Impact of anesthetic factors on prognosis of patients with non-small cell lung cancer after surgery

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Background: Nowadays, the influence of anesthesia management on the prognosis of cancer patients has been widely concerned. The goal of this study is to assess the association between anesthetic factors and the prognosis of patients with non-small cell lung cancer (NSCLC) after surgery.

Methods: Patients with NSCLC who underwent surgery from January 1, 2006, to December 31, 2009 were selected. Cox proportional hazards model and Logistic regression analysis model were used to screen the independent predictors of prognosis of patients. The primary endpoint was postoperative overall survival (OS), and the secondary endpoint was postoperative recurrence-free survival (RFS) and postoperative pulmonary complications (PPCs).

Results: A total of 588 patients were included into the final analysis. The overall RFS was 4.4 [interquartile range (IQR), 1.1–10.1] years, and the OS was 6.2 (IQR, 2.4–10.2) years. Age ≥60 years, advanced tumor stage, and maximal tumor size >3 cm were associated with shortened survival, whereas high BMI grade, mediastinal lymph node dissection, perioperative fentanyl equivalents >28.2 µg/kg, and high tumor grade were associated with prolonged survival (P<0.05); perioperative glucocorticoid administration delayed recurrence (P<0.05); advanced tumor stage and perioperative fentanyl equivalents >28.2 µg/kg were associated with an increased PPCs risk (P<0.05).

Conclusions: The findings from this study revealed that perioperative anesthetic factors may impact the prognosis of patients with NSCLC after surgery. Perioperative opioid and glucocorticoid exposure were independent predictors for outcomes. However, perioperative fentanyl equivalents over 28.2 µg/kg seemed to be beneficial to OS, but contribute to the occurrence of PPCs.

Keywords: Anesthetic factor; non-small cell lung cancer (NSCLC); prognosis; opioid

Introduction

According to the global cancer statistics in 2020, there were 2,206,771 new cases of lung cancer worldwide, and at least 1,766,144 patients died of lung cancer (1). One of the leading causes of cancer mortality in both sexes is lung cancer. According to the American Cancer Society for Lung Cancer in the United States for 2020, it accounted for 25% of all cancer deaths (1). Non-small cell lung cancer (NSCLC) accounts for about 84% of all lung cancer cases and there has been a revolution of new advances in

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the management of NSCLC with remarkable progresses in screening, diagnosis, and treatment since the past decade (2). If the patient condition is feasible, surgical resection remains the single most recommended and successful option for cure (3). However, some patients experience recurrence and metastasis of lung cancer after surgery (4). The perioperative period constitutes an important stage of disease management in cancer surgery because circulating tumor cells shed from the primary tumor into the patient's bloodstream might lead to the formation of new micro-metastases (5). Experimental and observational research suggests that the immune function of patients is blunted due to the cytotoxic effect of natural killer (NK) cells and the reaction of T cells attenuated by perioperative traumatic stress response during the perioperative period (6). Various perioperative anesthetic factors, including anesthesia techniques, anesthetic agents, intraoperative blood transfusion and so forth, have been implicated in tumor recurrence or metastasis through effects on cancer cell signaling, the immune response, or modulation of the neuroendocrine stress response (7), but it seems to be difficult to reach a conclusion whether they promote or inhibit the progression of cancer. The previous study has revealed the perioperative administration of dexamethasone and flurbiprofen axetil, which is a kind of nonselective cyclooxygenase (COX) inhibitor with high binding affinity to the site of lesion, may improve patients' long-term survival after surgery for NSCLC (8).

Several literatures have also shown that the association

of perioperative anesthesia management and postoperative complications (9,10). Postoperative pulmonary complications (PPCs) which refers to a series of lung complications that occur after surgery such as atelectasis and pneumonia, are the most frequently observed complications following lung resection (11). PPCs have a significant clinical impact associated with the short-term rehabilitation of patients (12). The decrease of complications is conducive to promote postoperative rehabilitation and improve the short-term prognosis of patients (13).

So far, there are not many retrospective studies on NSCLC with the follow-up period of over 10 years and a combination of long-term survival with short-term outcomes to comprehensively analyze the correlation between perioperative factors and prognosis of patients. The aim of this study was to retrospectively investigate the prognostic factors of patients with NSCLC undergoing surgery through analysis of 10-year follow-up data, and to evaluate the effect of perioperative anesthesia management on postoperative short-term rehabilitation and long-term survival of patients, in order to provide a theoretical basis for optimizing perioperative management and improving the prognosis of cancer patients. We present this article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-1812/rc).

