



Intraoperative Fractions of Inspiratory Oxygen Are Associated With Recurrence-Free Survival After Elective Cancer Surgery

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Background: Choice of the fraction of inspiratory oxygen (FiO₂) is controversial. The objective of this analysis was to evaluate whether intraoperative FiO₂ was associated with recurrence-free survival after elective cancer surgery.

Methods and Analysis: In this single-center, retrospective study, we analyzed 1,084 patients undergoing elective resection of pancreatic ($n = 652$), colorectal ($n = 405$), or hepatic cancer ($n = 27$) at Heidelberg University Hospital between 2009 and 2016. Intraoperative mean FiO₂ values were calculated. For unstratified analyses, the study cohort was equally divided into a low- and a high-FiO₂ group. For cancer-stratified analyses, this division was done within cancer-strata. The primary outcome measure was recurrence-free survival until the last known follow-up. Groups were compared using Kaplan–Meier analysis. A stratified log rank test was used to control for different FiO₂ levels and survival times between the cancer strata. Cox-regression analyses were used to control for covariates. Sepsis, reoperations, surgical-site infections, and cardiovascular events during hospital stay and overall survival were secondary outcomes.

Results: Median FiO₂ was 40.9% (Q1–Q3, 38.3–42.9) in the low vs. 50.4% (Q1–Q3, 47.4–54.7) in the high-FiO₂ group. Median follow-up was 3.28 (Q1–Q3, 1.68–4.97) years. Recurrence-free survival was considerable higher in the high-FiO₂ group ($p < 0.001$). This effect was also confirmed when stratified for the different tumor entities ($p = 0.007$). In colorectal cancer surgery, increased FiO₂ was independently associated with increased recurrence-free survival. The hazard for the primary outcome decreased by 3.5% with every 1% increase in FiO₂. The effect was not seen in pancreatic cancer surgery and we did not find differences in any of the secondary endpoints.

Conclusions: Until definite evidence from large-scale trials is available and in the absence of relevant clinical conditions warranting specific FiO₂ values, perioperative care givers should aim for an intraoperative FiO₂ of 50% in abdominal cancer surgery as this might benefit oncological outcomes.

Keywords: supplemental oxygen therapy, postoperative complications, perioperative management, oxygen related effects, recurrence-free survival

INTRODUCTION

An increased fraction of inspiratory oxygen (FiO₂) is frequently used in anesthesia, intensive care, and emergency medicine. A concept of using 80 vs. 30% FiO₂ has been proposed for the prevention of surgical site infections (SSI) more than 20 years ago (1) and has been evaluated in several subsequent randomized controlled trials (RCTs) (1–3). Based on a systematic review and meta-analysis (4), the WHO and other societies (5–7) issued guidelines advocating the use of 80% FiO₂ during surgery. These recommendations have caused considerable concern, as the authors of other systematic reviews and meta-analyses arrive at opposing conclusions (8, 9) and because the relevance of potential oxygen-mediated side effects is still under debate (9, 10). In a *post-hoc* analysis of the PROXI trial, administration of 80% oxygen in the perioperative period was associated with increased long-term mortality in patients undergoing cancer surgery (11), and after a median follow-up of 3.9 years, cancer-free survival was significantly reduced in the 80% oxygen group compared with patients randomized to 30% FiO₂ (12). Outside of clinical trials and before the first WHO recommendation regarding supplemental oxygen (13) was published, intraoperative FiO₂ was typically used in the range of 30% to more than 90%, and the choice for the actual FiO₂ did depend on patients' requirements, type of surgical intervention, and anesthesiologist's preferences (14).

Currently, it is unknown whether the choice of higher or lower FiO₂ in a real-world setting outside of clinical trials is associated with long-term outcomes after cancer surgery. Therefore, we conducted a retrospective and exploratory study to evaluate the association of perioperative FiO₂ and recurrence-free survival after elective cancer surgery was performed before the WHO recommendation advocating supplemental oxygen for prevention of SSI was published.

METHODS

Study Design and Population

We performed a retrospective and exploratory study in patients receiving general anesthesia for elective abdominal cancer surgery in the period from January 1, 2009, to December 31, 2016, at the Department of General-, Visceral-, and Transplant Surgery, Heidelberg University Hospital, Heidelberg, Germany. The study protocol conformed to the "Strengthening the Reporting of Observational studies in Epidemiology (STROBE)" guidelines (15), and the principles of the Declaration of Helsinki

Abbreviations: ASA, American Society of Anesthesiologists physical status classification; B, Coefficient of variable; BMI, Body Mass Index; COPD, Chronic Obstructive Pulmonary Disease; CI, Confidence Intervals; CRC, Colorectal cancer; FAP, Familial Adenomatous Polyposis; FiO₂, Fraction of inspiratory oxygen; FFP, Fresh frozen plasma; HC, Hepatic cancer; HIF-1, Hypoxia-inducible factor 1; HR, Hazard Ratio; IORT, IntraOperative Radiation Therapy; paO₂, Arterial oxygen pressure; PC, Pancreatic cancer; PLT, Platelet concentrates; Q, Quartile; R 0, No residual tumor; R 1, Microscopic residual tumor; RBC, Red blood cells; RCT, Randomized controlled trial; ROS, Reactive Oxygen Species; SD, Standard Deviation; SE, Standard Error; SSI, Surgical Site Infections; TNM, Tumor, Node, Metastasis; TU, Transfusion units; UICC, Tumor classification according to the Union for International Cancer Control; WHO, World-Health-Organization.

and was approved by the local Ethics Committee of the Medical Faculty of the Ruprecht-Karls-University, Heidelberg (S-326/2019, August 9, 2019). We assessed whether perioperative FiO₂ was associated with recurrence-free survival after surgery for three exemplary abdominal cancer entities. Patients with elective surgery of the pancreas, colon or rectum, or liver were included. Subgroup analysis was performed for the three tumor entities. Data were retrieved for all patients \geq 18 years of age who underwent elective resection of pancreatic (PC), colorectal (CRC,) or hepatic cancer (HC) with R0 (no residual tumor) or R1 (microscopic residual tumor) resection, without distant metastases at the time of surgery, and with follow-up for at least 180 days. Exclusion criteria were intraoperative detection of peritoneal carcinomatosis or if histology analysis could not reveal cancer tissue i.e., after neoadjuvant chemo- or radiotherapy. Patients were also excluded if they suffered familial adenomatous polyposis or did receive home oxygen therapy in the preoperative period.

Data Collection

Baseline data retrieved from the prospectively maintained electronic pancreas, colorectal, and liver databases of the Department of Surgery at Heidelberg, University Hospital and from the electronic patient file were: demographic data, weight, height, body mass index (BMI), American Society of Anesthesiologists physical status classification (ASA), preexisting diseases including diabetes mellitus and chronic obstructive pulmonary disease (COPD), history of smoking, duration of surgery, need for postoperative ventilation, reintubation, use of epidural anesthesia, intraoperative dose of sufentanil, units of red blood cells (RBC), fresh frozen plasma (FFP), and platelet concentrates (PLT) transfused during surgery and during the entire hospital stay, use of intraoperative radiation therapy (IORT), neoadjuvant and adjuvant radio-, and chemotherapy. For colorectal and pancreatic cancer, tumor site was differentiated as follows: pancreatic head vs. body/tail cancer and rectal vs. colon cancer. Resection margin status, TNM (tumor, node, metastasis) classification, and tumor grading were retrieved from pathology reports. For every patient mean FiO₂ was calculated on the basis of the FiO₂ levels documented in the anesthesia protocol at 15-min intervals after induction of anesthesia (first 45 min) until extubation. Furthermore, the measurements of partial pressure of oxygen in arterial blood gases (paO₂) during surgery were collected. For outcome analyses, intensive care unit and hospital length of stay, date of local recurrence or occurrence of distant metastases, and date and cause of death were collected.

