427 (42.8%) from the three hospitals, respectively. No cases were converted from intraoperative CO₂ pneumothorax to one-lung ventilation. The unmatched baseline characteristics of the cohort are listed in Table 1. Patients in the one-lung ventilation group had a significantly earlier pT stage ($P < 0.001$). The R0 resection rates were 99.1% and 99.5% in the one-lung ventilation and CO₂ pneumothorax group, respectively. The patients tended to be elderly and had a relatively late pN stage in the one-lung ventilation group, whereas a higher percentage of smoking and alcohol-drinking patients were in the one-lung ventilation group (Table 1).

To make a reliable comparison, the propensity score and IPTW were constructed. The covariates included in the propensity score matching were age, sex, smoking status, alcohol consumption status, pT stage, pN stage, and adjuvant therapy. The balanced baseline characteristics after matching are shown in Table 1.

Table 2

The 5-year OS and DFS of patients received CO₂ pneumothorax versus one-lung ventilation before and after matching.

Variables	CO ₂ pneumothorax (%)	One-lung ventilation (%)	P
Before matching (95% CI)			
OS	70.8 (66.8–75.0)	65.8 (61.2–70.8)	0.140
DFS	69.0 (65.1–73.2)	62.4 (57.8–67.5)	0.088
Propensity score matching (95% CI)			
OS	64.7 (59.7–70.2)	65.3 (60.3–70.6)	0.63
DFS	64.2 (59.0–69.7)	62.4 (57.5–67.8)	0.76
IPTW (95% CI)			
OS	68.7 (64.5–73.1)	69.1 (63.9–74.8)	0.140
DFS	67.3 (63.2–71.8)	65.8 (60.6–71.6)	0.088

DFS, disease-free survival; OS, overall survival.