Methods

Patients

The electronic medical records system of Peking University Cancer Hospital was reviewed to screen consecutive patients undergoing surgical procedures between January 1, 2006 and December 31, 2009. The inclusion criteria were: (I) pathologically confirmed NSCLC; (II) underwent segmentectomy, lobectomy or total pneumonectomy. The exclusion criteria were as follows: (I) combined with other primary malignant tumors; (II) recurrent lung tumor; (III) long-term steroid exposure; (IV) impossible follow-up because of missing data. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The Clinical Research Ethics Committee of Peking University Cancer Hospital approved the study (No. 2019YJZ22-GZ02) and waived the need for written informed consent given that all patients were operated on many years ago and lived all over the country. But oral consent was obtained from each patient included in the study.

Highlight box

Key findings
- Perioperative opioid and glucocorticoid exposure were independent predictors for outcomes.

What is known and what is new?
- Perioperative anesthesia management affects the prognosis of patients with lung cancer after surgery to some extent.
- This study found that perioperative opioid exposure seems to be beneficial to long-term survival, but has unfavorable effect on short-term outcomes of patients with non-small cell lung cancer after surgery.

What is the implication, and what should change now?
- This study suggested that the rational use of opioids should be able to balance the pros and cons of opioids, and clinicians should take into account of the cancer subtypes and the specific features of each individual patient on the development of perioperative analgesia strategies for patients with non-small cell lung cancer.

Anesthesia method

Patients was induced with intravenous anesthetics (propofol and/or etomidate) and opioids (fentanyl or sufentanil). Anesthesia was maintained with inhalational anesthetics (sevoflurane or isoflurane, with or without nitrous oxide) and opioids (fentanyl and/or sufentanil). In some cases, combined epidural anesthesia was also administered with local anesthetics (lidocaine and/or ropivacaine) according to the preference of anesthesiologists. After surgery, postoperative analgesia was provided with patient-controlled analgesia pumps, which were performed with ropivacaine for epidural analgesia or opioids (morphine or sufentanil) for intravenous analgesia.

Data collection

Information of patients were collected and sorted through the medical record system as follows: demographic characteristics (age, gender, height and weight), preoperative information (comorbidity, American Society of Anesthesiologists classification, tumor location, lymph node metastasis according to imageological examination, history of smoking and drinking, and preoperative chemotherapy), anesthesia-related information (anesthesia technique, anesthetics administration, intraoperative fluid infusion, intraoperative blood transfusion, perioperative total amount of fentanyl equivalents, perioperative glucocorticoids, and nonsteroidal anti-inflammatory drugs administration), surgical information (surgical procedure, mediastinal lymph node dissection, duration of surgery), and postoperative information (PPCs, maximal tumor size, pathological diagnosis, grade of tumor cell differentiation, chemotherapy and/or radiotherapy). The consumption of opioids was involved in preoperative sedation, intraoperative anesthesia, patient control analgesia and remedial medications due to insufficient postoperative analgesia, and eventually converted to fentanyl equivalents. The fentanyl equivalents conversion is sufentanil 0.1 µg, remifentanil 1 µg, or 110 µg morphine for 1 µg fentanyl. Data assignment was conducted with reference to the previously published study (8).

Follow-up

All patients were followed up by specially assigned personnel through outpatient review and telephone inquiry. Patients were followed up every 6 months within 1 year after surgical procedures, and once a year thereafter. Tumor recurrence and patient survival were confirmed during each follow-up. The time of tumor recurrence and death was recorded. Tumor recurrence including local recurrence or distant recurrence/metastasis was confirmed by imageological examination. The time of recurrence was the earliest date of clinical diagnosis made by surgeons or radiologists according to imageological evidence. The time of death was the date appeared in the medical certificate of death. The termination of follow-up were death, loss of follow-up or completed follow-up of 10 years. Last follow-up date was on July 1, 2020.