Outcome Analysis

The primary outcome measure was recurrence-free survival in the period from index surgery until the last known follow-up. Recurrence-free survival was defined as the time from index surgery to the first documented event of local cancer recurrence, newly diagnosed metastases, or death. Computer tomography, abdominal ultrasound, physical examination, and blood sampling were conducted in follow-up examinations at regular intervals or were prompted by new symptoms. If there

was no diagnosis of cancer recurrence, new metastases, or death documented, the last date of follow-up or doctor–patient contact with negative findings was recorded. Secondary outcomes were overall survival, sepsis, reoperations due to surgical complications, SSI (superficial incisional, deep incisional, and organ space) and cardiovascular events (myocardial infarction, cerebral infarction, or transitory ischemic attack) during hospital stay were recorded.

Statistical Analysis

The entire patient cohort was sorted based on ascending mean intraoperative FiO₂ values and was then divided into two equal sized groups. The low-FiO₂ group and the high-FiO₂ group comprised 542 patients each. Descriptive analyses comprised calculation of mean, standard deviation (SD), median, and first and third quartile for continuous variables and absolute and relative proportions for categorical variables. The distribution of categorical variables in the different groups was compared using the chi-square test. Differences in continuous variables were evaluated using the Mann–Whitney *U* test. The primary survival analysis for the prespecified primary endpoint recurrence-free survival was performed using the Kaplan–Meier method (16) and groups were compared by means of the log-rank test (17). As the three tumor entities were not equally distributed over the low- and high-FiO₂ groups, and because the tumor entities analyzed in our study differed regarding long-term survival rates, we performed an additional analysis to control for tumor entity. First, within each of the three tumor entities, patients were sorted by ascending intraoperative mean FiO₂ values before patients were equally divided into a low- and high-FiO₂ group within each entity. Kaplan–Meier curves of these groups were compared within entities. Then patients from the three–tumor entity specific low-FiO₂ groups were combined into one-entity-controlled low-FiO₂ group, and patients from the three-tumor entity specific high-FiO₂ groups were combined in one entity-controlled high-FiO₂ group. These two groups were compared using a stratified log-rank test with the different tumor entities as strata. Thereafter, the primary outcome was analyzed within the tumor entities PC and CRC by the Cox proportional hazard model (18) in which the effect of mean FiO₂ on recurrence-free survival adjusted for the following covariates was estimated: gender, age, body mass index, nicotine use, diabetes mellitus, UICC (Tumor classification according to the Union for International Cancer Control) stage, tumor localization, tumor grading, resection margin status, use of epidural anesthesia, intraoperative dose of sufentanil, units of RBC, FFP, and PLT transfused during the entire hospital stay, intraoperative, neoadjuvant and adjuvant radio- and chemotherapy, and laparoscopic surgery in patients with CRC. If fentanyl was used as the opiate instead of sufentanil, the fentanyl dose was multiplied by a factor of 0.1 to calculate the equivalent sufentanil dose (19).

Mean FiO₂, age, PLT transfusion, intraoperative dose of sufentanil, and BMI are continuous variables, and the other variables are categorical. *P*-values of regression coefficients were obtained by the Wald-Test. Hazard ratios (HRs) estimated from the Cox analysis were reported with corresponding 95% CIs and a

two-sided *p* < 0.05 was denoted as considerable. The HC-stratum was too small to fit a covariate-adjusted cox regression. The 1-year and 5-year overall survival was estimated by the Kaplan–Meier method. *P*-value is referred to the stratified log rank test with entities as strata.

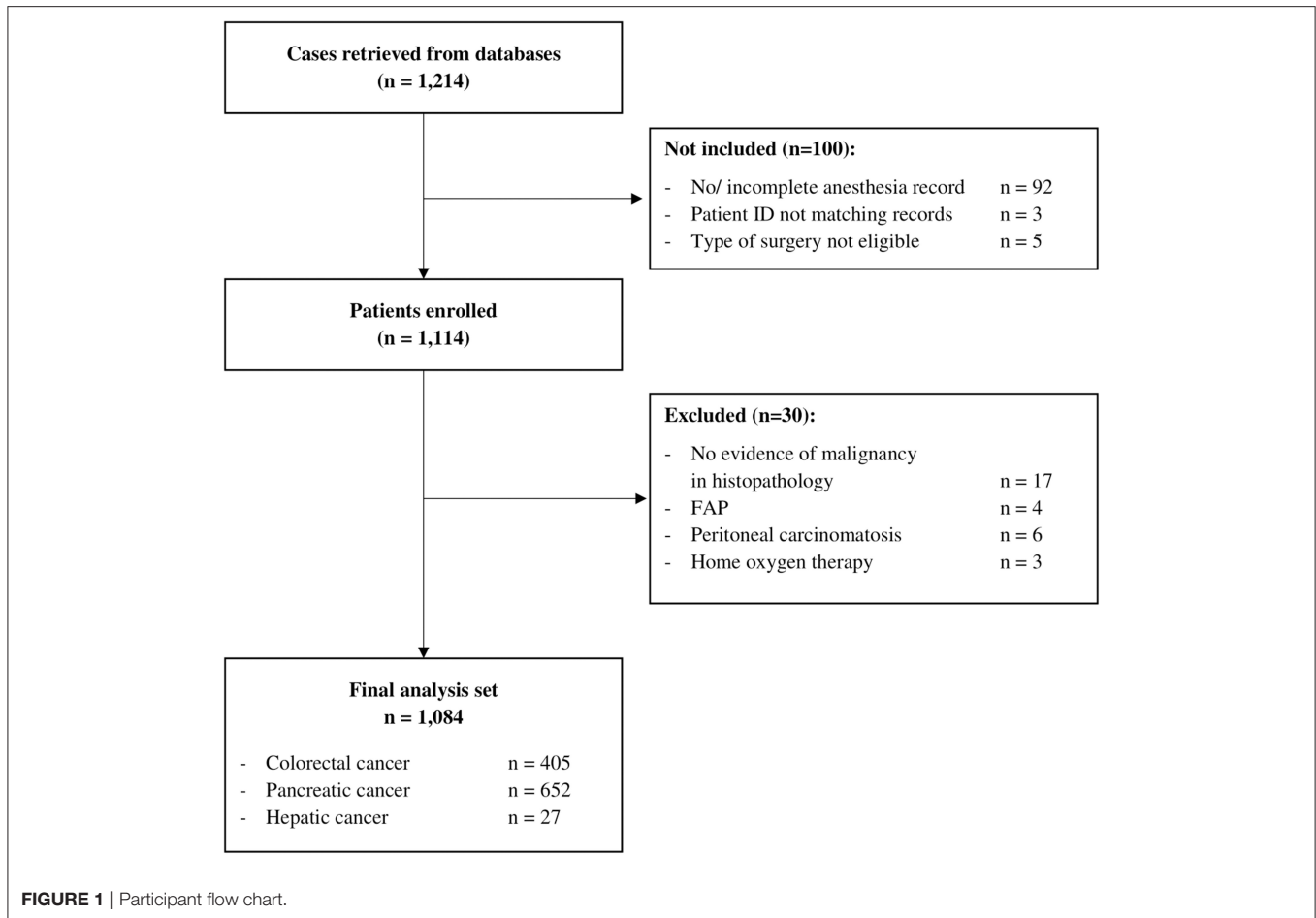
Statistical analyses were performed using IBM SPSS Statistics 26.0 (SPSS, Chicago, IL) and Prism 9.0.0 (GraphPad Prism Software, Inc, San Diego, CA).

RESULTS

Data from 1,214 patients were retrieved from databases. Datasets from 100 patients could not be assessed for eligibility because of incomplete or missing anesthesia records since the patient ID retrieved from the database did not match with a case in the hospital information system, or because the type of surgery was not eligible, i.e., non-tumor surgery. Considering exclusion criteria, 30 patients had to be excluded. Therefore, 1,084 patients were included in the final analysis set (Figure 1) with a median follow-up of 3.28 (Q1–Q3, 1.68–4.97) years.