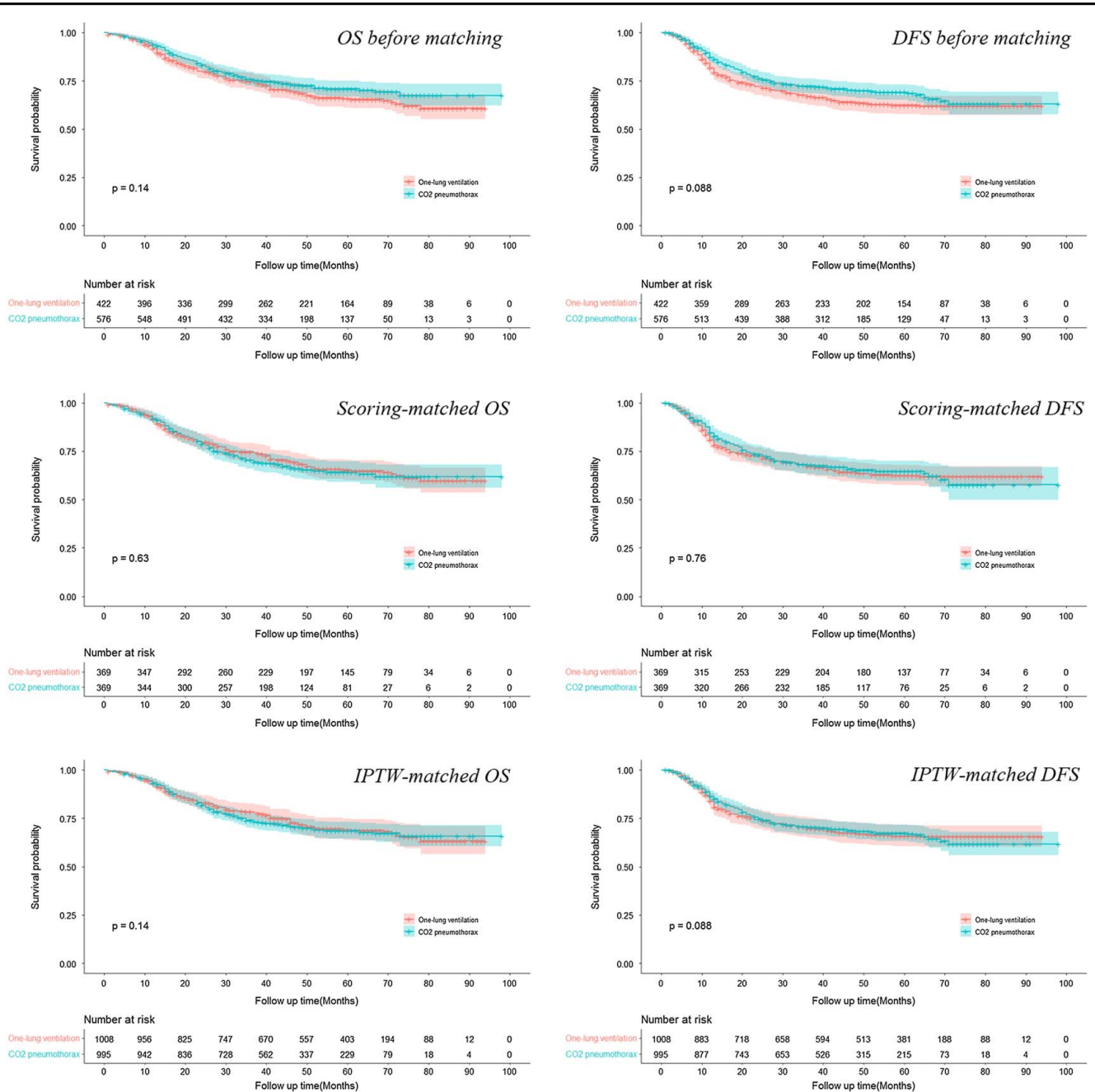


Figure 1. The survival curves of patients before and after propensity score matching and inverse probability of treatment weight matching. DFS, disease-free survival; OS, overall survival.

Ventilation methods and long-term survival

The median follow-up of the patient cohort was 55.2 months. The overall 5-year survival rates and corresponding P values are shown in Table 2. In the propensity score matching model, both the 5-year OS and DFS showed no significant difference between the CO₂ pneumothorax and one-lung ventilation groups by Cox proportional hazard regression analysis (OS: HR = 1.06, 95% CI, 0.83–1.37; DFS: HR = 0.96, 95% CI, 0.75–1.23). In addition, the IPTW model also suggested similar outcomes (OS: HR = 1.06, 95% CI, 0.95–1.35; DFS:

HR = 0.98, 95% CI, 0.77–1.26), which indicated the comparable oncological impacts of CO₂ pneumothorax versus one-lung ventilation methods. Survival curves of propensity score matching and IPTW models depicted no significant difference between the two groups as well (Fig. 1).

Effects of ventilation method on ESCC relapse

A total of 324 (32.5%) patients, including 148 (35.1%) and 176 (30.6%) patients in the one-lung ventilation and CO₂-induced pneumothorax groups, respectively, suffered from

Before matching

Variables	CO2(Yes/No, %)	One-lung(Yes/No, %)	HR (95%CI)	P-value
Tumor relapse	176/400(30.6)	148/274(35.1)	0.82(0.62-1.06)	0.13
Anastomosis relapse	12/564(2.6)	11/411(2.1)	0.80(0.35-1.82)	0.59
Regional lymph node relapse	77/499(13.4)	57/208(13.5)	0.99(0.68-1.43)	0.95
Single distant organ metastasis	21/555(3.6)	23/399(5.5)	0.66(0.36-1.20)	0.17
Multiple metastasis	66/510(11.5)	57/208(13.5)	0.83(0.57-1.21)	0.33