Endpoints and statistical analysis

The primary endpoint was overall survival (OS), which is defined as the duration in years from surgery to death from any cause. The secondary endpoint was recurrence-free survival (RFS), which was defined as the duration in years from surgery to recurrence or death, whichever happened first, and PPCs, including prolonged air leakage over 5 days, pleural effusion requiring drainage, atelectasis and pneumonia, were diagnosed by postoperative imageological examination and clinicians.

Numeric data with abnormal distribution were presented as median [interquartile range (IQR)]. Categorical data were presented as numbers (%). Time-to-event endpoints including RFS and OS were estimated using the Kaplan-Meier univariable analyses, and were compared using log-rank tests between layers. For continuous variables, cutoff values between layers were selected based on clinical significance, literatures, or median values. Relevant variables with P value <0.10 in Kaplan-Meier survival analyses were included into the Cox proportional hazard model for multivariable analyses to identify independent factors that were associated with RFS or OS. Univariable and multivariable logistic regression were performed to estimate the association between perioperative factors and PPCs. Variables that were possibly associated with the PPCs (P value <0.05) in univariable logistic regression analyses were included in the multivariable model to determine potentially independent risk factors for PPCs. Statistical analysis was performed using SPSS19.0 (SPSS, Inc., Chicago, IL, USA). Statistical significance was set at a two-sided P value <0.05.

Results

Patient recruitment and follow-up

A total of 659 consecutive patients with NSCLC who had undergone lung resection between January 1, 2006 and
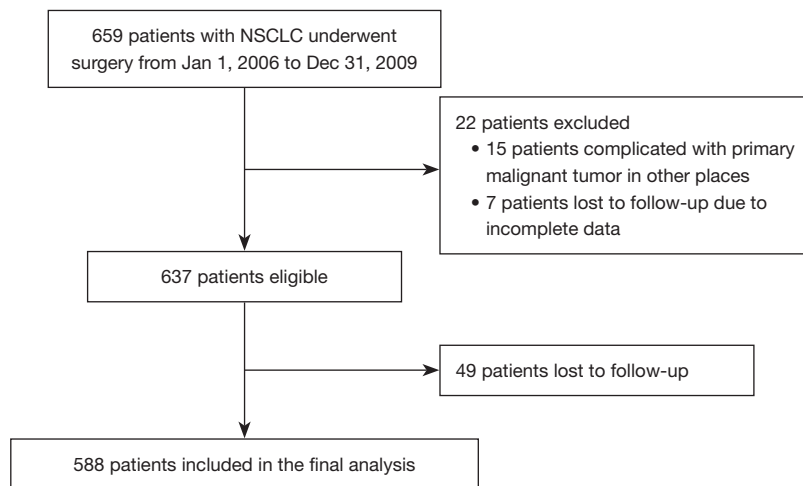
Figure 1 Flowchart of the study. NSCLC, non-small cell lung cancer.

December 31, 2009 were retrospectively reviewed in the study. With in depth consideration of the data, 22 cases were excluded, among which 15 cases were complicated with other primary malignant tumors, and 7 cases had missing clinical data. During the follow-up period, 49 patients were lost to follow-up, and the loss rate was 7.4% (49/659). In total, 588 patients were enrolled in the statistical analysis finally (*Figure 1*).

The postoperative follow-up was terminated on June 30, 2020. The median duration of postoperative follow-up was 7.4 (IQR, 3.3–10.2) years. By the end of follow-up, 342 of 588 patients died, with a total mortality rate of 58.2% and an overall recurrence/mortality rate of 61.7%. The overall RFS was 4.4 (IQR, 1.1–10.1) years, and the OS was 6.2 (IQR, 2.4–10.2) years (*Table 1*). The cumulative RFS rate and OS rate at 1, 3, 5, and 10 years were 65.0%, 51.4%, 43.6 %, 37.7% and 79.3%, 62.1%, 52.2%, 40.4% respectively (*Table 2*).

Predictor analysis

OS

Kaplan-Meier univariable analyses was used to screen out fifteen factors (P<0.10), including age, BMI, hypertension history, preoperative chemotherapy, tumor stage, surgery procedure, mediastinal lymph node dissection, duration of surgery, intraoperative blood transfusion, perioperative fentanyl equivalents, perioperative glucocorticoids administration, tumor grade, maximal tumor size, postoperative radiotherapy and chemotherapy (*Table 3*,

Figure 2).