Patient Characteristics

Main clinical and demographical baseline characteristics are presented in Table 1 and the Supplementary Material. A total of 1,084 patients underwent elective PC (*n* = 652), CRC (*n* = 405), or HC surgery (*n* = 27). The mean age was 63 ± 11 years. Male participants were slightly more than female participants. At the time of surgery, the most common cancer stage was UICC 2 and the most common tumor grades were 1 and 2. Around 45% of patients' tumor resection margin status in the pathology report was classified as R1. In the majority of patients with PC, “pancreatic head” was found as the tumor localization; in the majority of patients with CRC “rectum” was found as the tumor localization. Patients received neoadjuvant chemotherapy or neoadjuvant radiotherapy in 15% of cases and 70% received adjuvant chemotherapy. IORT was conducted in 3%. General anesthesia was performed as balanced anesthesia except in four patients. In a small proportion (four patients (0.3%)), fentanyl was used instead of sufentanil and the corresponding equivalent dose was calculated. Intraoperative dose of sufentanil was slightly higher in the low-FiO₂-groups of patients with CRC and PC (CRC: 88.45 μg ± 45.04 vs. 80.12 μg ± 32.37; low vs. high-FiO₂, *p* = 0.012; PC: 80.86 μg ± 51.16 vs. 72.22 μg ± 42.85; low vs. high-FiO₂, *p* = 0.002; HC: 73.21 μg ± 42.23 vs. 66.92 μg ± 27.80; low- vs. high-FiO₂, *p* = 1.0). Epidural anesthesia was more common in the high-FiO₂-groups of patients with CRC and PC (CRC: 21(10%) vs. 39 (19%); low- vs. high-FiO₂, *p* = 0.011; PC: 230 (71%) vs. 258 (79%); low- vs. high-FiO₂, *p* = 0.011; HC: 10 (71%) vs. 10 (77%), *p* = 0.745). In total, 111 (10.2%) patients were transfused intraoperatively and 284 (26.2%) during their entire hospital stay. There was no difference between the entity-controlled low-FiO₂ and entity-controlled high-FiO₂ groups (intraoperative transfusion: 54 (9.9%) vs. 57 (10.5%); entity-controlled low-FiO₂ vs. entity-controlled high-FiO₂; *p* = 0.784; transfusions during entire hospital stay: 139



(25.6%) vs. 145 (26.8%); entity-controlled low-FiO₂ vs. entity-controlled high-FiO₂; $p = 0.652$).

The average age was higher in the low-FiO₂ group (64 ± 10.5 vs. 62 ± 11 years, low- vs. high-FiO₂, $p = 0.003$). For none of the tumor entities, differences with regard to diabetes, history of smoking, or gender were detected. Also, for neither of the tumor entities we observed differences regarding tumor grading status, UICC stage, resection margin status, neoadjuvant, adjuvant therapy, or IORT. In PC surgery, tumor localization in the pancreatic head was more common in the low-FiO₂ group (81 vs. 72%, $p = 0.009$; low- vs. high-FiO₂). There was no difference in CRC patients with regard to tumor localization between both groups. In CRC surgery, open surgery was more common in the high-FiO₂ group (85 vs. 92%, $p = 0.029$; low- vs. high-FiO₂). PC and HC surgery were always performed as open surgery. Robotic surgery was not performed in our patient cohort. The proportions of the three tumor entities differed between the low and high-FiO₂ group (PC: 72.1%, CRC: 26.8%, HC: 1.1% vs. PC 48.2%, CRC 48.0%, HC 3.9%, $p < 0.001$; low- vs. high-FiO₂). The average duration of PC surgery was longer than the duration of CRC and HC surgery (PC: 313 min \pm 103, CRC 221 min \pm 83, HC: 168 min \pm 69, $p < 0.001$).

Observed FiO₂ and PaO₂

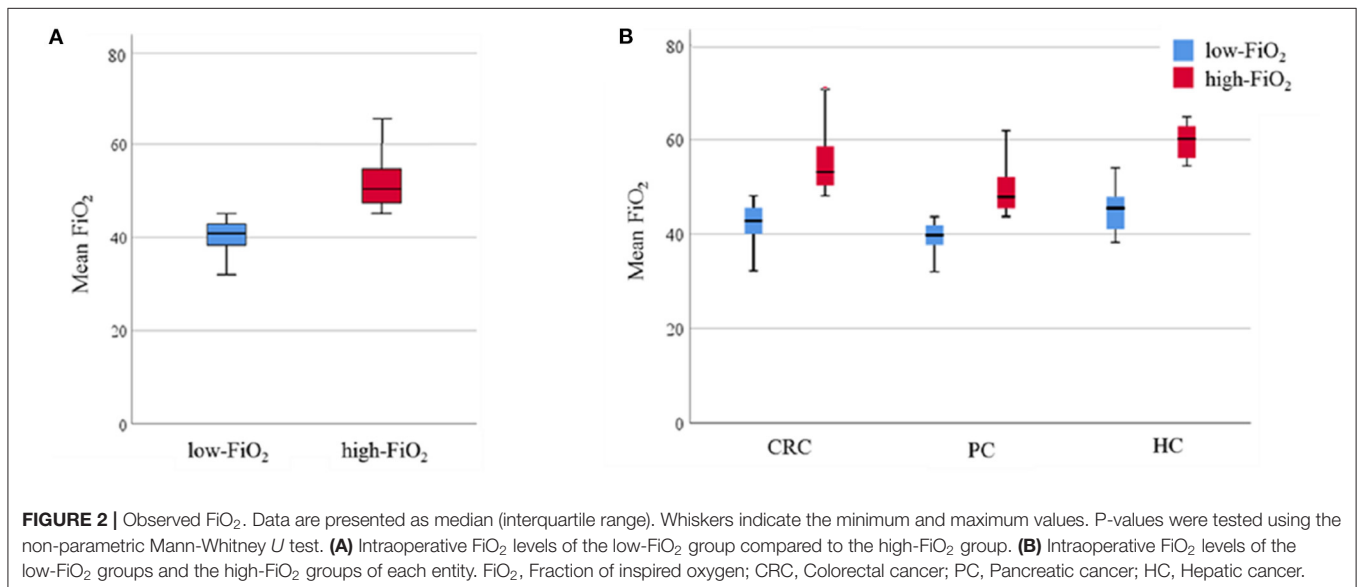
After dividing the cohort into low and high FiO₂ patients, the cut off value between the two groups was 45.1%, the median of patients' intraoperative FiO₂ mean [Q1; Q3] in the low-FiO₂ group was 40.9 [38.3; 42.9] vs. 50.4% [47.4; 54.7] in the high-FiO₂ group (**Figure 2A**). In CRC surgery, the calculated cut off value was 48.1%, the median of patients' FiO₂ means in the low-FiO₂ group was 42.8 [40.0; 45.6] vs. 53.1% [50.3; 58.6] in the high-FiO₂ group. In PC surgery, the calculated cut off value was 43.6%, the median of patients' FiO₂ means in the low-FiO₂ group was 39.8 [37.7; 41.8] vs. 47.9% [45.5; 52.1] in the high-FiO₂ group. In HC surgery, the calculated cut off value was 54.0%, the median of patients' FiO₂ means in the low-FiO₂ group was 45.5 [41.0; 47.9] vs. 60.2% [56.1; 62.8] in the high-FiO₂ group (**Figure 2B**).

The mean paO₂ during surgery was significantly higher in the high-FiO₂ group (median of patients' intraoperative paO₂ mean: 172.7 mmHg [152.15; 193.05] vs. 200.7 mmHg [173.2; 235.8], low- vs. high-FiO₂) (**Figure 3A**). After stratifying for tumor entities, median paO₂ values were also significantly lower in the low-FiO₂ groups compared to the high-FiO₂ groups (CRC: Median of patients' intraoperative paO₂ mean: 167.9 mmHg [146.5; 188.0] vs. 190.0 mmHg [147.0; 217.5], low- vs. high-FiO₂; PC: Median of patients' intraoperative paO₂ mean: 172.38 mmHg

TABLE 1 | Clinical baseline characteristics of the study cohort.