0.2 2.5

Scoring-matched

Variables	CO2(Yes/No, %)	One-lung(Yes/No, %)	HR (95%CI)	P-value
Tumor relapse	124/245(33.6)	130/239(35.2)	0.93(0.69-1.26)	0.64
Anastomosis relapse	7/362(1.9)	8/361(2.2)	0.87(0.31-2.43)	0.79
Regional lymph node relapse	57/312(15.4)	52/317(14.1)	1.11(0.74-1.67)	0.6
Single distant organ metastasis	14/355(3.8)	20/349(5.4)	0.69(0.34-1.38)	0.3
Multiple metastasis	46/323(12.5)	50/319(13.6)	0.91(0.59-1.40)	0.66

0.2 2.5

IPTW-matched

Variables	CO2(Yes/No, %)	One-lung(Yes/No, %)	HR (95%CI)	P-value
Tumor relapse	315/680(31.7)	323/685(32.0)	0.98(0.81-1.18)	0.84
Anastomosis relapse	19/976(1.9)	21/987(2.1)	0.93(0.50-1.74)	0.82
Regional lymph node relapse	139/856(14.0)	125/883(12.4)	1.15(0.89-1.49)	0.3
Single distant organ metastasis	39/956(3.9)	48/960(4.8)	0.82(0.54-1.27)	0.38
Multiple metastasis	117/878(11.8)	129/879(12.8)	0.91(0.70-1.19)	0.48

0.2 2.5

Figure 2. The forest plot showing hazard ratios of CO₂ pneumothorax versus one-lung ventilation for esophageal squamous cell carcinoma patients who received esophagectomy.

tumor recurrence or metastasis following radical esophagectomy in the study cohort. All relapses were further classified into three categories based on the first identified tumor relapse site: (1) anastomosis relapse, (2) regional lymph node relapse, and (3) single distant organ metastasis^[9]. Nevertheless, patients with multiple sites of recurrence at the first diagnosis were also included and therefore classified as the fourth category as multiple metastases. The total number of cases with relapse was 23 (2.3%), 134 (13.4%), 44 (4.4%), and 123 (12.3%) for anastomosis, regional lymph node, single distant organ relapse, and multiple metastasis, respectively. The following logistic analysis revealed that the application of two ventilation methods was not correlated with different ESCC relapse patterns (Fig. 2).

Discussions

In general, special ventilation methods must be applied to keep the surgical side of the lung compressed for ease of procedures in thoracic operations. CO₂ gas pressure in abdominal oncological operations may be involved in tumor cell spillage and worse long-term survival^[5,6]. Therefore, the oncological impacts should be considered before using the CO₂ pneumothorax ventilation method. In this study, we performed a multicenter analysis using propensity score matching and IPTW models to compare the long-term effects of CO₂ pneumothorax with those of the traditional one-lung ventilation method.

Our results conflict with the findings in the LACC trial, which indicated that usage of CO₂-induced pneumoperitoneum might be the reason for shorter OS resulting from minimally invasive

radical hysterectomy^[4]. Although the mechanisms of CO₂-induced tumor metastasis or relapse were not the objective of our study, we presume that the possible reason for the different outcomes could be that the CO₂ pressures were lower, ranging from 6 to 8 mmHg in thoracic surgery. In contrast, the insufflation pressures generally range from 12 to 15 mmHg in abdominal operations^[10]. By simulating the thoracoscopic CO₂ pneumothorax environment *in vitro*, Jiang *et al.*^[3] suggested that only higher-pressure CO₂ pneumothorax (over 12 mmHg) significantly increased esophageal cancer cell invasion and metastasis, while a pressure lower than 8 mmHg was clinically safe. Our study investigated the oncological effects of CO₂ pneumothorax in ESCC, which is essential to translate these *in-vitro* results into clinical recommendations.