All the fifteen factors were taken into consideration in multivariable Cox regression model and 8 independent factors were eventually identified. Among them, age ≥60 years (HR =1.372, 95% CI: 1.096–1.719, P=0.006), advanced tumor stage (HR =1.525, 95% CI: 1.361–1.710, P<0.001), maximal tumor size >3 cm (HR =1.364, 95% CI: 1.092–1.703, P=0.006) were associated with shortened survival, whereas high BMI grade (HR =0.796, 95% CI: 0.679–0.933, P=0.005), mediastinal lymph node dissection (HR =0.588, 95% CI: 0.400–0.862, P=0.007), perioperative fentanyl equivalents >28.2 µg/kg (HR =0.779, 95% CI: 0.619–0.980, P=0.033), and high tumor grade (HR =0.853, 95% CI: 0.749–0.971, P=0.017) were associated with prolonged survival (*Table 4*).

RFS

The Kaplan-Meier univariable analysis indicated that the following factors (P<0.10) were significantly associated with RFS: BMI, hypertension history, diabetes, preoperative chemotherapy, tumor stage, surgery procedure, mediastinal lymph node dissection, duration of surgery, intraoperative blood transfusion, perioperative fentanyl equivalents, perioperative glucocorticoids administration, tumor grade, maximal tumor size, PPCs, postoperative radiotherapy and chemotherapy (*Table 3*, *Figure 3*).

The sixteen factors above were included into multivariable Cox regression model and 6 independent factors were eventually identified. Upon multivariable analyses, advanced tumor stage (HR =1.526, 95% CI:

Table 1 Baseline and perioperative data

Variables	Median [IQR] or n (%)
Age (years)	61 [53–67]
BMI (kg/m^2)	24.2 [22.2–26.2]
Gender	
Female	214 (36.4)
Male	374 (63.6)
Preoperative complication	
Coronary heart disease	37 (6.3)
Hypertension	156 (26.5)
Arrhythmia	41 (7.0)
Diabetes	62 (10.5)
Smoking	313 (53.2)
Drinking	135 (23.0)
Preoperative chemotherapy	60 (10.2)
ASA	
I	215 (36.6)
II	373 (63.4)
Tumor stage[†]	
I	265 (45.1)
II	114 (19.4)
III	161 (27.4)
IV	48 (8.1)
Anesthesia technique	
General anesthesia	448 (76.2)
Combined epidural-general anesthesia	140 (23.8)
Duration of surgery (h)	3.8 [3.1–4.4]
Total intraoperative fluid volume (mL)	1,600 [2,000–2,500]
Intraoperative blood transfusion	9 (1.5)
Perioperative fentanyl equivalents (µg/kg)	28.2 [7.7–35.9]
Perioperative NSAIDs administration	332 (53.5)
Perioperative glucocorticoids administration	353 (56.8)
Surgical procedure	
Segmentectomy	131 (22.3)
Lobectomy	436 (74.1)
Total pneumectomy	21 (3.6)

Table 1 (continued)

Table 1 (continued)

Variables	Median [IQR] or n (%)
Mediastinal lymph node dissection	527 (89.6)
Grade of tumor cell differentiation	
Undifferentiation	81 (13.8)
Poor differentiation	75 (12.8)
Moderate differentiation	364 (61.9)
High differentiation	68 (11.6)
Maximal tumor size (cm)	3 [2.0–4.2]
PPCs	413 (70.2)
Prolonged air leakage over 5 days	359 (61.1)
Pleural effusion requiring drainage	74 (12.6)
Atelectasis	27 (4.5)
Pneumonia	21 (3.7)
Postoperative radiotherapy	24 (4.1)
Postoperative chemotherapy	285 (48.5)
Death	342 (58.2)
Recurrence or death	363 (61.7)
Overall survival (years)	6.2 [2.4–10.2]
Recurrence-free survival (years)	4.4 [1.1–10.1]
Postoperative follow-up (years)	7.4 [3.3–10.2]

[†], tumor stage according to the 8th edition of TNM staging system for lung cancer. ASA, American Society of Anesthesiologists; BMI, body mass index; NSAIDs, non-steroid anti-inflammatory drugs; IQR, interquartile range; PPCs, postoperative pulmonary complications.