Variable	Analysis set (n = 1084)	low-FiO ₂ (n = 542)	high-FiO ₂ (n = 542)	p value
Cancer entity, n (%)				
Colorectal cancer (CRC)	405 (37.4)	145 (26.8)	260 (48.0)	<0.001
Pancreatic cancer (PC)	652 (60.1)	391 (72.1)	261 (48.2)	
Hepatic cancer (HC)	27 (2.4)	6 (1.1)	21 (3.9)	
Age (years), mean ± SD	63.11 ± 10.87	62.17 ± 11.18	64.06 ± 10.47	0.003
Male, n (%)	614 (57)	305 (50)	309 (50)	0.806
BMI (kg/m ²), mean ± SD	25.63 ± 4.14, n = 1082	25.41 ± 3.72, n = 542	25.86 ± 4.52, n = 540	0.322
Smokers, n (%)				
active	217 (20)	99 (18)	118 (22)	0.196
previous	109 (10)	61 (11)	48 (9)	
ASA status, n (%)				
1–2	661 (61)	338 (62)	323 (60)	0.350
3–4	423 (39)	204 (38)	219 (40)	
Diabetes mellitus, n (%)	216 (20)	109 (20)	107 (20)	0.879
COPD, n (%)	63 (6)	29 (5)	34 (6)	0.516
Duration of surgery (min), mean ± SD	274.81 ± 106.20	298.63 ± 103.75	250.99 ± 103.75	<0.001
Intensive care stay, n (%)	522 (48)	273 (50)	249 (46)	0.145
Duration of intensive care stay (d), mean ± SD	16.78 ± 195.63	14.51 ± 155.31	19.27 ± 232.25	0.296
Postoperative ventilation, n (%)	10 (1)	4 (1)	6 (1)	0.525
Duration of postoperative ventilation (d), mean ± SD	50.60 ± 55.30	69.13 ± 73.26	38.25 ± 42.74	1.000
Reintubation, n (%)	27 (3)	13 (2)	14 (3)	0.845
Duration of ventilation after reintubation (d), mean ± SD	190.15 ± 131.56	140.92 ± 241.28	239.38 ± 375.98	0.390
Duration of hospitalization (d), mean ± SD	16.37 ± 13.24	16.33 ± 11.75	16.41 ± 14.58	0.164

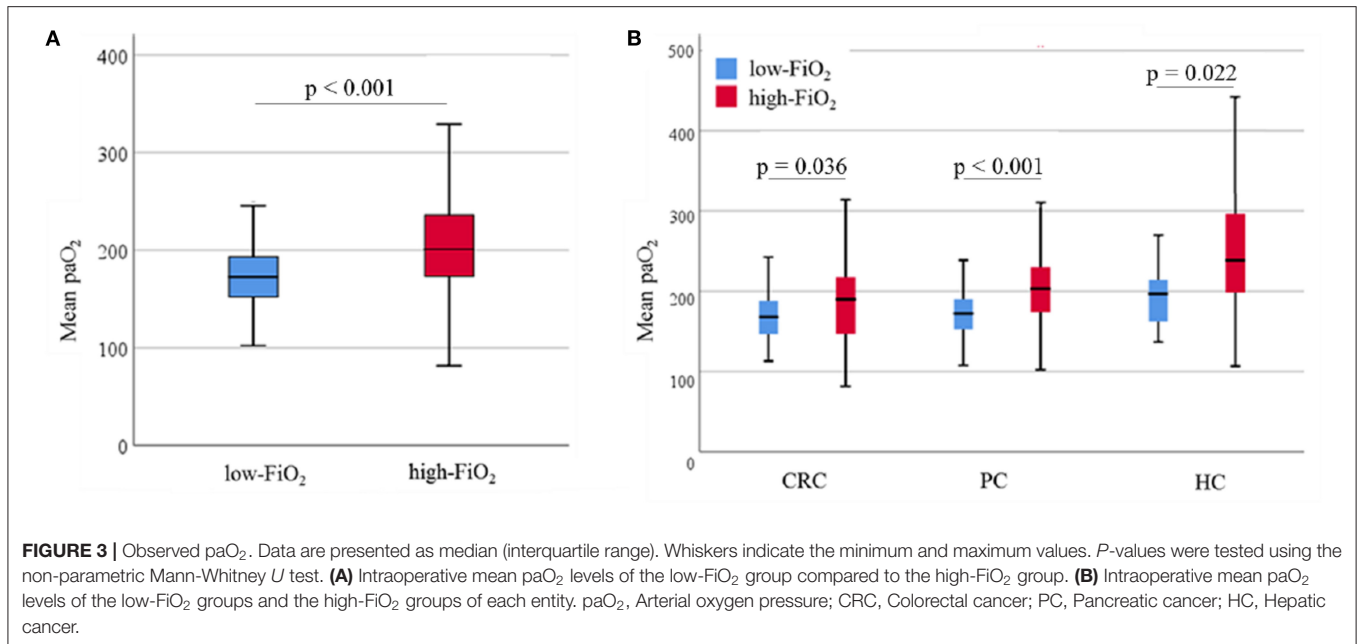
Data are presented as mean ± SD, or as absolute number (percentage). P-values refer to the comparison between low-FiO₂ vs. high-FiO₂ patients. Continuous data were compared using the Mann-Whitney U test. Categorical variables were compared using the chi-square test. Boldface indicates p-values < 0.05. FiO₂, Fraction of inspired oxygen; SD, Standard deviation; BMI, Body mass index; ASA, risk classification according to the American Society of Anesthesiologists; COPD, Chronic obstructive pulmonary disease.



[152.6; 190.3] vs. 203.4 mmHg [174.1; 230.0], low-vs. high-FiO₂; HC: Median of patients' intraoperative paO₂ mean: 197.0 mmHg [162.3; 214.3] vs. 238.33 mmHg [198.3; 296.4], low-vs. high-FiO₂) (**Figure 3B**).

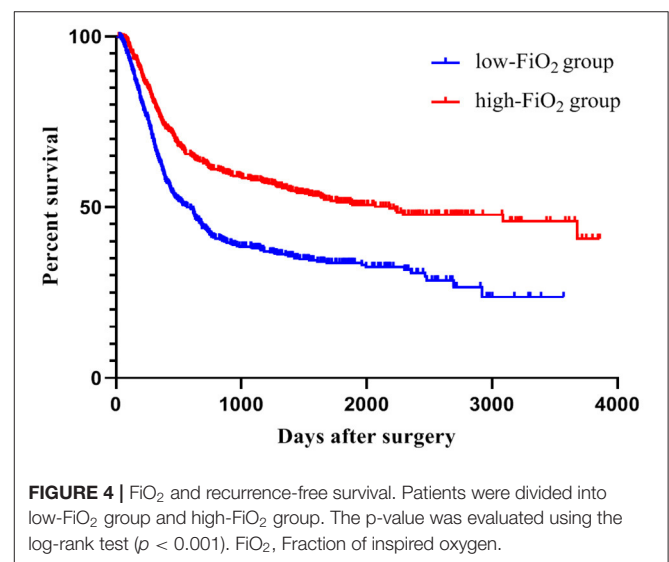
Survival Analysis

In total, cancer recurrence between index surgery and last follow-up was diagnosed in 588 patients (54%). Among those patients, 136 (23.1%) experienced local recurrence and no