Additionally, our findings suggested that CO₂ pneumothorax was neither associated with the risk of tumor relapse nor with relapse in different patterns. The correlations between CO₂ insufflation and tumor relapse can be found in previous publications. Kuntz *et al.*^[11] suggested that a lower pH level secondary to CO₂ pneumoperitoneum destroyed the defensive function of the peritoneum and therefore explained the higher incidence of port-site metastasis of oncological laparoscopic surgery. However, there were no port-site metastases in our cohort, and one patient suffered from pleural dissemination and malignant effusion. However, the patient was in the one-lung ventilation group. Therefore, our study did not have enough data to support the relationship between CO₂ pneumothorax and pleural metastasis. In addition, although evidence could not be found in previous studies, tumor cells can presumably have higher chances of reaching the lymphovascular system after mediastinal lymph node

dissection, which damages the normal barrier of the pleural membrane. Notably, the gross esophageal sample will stay in the chest cavity longer when using CO₂ pneumothorax. However, the correlation analysis between CO₂ pneumothorax and tumor relapse in the lymph nodes or distant organs was negative, which suggested that the hypothesis that CO₂ pneumothorax may lower the risk of ESCC metastasis could be false.

DFS and OS are two common endpoints applied in evaluating the outcomes of radical surgery for malignancies. According to Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics Guidance for Industry of FDA, DFS usually presents greater difference compared with OS between treatment and control groups. Greater difference would actually require less sample size and shorter follow-up time^[12]. When calculating the sample size, the difference of DFS was 10.1% (62.9% and 52.8% in CO₂ pneumothorax and one-lung ventilation groups), which was indeed greater than 9.4% in OS (65.7% and 56.3% in CO₂ pneumothorax and one-lung ventilation groups), and resulted in a smaller sample size requirement. The 5-year OS, rather than DFS, was therefore applied in sample size calculation to further ensure the reliability of the results.

Propensity score matching can effectively balance the potential confounding factors for further analysis. Although different opinions exist regarding the kinds of covariates that should be selected into the matching model, it is more important to balance prognostically correlated variables than other covariates that affect treatment selection but have no influence on the outcome^[13]. In addition, a study showed that further inclusion of variables that did not affect outcome can introduce bias^[14]. In the present study, we first included all covariates that were distributed differently between the two groups and then considered variables that influence prognosis after esophagectomy. Therefore, age, adjuvant therapies, R0 resection, and pathological T and N stages were all included in the propensity score model. The effect size indices of matched characteristics were balanced.

Retrospective studies have certain inherent limitations. Despite the use of matching, the effects of unobserved cofounding variables remained in the comparison. Obviously, our study was only concerned the oncological effects of CO₂ pneumothorax on ESCC; however, the response of other tumors to CO₂ pressure may be different. All these limitations should be considered when interpreting the results. Further large-scale prospective randomized trials are necessary to confirm our results.

In summary, the study demonstrates that CO₂ pneumothorax is comparable to the traditional one-lung ventilation method in terms of the long-term survival outcomes and risk of tumor relapse in different patterns. Therefore, the two methods are both viable options in esophagectomy.

Ethical approval

The study was approved by the IRB of Sun Yat-sen University Cancer Center (Approval Number: B2022-593-01).

Consent

The study was approved by the IRB of Sun Yat-sen University Cancer Center and patients' consents were waived.

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Author contribution

J.C.: conceptualization, methodology, software, and writing – original draft preparation; H.J.: data curation, conceptualization, and data validation; B.Z.: data curation, conceptualization, data validation, and writing – reviewing and editing; T.Z.: data curation; H.W.: data validation; Y.L.: data curation and data validation; W.G.: data curation and writing – original draft preparation; P.W.: data validation and writing – reviewing and editing; C.C.: methodology, writing – reviewing and editing, and supervision; L.T.: conceptualization, writing – reviewing and editing, and investigation; J.F.: conceptualization, methodology, investigation, and writing – reviewing and editing.

Conflicts of interest disclosure

No authors reported any conflicts of interest.

Research registration unique identifying number (UIN)

1. Name of the registry: Research Data.
2. Unique identifying number or registration ID: 2302250001.
3. Hyperlink to your specific registration (must be publicly accessible and will be checked): www.researchdata.org.cn

Guarantor

Dr Jianhua Fu.

Data availability statement

Data in our submission can be accessible upon reasonable requirements for research purposes.

Provenance and peer review

None.

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