Table 2 The survival status of patients after surgery

Survival rate	OS (%)	RFS (%)
Survival rate at 1 year	79.3 (75.7–82.3)	65.0 (61.0–68.7)
Survival rate at 3 years	62.1 (58.0–65.9)	51.4 (47.3–55.3)
Survival rate at 5 years	52.2 (48.0–56.1)	43.6 (39.6–47.6)
Survival rate at 10 years	40.4 (36.2–44.5)	37.7 (33.7–41.7)

Results are mean (95% confidence interval). OS, overall survival; RFS, recurrence-free survival.

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Table 3 Predictors of survival (Kaplan-Meier univariable analyses)

Variables	N	RFS		OS	
		n (%)	P value	n (%)	P value
Age (years)			0.123		0.053
<60	258	112 (43.4)		122 (47.3)	
≥60	330	113 (34.2)		124 (37.6)	
Gender			0.962		0.118
Female	214	81 (37.9)		96 (44.9)	
Male	374	144 (38.5)		150 (40.1)	
BMI (kg/m²)			0.083		0.031
<18.5	19	4 (21.1)		5 (26.3)	
18.5–24.9	343	123 (35.9)		135 (39.4)	
25–27.9	170	67 (39.4)		72 (42.4)	
≥28	56	31 (55.4)		34 (60.7)	
Coronary heart disease			0.139		0.657
No	551	208 (37.7)		229 (41.6)	
Yes	37	17 (45.9)		17 (45.9)	
Hypertension			<0.001		0.002
No	432	147 (34.0)		164 (38.0)	
Yes	156	78 (50.0)		82 (52.6)	
Arrythmia			0.476		0.398
No	547	212 (38.8)		231 (42.2)	
Yes	41	13 (31.7)		15 (36.6)	
Diabetes			0.093		0.189
No	526	195 (37.1)		215 (40.9)	
Yes	62	30 (48.4)		31 (50.0)	
Smoking			0.734		0.221
No	275	103 (37.5)		120 (43.6)	
Yes	313	122 (39.0)		126 (40.3)	
Drinking			0.900		0.472
No	453	172 (38.0)		192 (42.4)	
Yes	135	53 (39.3)		54 (40.0)	
Preoperative chemotherapy			0.063		0.028
No	528	206 (39.0)		226 (42.8)	
Yes	60	41 (31.7)		20 (33.3)	
ASA			0.342		0.303
I	215	81 (37.7)		86 (40.0)	
II	373	144 (38.6)		160 (42.9)	

Table 3 (*continued*)

Table 3 (*continued*)

Variables	N	RFS		OS	
		n (%)	P value	n (%)	P value
Tumor stage[†]			<0.001		<0.001
I	265	146 (55.1)		158 (59.6)	
II	114	44 (38.6)		46 (40.4)	
III	161	29 (18.0)		35 (21.7)	
IV	48	6 (12.5)		7 (14.6)	
Surgical procedure			<0.001		<0.001
Segmentectomy	131	36 (27.5)		38 (29.0)	
Lobectomy	436	178 (40.8)		197 (45.2)	
Total pneumectomy	21	11 (52.4)		11 (52.4)	
Mediastinal lymph node dissection			<0.001		<0.001
No	61	10 (16.4)		11 (18.0)	
Yes	527	215 (40.8)		235 (44.6)	
Anesthesia technique			0.168		0.399
General anesthesia	448	166 (37.1)		184 (41.1)	
Combined epidural-general anesthesia	140	59 (42.1)		62 (44.3)	
Duration of surgery (h)			0.019		0.012
≤3.0	129	40 (31.0)		42 (32.6)	
>3.0	459	185 (40.3)		204 (44.4)	
Total intraoperative fluid volume (mL)			0.492		0.659
≤2,000	306	116 (37.9)		127 (41.5)	
>2,000	282	109 (38.7)		119 (42.2)	
Intraoperative blood transfusion			0.099		0.027
No	579	224 (38.7)		245 (42.3)	
Yes	9	1 (11.1)		1 (11.1)	
Perioperative fentanyl equivalents (µg/kg)			0.081		0.007
≤28.2	294	101 (34.4)		110 (37.4)	
>28.2	294	117 (42.2)		136 (46.3)	
Perioperative NSAIDs administration			0.591		0.251
No	267	97 (36.3)		105 (39.3)	
Yes	321	128 (39.9)		141 (43.9)	
Perioperative glucocorticoids administration			0.016		0.047
No	256	90 (35.2)		98 (38.3)	
Yes	332	135 (40.7)		148 (44.6)	