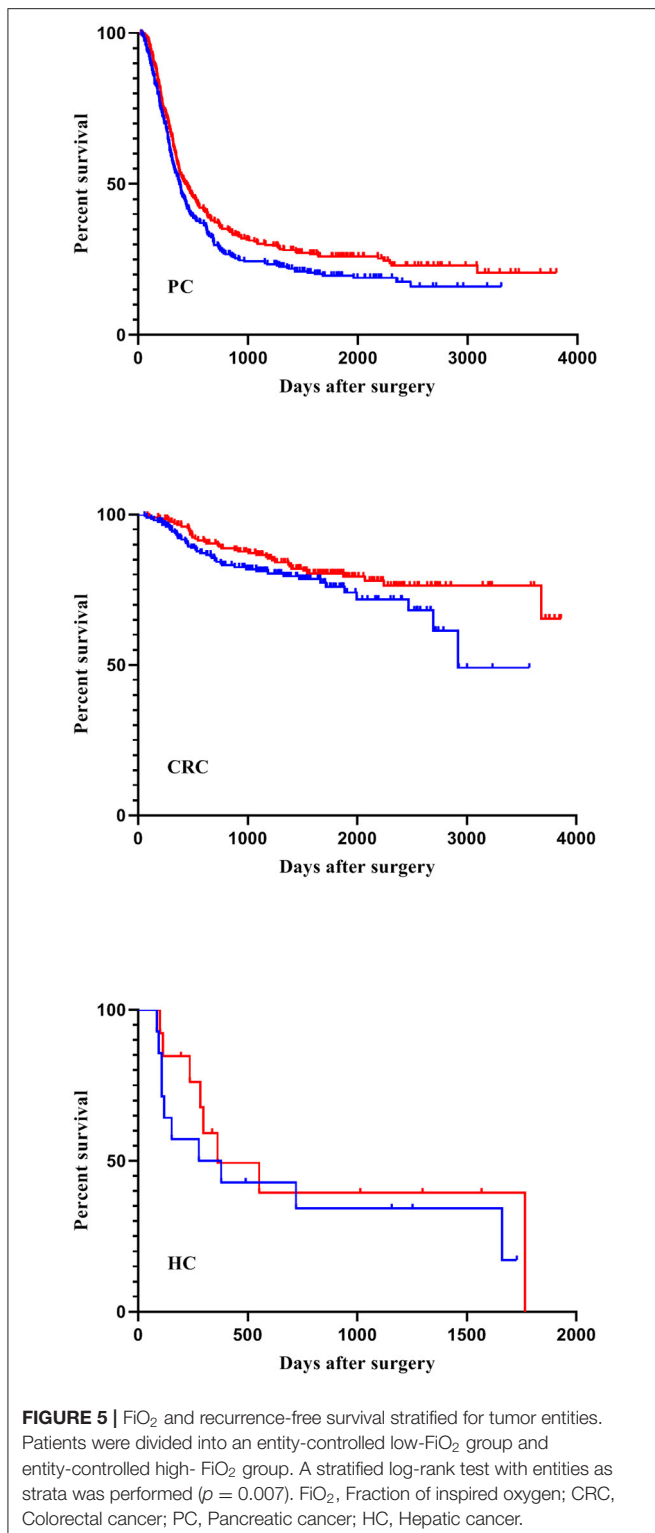
distant metastases, 309 (52.5%) had distant metastases without local recurrence, and 133 patients (22.6%) suffered from both local relapse and distant metastases. For 10 patients (1.7%), information about the type of recurrence was not available. During the observation period, 402 patients (37.1%) died, mostly (381 cases) due to their malignant disease. Two patients died due to postoperative complications; four patients because of cardiovascular events after hospital discharge. In 15 patients, the cause of death was unknown. Recurrence-free survival was considerably higher in the high-FiO₂ group (log-rank test: $p < 0.001$) (Figure 4). This effect was preserved in the entity-controlled groups. Recurrence-free survival was lower in the entity-controlled -low-FiO₂ group compared to the entity-controlled -high-FiO₂ group (stratified log rank test: $p = 0.007$) (Figure 5).

The cancer entity itself plays a relevant role in the average survival time of a patient (20–22). Therefore, we performed subgroup analyses for PC and CRC patients respectively using a Cox proportional hazard model, considering factors influencing the observed effect. These analyses revealed an independent association for mean FiO₂ and recurrence-free survival in patients undergoing CRC surgery ($B = -0.035$; $p = 0.025$). Recurrence-free survival was longer in patients with higher mean FiO₂. The hazard ratio (HR) for the variable mean FiO₂ was 0.965, and thus, HR is $0.965^5 = 0.837$ between two patients whose mean FiO₂ differ by 5%; per 1% rise of mean FiO₂ the hazard for the primary outcome decreases by 3.5% ($\text{Exp}(B)$: 0.965; 95% CI: 0.936–0.996) (Table 2). There was no evidence for an association of FiO₂ mean with recurrence-free survival in patients undergoing PC surgery ($B = -0.01$; $\text{Exp}(B) = 0.990$; CI: 0.975–1.01; $p = 0.217$) (Table 3). Because the HC group consists of 27 patients only, it was not considered suitable for an individual Cox regression analysis.



Secondary Endpoints

We examined 1-year and 5-year survival rates in patients with CRC, PC, and HC separately. In CRC patients, 1-year survival was 100% in both the low- and the high-FiO₂ group. After 5 years, five out of 203 patients had died (5-year survival 96.2%) in the low-FiO₂ group, whereas eight out of 202 patients had died in the high-FiO₂ group (5-year survival 94.6%). In PC patients, 39 out of 326 patients had died after 1 year (1-year survival 87.9%) in the low-FiO₂ group, whereas in the high-FiO₂ group 43 out of 326 patients had died (1-year survival 86.7%). After 5 years, 188 patients in the low-FiO₂ group had died (5-year survival 36.0%) vs. 183 patients in the high-FiO₂ group (5-year survival 38.5%). In HC patients, 1-year and 5-year survival was 100% in



both the low- and the high-FiO₂ group. Neither 1- nor 5-year survival was different between the entity-controlled low-FiO₂ and entity-controlled high-FiO₂ group ($p = 0.525$) (Table 4).

Cardiovascular events (5 vs. 5, low- vs. high-FiO₂, $p = 1$) and incidence of sepsis (5 vs. 6, low- vs. high-FiO₂, $p = 0.76$) did not differ between groups. There was no difference in the rate of SSI (61 vs. 55, low- vs. high-FiO₂, $p = 0.556$), and the occurrence of reoperations was not different (40 vs. 36, $p = 0.634$, low- vs. high-FiO₂) (Table 4).

DISCUSSION

In this retrospective exploratory study, we demonstrated in a real-world setting that higher intraoperative FiO₂ during abdominal cancer surgery was associated with better recurrence-free survival. In CRC surgery, higher FiO₂ was independently associated with increased recurrence-free survival. The hazard for the primary outcome decreased by 3.5% with every 1% increase in FiO₂. In PC surgery, we did not observe a significant effect and we did not find differences in any of the secondary endpoints.

The patient cohort under investigation had undergone surgery before the first WHO recommendation advocating supplemental oxygen for prevention of SSI (13) was published. Therefore, the decision for a specific FiO₂ was a clinical decision mainly based on the patients' respiratory function and the anesthesiologists' preference.

Oxygen has known pro- and anticarcinogenic effects. Hyperoxia may not only cause direct cell damage through the generation of reactive oxygen species (ROS) but also mediates cancerous effects (12, 23, 24), such as promotion of proliferation, invasiveness, angiogenesis, and metastasis. Interestingly, ROS generation may be accelerated under hyperoxia and also hypoxia (14). In addition, hypoxia can lead to organ dysfunction, lactic acidosis, cell death (25), and an increased expression of the hypoxia-inducible factor 1 (HIF-1) (26, 27) an intrinsic survival factor of tumor cells. Therefore, hypoxia can induce a vast number of gene products that control neovascularization, cell survival, energy metabolism, intracellular pH, and cell migration and are often associated with increased tumor aggressiveness, therapeutic resistance, and mortality (26, 28–31).

In clinical studies, evidence for FiO₂-mediated effects associated with long-term outcome after abdominal cancer surgery is sparse and controversial. In a *post-hoc* analysis of the PROXI trial, cancer-free survival was significantly shorter in the high oxygen group (12). In line, after a median follow-up of 2.3 years, a subsequent analysis of the same trial found increased long-term mortality in patients receiving 80% oxygen during cancer surgery (11). Contrarily, authors of other *post-hoc* analysis, combining mortality data from different RCTs, found that there was neither a difference in long-term mortality nor did they find differences in overall survival for patients randomly assigned to 30% vs. 80% FiO₂ (32, 33). The median follow-up was 12.8 (3.8, 13.6) years in the trial by Greif, 4.3 (3.6, 4.8) years in the trial by Kurz, and 3.2 (0.5, 4.9) years in the study by Jiang (1, 33, 34). This is in line with our finding that overall survival did not differ between high and low FiO₂ groups with a median follow-up of 3.28 (1.68, 4.97) years. Although FiO₂ appears to affect cancer recurrence, follow-up in our study might have

TABLE 2 | Independent effects of FiO₂ on recurrence-free survival in patients with CRC.

	B	SE	Sig.	Exp(B)	95% CI for Exp(B)	
					Lower	Upper
Female Sex	0.273	0.285	0.339	1.314	0.751	2.299
Age at time of surgery (y)	0.014	0.011	0.217	1.014	0.992	1.037
BMI (kg/m ²)	0.046	0.031	0.144	1.047	0.984	1.113
No smoking (<i>reference</i>)			0.062			
Former smoking	0.254	0.409	0.534	1.290	0.578	2.875
Current smoking	0.684	0.293	0.019	1.982	1.117	3.516
Diabetes mellitus	-0.244	0.380	0.521	0.784	0.372	1.650
Dose of sufentanil	0.004	0.003	0.222	1.004	0.998	1.009
Epidural anesthesia	0.300	0.381	0.432	1.350	0.639	2.849
No RBC (<i>reference</i>)			0.962			
RBC (1–5 TU)	0.285	0.382	0.456	1.329	0.629	2.809
RBC (6–10 TU)	-13.14	710.33	0.985	0.000	0.000	.
RBC (11–15 TU)	-0.194	1.036	0.852	0.824	0.108	6.276
RBC (> 15 TU)	-10.03	882.63	0.991	0.000	0.000	.
PLT (TU)	-10.43	287.61	0.971	0.000	0.000	1.922E + 240
No FFP (<i>reference</i>)			0.994			
FFP (1–5 TU)	-0.084	0.778	0.914	0.919	0.200	4.227
FFP (>5 TU)	-12.55	1210.6	0.992	0.000	0.000	.
Laparoscopic surgery	0.009	0.422	0.983	1.009	0.441	2.307
UICC stage 0–1 (<i>reference</i>)			0.000			
UICC stage 2	1.394	0.522	0.008	4.031	1.449	11.213
UICC stage 3	2.440	0.524	0.000	11.468	4.104	32.044
Grading G 1–2 (<i>reference</i>)			0.062			
No grading due to neoadjuvant therapy	-1.102	0.549	0.045	0.332	0.113	0.975
Grading G 3–4	-0.655	0.447	0.143	0.519	0.216	1.247
Resection margin status R1	1.132	0.642	0.078	3.102	0.882	10.907
Rectal cancer	-0.063	0.306	0.837	0.939	0.515	1.711
Neoadjuvant chemotherapy	1.261	0.481	0.009	3.529	1.375	9.060
Neoadjuvant radiotherapy	0.279	0.572	0.626	1.321	0.431	4.053
IORT	2.152	1.140	0.059	8.605	0.921	80.377
Adjuvant therapy	0.270	0.299	0.366	1.310	0.729	2.352
Mean FiO ₂	-0.035	0.016	0.025	0.965	0.936	0.996

The *p*-values of the regression coefficients were calculated using the Wald-Test. Hazard ratios (Exp(B)) estimated from the Cox analysis were reported as relative risks with corresponding 95% CIs. Boldface indicates *p*-values < 0.05. CRC, Colorectal cancer; B, Coefficient of variable; SE, Standard error; BMI, Body mass index; UICC, Tumor classification according to the Union for International Cancer Control; IORT, intraoperative radiation therapy; FiO₂, Fraction of inspired oxygen; RBC, Red blood cells; FFP, Fresh frozen plasma; PLT, Platelet concentrates; TU, Transfusion units.

been too short to observe effects on mortality after recurrence. Also, overall survival did not differ between the two groups investigated here, probably because overall survival depends on a variety of other factors not assessed in this study.

In most prospective studies, comparing different FiO₂ concentrations, patients were randomized for either 30 or 80% FiO₂. However, both targets have been accused to cause considerable side effects. Outside of clinical trials and before guidelines advocating high levels of supplemental oxygen were published, most anesthetists chose moderate FiO₂ levels between the high and low extremes. As a result, in our retrospective study, mean FiO₂ levels in the low- and high-FiO₂ groups were closer together than in other studies. Importantly, our institutional standards suggest avoiding not

only hypoxia but also hyperoxia as both conditions might cause adverse events.

Pro and anticarcinogenic effects of oxygen might explain why, on one hand, 80% FiO₂ has adverse effects over 30% FiO₂ in some studies, but on the other hand, in our study, FiO₂ in the range of 50% compared with lower FiO₂ concentrations was beneficial with regard to recurrence-free survival. It is conceivable that the optimal FiO₂ for tumor surgery patients is neither met with an FiO₂ of 30% nor 80%. In fact, the association of FiO₂ or paO₂ respectively and recurrence-free survival may follow a V-shaped curve.

Oxygen related effects in tumor biology may also differ for distinct types of tumors. The association of tumor-associated transcription factors and tumor progress varies among different

TABLE 3 | Independent effects of FiO₂ on recurrence-free survival in patients with PC.

	B	SE	Sig.	Exp(B)	95% CI for Exp(B)	
					Lower	Upper
Female Sex	-0.014	0.097	0.884	0.986	0.815	1.192
Age at time of surgery (y)	-0.003	0.005	0.491	0.997	0.987	1.006
BMI (kg/m ²)	-0.018	0.013	0.175	0.983	0.958	1.008
No smoking (<i>reference</i>)			0.730			
Former smoking	-0.112	0.171	0.514	0.894	0.639	1.251
Current smoking	-0.069	0.128	0.589	0.933	0.726	1.200
Diabetes mellitus	0.012	0.115	0.915	1.012	0.808	1.268
Dose of sufentanil	0.001	0.001	0.194	1.001	0.999	1.003
Epidural anesthesia	-0.076	0.120	0.527	0.927	0.732	1.173
No RBC (<i>reference</i>)			0.722			
RBC (1–5 TU)	0.018	0.122	0.882	1.018	0.802	1.294
RBC (6–10 TU)	0.242	0.278	0.385	1.274	0.738	2.199
RBC (11–15 TU)	-0.526	0.553	0.341	0.591	0.200	1.746
RBC (> 15 TU)	0.217	0.670	0.747	1.242	0.334	4.619
PLT (TU)	0.236	0.225	0.295	1.266	0.814	1.968
No FFP (<i>reference</i>)			0.454			
FFP (1–5 TU)	0.218	0.200	0.278	1.243	0.839	1.841
FFP (>5 TU)	0.381	0.425	0.370	1.464	0.637	3.363
UICC stage 2b–3	0.816	0.129	0.000	2.260	1.756	2.909
Grading G 1-2 (<i>reference</i>)			0.000			
No grading due to neoadjuvant therapy	-0.350	0.328	0.286	0.705	0.370	1.340
Grading G 3-4	0.552	0.105	0.000	1.737	1.414	2.134
Resection margin status R1	0.264	0.122	0.030	1.302	1.026	1.653
Pancreatic head cancer	-0.362	0.119	0.002	0.696	0.552	0.878
Neoadjuvant chemotherapy	0.626	0.299	0.036	1.871	1.042	3.358
Neoadjuvant radiotherapy	-0.305	0.355	0.391	0.737	0.367	1.479
IORT	0.674	0.349	0.054	1.963	0.990	3.893
Adjuvant therapy	-0.314	0.156	0.044	0.731	0.539	0.991
Mean FiO ₂	-0.010	0.008	0.217	0.990	0.975	1.006

The *p*-values of the regression coefficients were calculated using the Wald-Test. Hazard ratios (Exp(B)) estimated from the Cox analysis were reported as relative risks with corresponding 95% CIs. Boldface indicates *p*-values < 0.05. PC, Pancreatic cancer; B, Coefficient of variable; SE, Standard error; BMI, Body mass index; UICC, Tumor classification according to the Union for International Cancer Control; IORT, intraoperative radiation therapy; FiO₂, Fraction of inspired oxygen; RBC, Red blood cells; FFP, Fresh frozen plasma; PLT, Platelet concentrates; TU, Transfusion units.

tumor entities (26). We included patients with CRC, PC, and HC. We demonstrated an independent association of FiO₂ with recurrence-free survival for CRC surgery patients but not for patients undergoing PC surgery. Interestingly, Podolyak et al. and Jiang et al. who did not find differences regarding cancer-free survival investigated only patients with elective colectomy in their *post-hoc* analysis, including RCTs (32, 33). In the *post-hoc* analysis of the PROXI trial, about half the patients underwent colorectal surgery (12). A subgroup analysis for non-colorectal procedures was not conducted, although cancer histology was considered (12).