Table 3 (*continued*)

Table 3 (*continued*)

Variables	N	RFS		OS	
		n (%)	P value	n (%)	P value
Grade of tumor cell differentiation			0.001		<0.001
Undifferentiation	81	36 (44.4)		38 (46.9)	
Poor differentiation	75	19 (25.3)		21 (28.0)	
Moderate differentiation	364	132 (36.3)		144 (39.6)	
High differentiation	68	38 (55.9)		43 (63.2)	
Maximal tumor size (cm)			<0.001		<0.001
≤3.0	327	142 (43.4)		157 (48.0)	
>3.0	261	83 (31.8)		89 (34.1)	
PPCs			0.080		0.117
No	175	78 (44.6)		83 (47.4)	
Yes	413	147 (35.6)		163 (39.5)	
Postoperative radiotherapy			<0.001		0.024
No	564	223 (39.5)		242 (42.9)	
Yes	24	2 (8.3)		4 (16.7)	
Postoperative chemotherapy			<0.001		<0.001
No	303	146 (48.2)		150 (49.5)	
Yes	285	79 (27.7)		96 (33.7)	

[†], tumor stage according to the 8th edition of TNM staging system for lung cancer. P<0.05 was considered statistically significant. RFS, recurrence-free survival; OS, overall survival; BMI, body mass index; ASA, American Society of Anesthesiologists; NSAIDs, Non-Steroid Anti-Inflammatory Drugs; PPCs, Postoperative pulmonary complications.
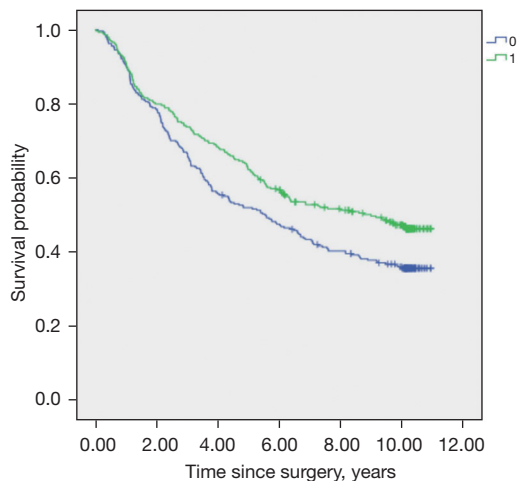

Figure 2 Kaplan-Meier curves showing overall survival for perioperative fentanyl equivalents (≤28.2 μg/kg =0, >28.2 μg/kg =1), P=0.007.

1.363–1.708, P<0.001), postoperative radiotherapy (HR =1.688, 95% CI: 1.050–2.714, P=0.031), and postoperative chemotherapy (HR =1.524, 95% CI: 1.223–1.899, P<0.001) were associated with early recurrence, whereas BMI (HR =0.825, 95% CI: 0.704–0.967, P=0.017), mediastinal lymph node dissection (HR =0.612, 95% CI: 0.421–0.889, P=0.010) and perioperative glucocorticoids administration (HR =0.791, 95% CI: 0.632–0.989, P=0.040) were associated with delayed recurrence (*Table 4*).

PPCs

Six factors (P<0.05) which were screened by univariable logistic regression analyses were included in the multivariable model (*Table 5*). Multivariable logistic regression analyses identified two independent factors: advanced tumor stage (OR =1.205, 95% CI: 1.002–1.448, P=0.047) and perioperative fentanyl equivalents >28.2 μg/kg

Table 4 Predictors of survival (multivariable Cox proportional hazard model)