Additional adverse effects of high-FiO₂ affecting the cardiovascular and respiratory systems have been reported in the literature. Hyperoxia induces increased peripheral vascular resistance, promotes reduced cardiac output, and mediates coronary vasoconstriction (14, 35). A *post-hoc* analysis of the PROXI-trial showed that patients with a

FiO₂ of 80% had a significantly increased risk of myocardial infarction, acute coronary syndrome, or death (36). Contrary, the authors of a systematic review and meta-analysis concluded, based on 17 RCTs and two non-randomized studies, that perioperative supplemental oxygen was not associated with relevant complications (10). Consistent with this report, our analysis did not reveal differences for secondary cardiovascular endpoints or redo surgery.

WHO, ACS (American College of Surgeons), and CDC (Centers for Disease Control and Prevention) recommends supplemental oxygen with the aim to prevent SSI. In our study, SSI did not differ between the high- and low-FiO₂ groups. One could argue that the FiO₂ in the high-FiO₂ group was not sufficiently high to prevent SSI. However, the incidence of SSI reported in this study is lower than reported in most of the RCTs testing different oxygen levels in abdominal cancer surgery patients.

TABLE 4 | Secondary outcome analysis.

Overall survival	Analysis set (n = 1084)	Entity-controlled low-FiO ₂ (n = 543)	Entity-controlled high-FiO ₂ (n = 541)	p value
(A) Overall Survival entity-controlled low-FiO₂ group compared to the entity-controlled high-FiO₂ group				
CRC:	n = 405	n = 203	n = 202	0.525
Number of patients alive after one year (1-year survival rate in %)	405 (100) 392 (96.8)	203 (100) 198 (97.5)	202 (100) 194 (96.0)	
Number of patients alive after five years (5-year survival rate in %)				
PC:	n = 652	n = 326	n = 326	
Number of patients alive after one year (1-year survival rate in %)	570 (87.4) 281 (43.1)	287 (88.0) 138 (42.3)	283 (86.8) 143 (43.9)	
Number of patients alive after five years (5-year survival rate in %)				
HC:	n = 27	n = 14	n = 13	
Number of patients alive after one year (1-year survival rate in %)	27 (100) 27 (100)	14 (100) 14 (100)	13 (100) 13 (100)	
Number of patients alive after five years (5-year survival rate in %)				
Secondary outcome	Analysis set (n = 1084)	low-FiO ₂ (n = 542)	high-FiO ₂ (n = 542)	p value
(B) Other secondary outcomes low-FiO₂ group compared to the high-FiO₂ group				
Cardiovascular event during hospitalization, n (%)	10 (0.9)	5 (0.9)	5 (0.9)	1.000
SSI, n (%)	116 (10.7)	61 (11.2)	55 (10.1)	0.556
Superficial incisional	60 (5.5)	31 (5.7)	29 (5.4)	0.791
Deep incisional	4 (0.4)	3 (0.6)	1 (0.2)	0.316
Organ/ space	52 (4.8)	27 (5.0)	25 (5.0)	0.776
Sepsis, n (%)	11 (1.0)	5 (0.9)	6 (1.1)	0.762
Reoperation during hospitalization, n (%)	76 (7.0)	40 (7.4)	36 (6.6)	0.634

(A) 1-year and 5-year overall survival were estimated by the Kaplan Meier method. P-value is referring to the stratified log rank test with entities as strata. **(B)** Categorical variables were compared using the chi-square test. Boldface indicates p-values < 0.05. Occurrence of myocardial infarction, cerebral infarction, or transitory ischemic attack during hospitalization was subsumed as cardiovascular events. FiO₂, Fraction of inspired oxygen; SSI, surgical site infection; CRC, Colorectal cancer; PC, Pancreatic cancer.

Our study has some limitations that need to be addressed. We performed a retrospective, single-center study with a limited set of exemplary tumor entities. The number of individuals included in the analysis was limited by the availability of digitalized anesthesia records, and only patients recruited in the surgical databases could be analyzed. The choice of FiO₂ values was not standardized and the patients were equally split into the low- and high-FiO₂ groups. The patients' intraoperative FiO₂ levels were compared by the calculation of the individual mean FiO₂, but the duration of exposure and individual dose during surgery were not included in this calculation. A consequence of the retrospective nature of our study is that we do not have full control over confounders. As tumor entity itself affects outcome, and we conducted an analysis stratified for entities and performed a cox regression analysis to control for confounders. However, we cannot fully exclude, that additional confounders affected findings reported in this study.

In conclusion, we demonstrate that, within a moderate range of FiO₂, higher FiO₂ during abdominal cancer surgery was associated with longer recurrence-free survival. In colorectal cancer surgery, increased FiO₂ was independently associated with increased recurrence-free survival. The findings will be instrumental for designing prospective studies delineating effects

of certain FiO₂ on cancer development and progression for specific patient populations. Until definite evidence from large-scale randomized controlled trials is available, anesthesiologist, in the absence of relevant clinical conditions warranting specific FiO₂ values, should aim for an intraoperative FiO₂ of 50% in abdominal cancer surgery as this might benefit oncological outcome.

DATA AVAILABILITY STATEMENT

The data analyzed in this study is subject to the following licenses/restrictions: Datenschutzgrundverordnung. Requests to access these datasets should be directed to jan.larmann@med.uni-heidelberg.de.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of the Medical Faculty of the Ruprecht-Karls-University, Heidelberg. Written informed consent for participation was not required for

this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

SD, VS, RK, and JL designed research and study protocol. SD, VS, LK, SK, and JL formal analysis. JL, SD, and VS statistical analysis. SK methodology and statistical consultation. SD, VS, RK, LK, KH, MS, TH, MB, and MW contributed to the data curation. SD, VS, and JL wrote the first draft of the manuscript. All authors critically reviewed and revised the manuscript and approved the final work.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fmed.2021.761786/full#supplementary-material>