Variable	RFS		OS	
	HR (95% CI)	P value	HR (95% CI)	P value
Age ≥60 years	–	–	1.372 (1.096–1.719)	0.006
BMI[†]	0.825 (0.704–0.967)	0.017	0.796 (0.679–0.933)	0.005
Preoperative hypertension	0.927 (0.707–1.214)	0.580	0.843 (0.640–1.110)	0.223
Preoperative diabetes	0.827 (0.653–1.048)	0.116	–	–
Preoperative chemotherapy	1.011 (0.716–1.429)	0.950	1.221 (0.862–1.729)	0.260
Tumor stage[‡]	1.526 (1.363–1.708)	<0.001	1.525 (1.361–1.710)	<0.001
Surgical procedure[§]	0.865 (0.678–1.103)	0.243	0.844 (0.655–1.087)	0.190
Duration of surgery >3.0 h	1.166 (0.883–1.540)	0.278	1.099 (0.830–1.456)	0.511
Intraoperative blood transfusion	1.360 (0.645–2.867)	0.419	1.808 (0.867–3.772)	0.115
Mediastinal lymph node dissection	0.612 (0.421–0.889)	0.010	0.588 (0.400–0.862)	0.007
Perioperative fentanyl equivalents >28.2 µg/kg	0.926 (0.741–1.158)	0.502	0.779 (0.619–0.980)	0.033
Perioperative glucocorticoids administration	0.791 (0.632–0.989)	0.040	0.812 (0.643–1.024)	0.078
Grade of tumor cell differentiation[¶]	0.914 (0.808–1.034)	0.153	0.853 (0.749–0.971)	0.017
Maximal tumor size >3 cm	1.179 (0.948–1.465)	0.138	1.364 (1.092–1.703)	0.006
PPCs	1.130 (0.890–1.434)	0.316	–	–
Postoperative radiotherapy	1.688 (1.050–2.714)	0.031	1.300 (0.798–2.115)	0.292
Postoperative chemotherapy	1.524 (1.223–1.899)	<0.001	1.112 (0.885–1.396)	0.363

[†], BMI was divided into four classes: underweight (<18.5 kg/m²), normal (18.5–24.9 kg/m²), overweight (25–28 kg/m²) and obesity (>28 kg/m²). The next class was compared to the last level. [‡], tumor stage was divided into four stages: I, II, III and IV. The next stage was compared to the last stage. [§], surgical procedure was divided into three categories: segmentectomy, lobectomy and total pneumectomy. Total pneumectomy was compared to lobectomy or segmentectomy. [¶], grade of tumor cell differentiation was divided into four grades: undifferentiation, poor differentiation, moderate differentiation and high differentiation. The next grade was compared to the last grade. P<0.05 was considered statistically significant. RFS, recurrence-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval; BMI, body mass index; PPCs, postoperative pulmonary complications.

(OR =1.623, 95% CI: 1.123–2.346, P=0.010) were associated with an increased PPCs risk (*Table 5*).

Discussion

NSCLC is one of the most common causes of cancer-deaths worldwide (14). Surgical treatment is the most effective method for early NSCLC. Previous literatures have demonstrated that tumor resection promotes local recurrence and distant metastasis (15,16). Explanations for this could include inadvertent spread of tumor cells due to surgical procedures, inhibited cell-mediated immunity in surgical stress response, and increased levels of vascular endothelial growth factor (VEGF) induced by surgery, which is closely related to tumor proliferation (17-19). For lung cancer patients, many perioperative factors apart from surgery may also affect patients' outcomes (20). Identifying these factors may provide valuable information for better strategy planning for perioperative management.

Patient-related and surgical factors

Lung cancer is a typical age-related disease. In the United States, the median age for lung cancer has reached 71 years old (21). In this cohort, the median age of patients with NSCLC was 61 (IQR, 53–67) years, and patients aged 60 years old or above accounted for 56.1% (*Tables 1,3*). Legras *et al.* reported that patients younger

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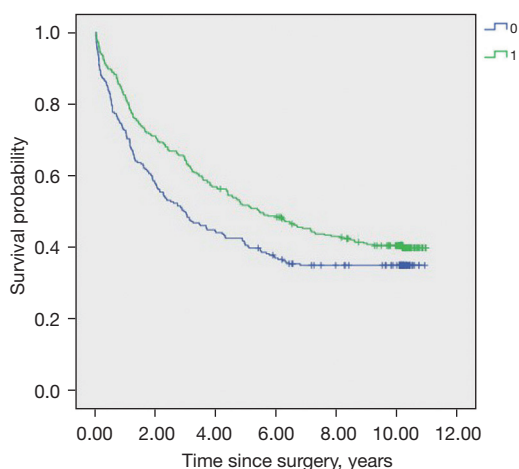

Figure 3 Kaplan-Meier curves showing recurrence-free survival for perioperative glucocorticoids administration (no =0, yes =1), P=0.016.

than 61 years old survived significantly longer than older patients (22). The findings from the study also suggested that age ≥60 years was associated with shortened survival, attributed to the declining function of the organs of the elderly and the disordered compensatory of vital organs induced by surgical stress stimulation (23). BMI is another important personal factor. A link between BMI and survival in cancer has always been sought since the past decade. It is reported that BMI <18.5 kg/m^2 was associated with shortened survival of lung cancer, and a decrease in BMI was associated with an increase in risk of death in all subsets of NSCLC (24,25). This is also found to be the case in this study.