REFERENCES

- Greif R, Akça O, Horn EP, Kurz A, Sessler DI. Supplemental perioperative oxygen to reduce the incidence of surgical-wound infection. *N Engl J Med.* (2000) 342:161–7. doi: 10.1056/NEJM200001203420303
- Qadan M, Akça O, Mahid SS, Hornung CA, Polk HC. Perioperative supplemental oxygen therapy and surgical site infection: a meta-analysis of randomized controlled trials. *Arch Surg.* (2009) 144:359–66. doi: 10.1001/archsurg.2009.1
- Pryor KO, Fahey TJ, Lien CA, Goldstein PA. Surgical site infection and the routine use of perioperative hyperoxia in a general surgical population: a randomized controlled trial. *Jama.* (2004) 291:79–87. doi: 10.1001/jama.291.1.79
- de Jonge S, Egger M, Latif A, Loke YK, Berenholtz S, Boermeester M, et al. Effectiveness of 80% vs 30–35% fraction of inspired oxygen in patients undergoing surgery: an updated systematic review and meta-analysis. *Br J Anaesth.* (2019) 122:325–34. doi: 10.1016/j.bja.2018.11.024
- Ban KA, Minei JP, Laronga C, Harbrecht BG, Jensen EH, Fry DE, et al. American college of surgeons and surgical infection society: surgical site infection guidelines, 2016 update. *J Am Coll Surg.* (2017) 224:59–74. doi: 10.1016/j.jamcollsurg.2016.10.029
- Berrios-Torres SI, Umscheid CA, Bratzler DW, Leas B, Stone EC, Kelz RR, et al. Centers for disease control and prevention guideline for the prevention of surgical site infection, 2017. *JAMA Surg.* (2017) 152:784–91. doi: 10.1001/jamasurg.2017.0904
- WorldHealthOrganization. *Global Guidelines for the Prevention of Surgical Site Infection.* © World Health Organization (2018).
- Cohen B, Schacham YN, Ruetzler K, Ahuja S, Yang D, Mascha EJ, et al. Effect of intraoperative hyperoxia on the incidence of surgical site infections: a meta-analysis. *Br J Anaesth.* (2018) 120:1176–86. doi: 10.1016/j.bja.2018.02.027
- Smith BK, Roberts RH, Frizelle FA. O(2) No Longer the Go(2): a systematic review and meta-analysis comparing the effects of giving perioperative oxygen therapy of 30% FiO(2) to 80% FiO(2) on surgical site infection and mortality. *World J Surg.* (2020) 44:69–77. doi: 10.1007/s00268-019-05224-3
- Mattishent K, Thavarajah M, Sinha A, Peel A, Egger M, Solomkin J, et al. Safety of 80% vs 30–35% fraction of inspired oxygen in patients undergoing surgery: a systematic review and meta-analysis. *Br J Anaesth.* (2019) 122:311–24. doi: 10.1016/j.bja.2018.11.026
- Meyhoff CS, Jorgensen LN, Wetterslev J, Christensen KB, Rasmussen LS. Increased long-term mortality after a high perioperative inspiratory oxygen fraction during abdominal surgery: follow-up of a randomized clinical trial. *Anesth Analg.* (2012) 115:849–54. doi: 10.1213/ANE.0b013e3182652a51
- Meyhoff CS, Jorgensen LN, Wetterslev J, Siersma VD, Rasmussen LS. Risk of new or recurrent cancer after a high perioperative inspiratory oxygen fraction during abdominal surgery. *Br J Anaesth.* (2014) 113:i74–81. doi: 10.1093/bja/aeu110
- WorldHealthOrganization. *Global Guidelines for the Prevention of Surgical Site Infection.* Geneva, (2016).
- Martin DS, Grocott MPlII. Oxygen therapy in anaesthesia: the yin and yang of O₂. *Br J Anaesth.* (2013) 111:867–71. doi: 10.1093/bja/aet291
- Cuschieri S. The STROBE guidelines. *Saudi J Anaesth.* (2019) 13:S31–s4. doi: 10.4103/sja.SJA_543_18
- Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc.* (1958) 53:457–81. doi: 10.1080/01621459.1958.10501452
- Mantel N. Evaluation of survival data and two new rank order statistics arising in its consideration. *Cancer Chemother Rep.* (1966) 50:163–70.
- Cox DR. Regression Models and Life-Tables. *J R Stat Soc B.* (1972) 34:187–220. doi: 10.1111/j.2517-6161.1972.tb00899.x
- Nielsen S, Degenhardt L, Hoban B, Gisev N. A synthesis of oral morphine equivalents (OME) for opioid utilisation studies. *Pharmacoepidemiol Drug Saf.* (2016) 25:733–7. doi: 10.1002/pds.3945
- Klaiber U, Schnaidt ES, Hinz U, Gaida MM, Heger U, Hank T, et al. Prognostic factors of survival after neoadjuvant treatment and resection for initially unresectable pancreatic cancer. *Ann Surg.* (2021) 273:154–62. doi: 10.1097/SLA.0000000000003270
- Strobel O, Hank T, Hinz U, Bergmann F, Schneider L, Springfield C, et al. Pancreatic cancer surgery: the new r-status counts. *Ann Surg.* (2017) 265:565–73. doi: 10.1097/SLA.0000000000001731
- Ulrich CM, Gigic B, Böhm J, Ose J, Viskochil R, Schneider M, et al. The colocale study: a paradigm of transdisciplinary science in colorectal cancer outcomes. *Cancer Epidemiol Biomarkers Prev.* (2019) 28:591–601. doi: 10.1158/1055-9965.EPI-18-0773
- Selvendiran K, Kuppusamy ML, Ahmed S, Bratasz A, Meenakshisundaram G, Rivera BK, et al. Oxygenation inhibits ovarian tumor growth by downregulating STAT3 and cyclin-D1 expressions. *Cancer Biol Ther.* (2010) 10:386–90. doi: 10.4161/cbt.10.4.12448
- Nishida N, Arizumi T, Takita M, Kitai S, Yada N, Hagiwara S, et al. Reactive oxygen species induce epigenetic instability through the formation of 8-hydroxydeoxyguanosine in human hepatocarcinogenesis. *Dig Dis.* (2013) 31:459–66. doi: 10.1159/000355245

25. Schneider M, Weitz J. Acute oxygen deprivation and hypoxia tolerance. *Dtsch Med Wochenschr.* (2008) 133:2168–72. doi: 10.1055/s-0028-1091258
26. Mabeesh N, Amir S. Hypoxia-inducible factor (HIF) in human tumorigenesis. *Histol Histopathol.* (2007) 22:559–72.
27. Ni J, Wang X, Stojanovic A, Zhang Q, Wincher M, Bühler L, et al. Single-Cell RNA sequencing of tumor-infiltrating NK cells reveals that inhibition of transcription factor HIF-1 α unleashes NK cell activity. *Immunity.* (2020) 52:1075–87.e8. doi: 10.1016/j.immuni.2020.05.001
28. Hirota K, Semenza GL. Regulation of angiogenesis by hypoxia-inducible factor 1. *Crit Rev Oncol Hematol.* (2006) 59:15–26. doi: 10.1016/j.critrevonc.2005.12.003
29. Semenza GL. Targeting HIF-1 for cancer therapy. *Nat Rev Cancer.* (2003) 3:721–32. doi: 10.1038/nrc1187
30. Ruan K, Song G, Ouyang G. Role of hypoxia in the hallmarks of human cancer. *J Cell Biochem.* (2009) 107:1053–62. doi: 10.1002/jcb.22214
31. Milano M, Schneider M. EPO in cancer anemia: benefits and potential risks. *Crit Rev Oncol Hematol.* (2007) 62:119–25. doi: 10.1016/j.critrevonc.2006.11.011
32. Podolyak A, Sessler DI, Reiterer C, Fleischmann E, Akça O, Mascha EJ, et al. Perioperative supplemental oxygen does not worsen long-term mortality of colorectal surgery patients. *Anesth Analg.* (2016) 122:1907–11. doi: 10.1213/ANE.0000000000001316
33. Jiang Q, Kurz A, Zhang X, Liu L, Yang D, Sessler DI. Supplemental intraoperative oxygen and long-term mortality: subanalysis of a multiple crossover cluster trial. *Anesthesiology.* (2021) 134:709–21. doi: 10.1097/ALN.0000000000003694
34. Kurz A, Fleischmann E, Sessler DI, Buggy DJ, Apfel C, Akça O. Effects of supplemental oxygen and dexamethasone on surgical site infection: a factorial randomized trial. *Br J Anaesth.* (2015) 115:434–43. doi: 10.1093/bja/aev062
35. Wijesinghe M, Perrin K, Ranchord A, Simmonds M, Weatherall M, Beasley R. Routine use of oxygen in the treatment of myocardial infarction: systematic review. *Heart.* (2009) 95:198–202. doi: 10.1136/hrt.2008.148742
36. Fønnes S, Gögenur I, Søndergaard ES, Siersma VD, Jørgensen LN, Wetterslev J, et al. Perioperative hyperoxia - Long-term impact on cardiovascular complications after abdominal surgery, a post hoc analysis of the PROXI trial. *Int J Cardiol.* (2016) 215:238–43. doi: 10.1016/j.ijcard.2016.04.104

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