TNM staging system is valid for defining prognosis and prognosis-related criteria in NSCLC (26). Advanced tumor stage reflects poor outcomes of patients with NSCLC. In the present study, advanced tumor stage showed a meaningful relationship in association with shortened survival (HR =1.525, 95% CI: 1.361–1.710, P<0.001), early recurrence (HR =1.526, 95% CI: 1.363–1.708, P<0.001), and high risk of PPCs (OR =1.205, 95% CI: 1.002–1.448, P=0.047), in accord with previous researches (27,28). Furthermore, metastasis to the lymph nodes is a main path of lung cancer metastasis and related to poor outcomes (29), while mediastinal lymph node dissection decreases the postoperative recurrence and death of patients with NSCLC (30). In this study, complete mediastinal lymph node dissection also prolonged survival and delayed recurrence. Meanwhile, larger tumor size indicates advanced clinical stages in some sense (31). A tumor size of 3 cm in

diameter has been regarded as the prognostic threshold in the staging of bronchogenic carcinoma since 1974 (32). Rena *et al.* found Tumor size ≤3 cm, adenocarcinoma histologic type and negative bronchial resection margins were associated with a more favorable outcome in their patient population (33). In this cohort, the tumor size over 3cm significantly shortened the OS rate. In addition, histological grading may be helpful for lung cancer management and deciding its prognosis (34). Similar to others, the results from this study found that high grade tumor-cell differentiation was associated with prolonged survival (34,35). It should also be mentioned that postoperative radiotherapy and chemotherapy were found to be associated with early recurrence in the current study. A possible reason is that most patients who received radiotherapy and chemotherapy were in advanced stages.

Perioperative opioids exposure

The perioperative use of opioids forms a crucial part of daily clinical practice in anesthesia. Opioids such as morphine, fentanyl, and sufentanil are the most widely used and effective analgesics (36), and previous study implicated that opioid impacted the oncological endpoint (37). Overall, reports on the relationship between opioid exposure and oncologic outcomes are contradictory and appear to reflect the influence of multiple factors of tumor biology and drug administration (38). For instance, morphine, the main component of opium, has the dual effect of on tumor development. Morphine may reduce NK cell activity and T-lymphocyte proliferation as well as cytokine secretion, and eventually promote tumor growth and metastasis (39). On the other hand, morphine was shown to inhibit the migration of tumor-infiltrating leukocytes and suppress angiogenesis associated with tumor growth (40). Silagy *et al.* and Zylla *et al.* reported opioid exposure was associated with shortened progression-free survival and OS in advanced-stage prostate cancer and renal cell carcinoma (41,42), whereas Du *et al.* and Montagna *et al.* demonstrated that opioids were protective against recurrence and associated with improved RFS in squamous oesophageal cancer and triple-negative breast cancer (43,44).

As far as lung cancer is concerned, we noted opioids were generally considered to have a negative effect on cancer and linked to worse oncologic outcomes in most of the literatures. Preclinical and retrospective data demonstrate that opioids promote lung cancer progression and metastasis and reduce survival (45). However, there

Table 5 Logistic regression analysis for postoperative pulmonary complications

Variable	Univariable		Multivariable	
	OR (95% CI)	P value	OR (95% CI)	P value
Age ≥60 years	1.227 (0.860–1.750)	0.259	–	–
Male gender	1.814 (1.263–2.605)	0.001	1.384 (0.844–2.271)	1.198
BMI[†]	1.021 (0.795–1.311)	0.871	–	–
Preoperative hypertension	0.863 (0.581–1.282)	0.466	–	–
Preoperative coronary heart disease	1.880 (0.810–4.365)	0.142	–	–
Preoperative arrythmia	1.168 (0.571–2.386)	0.671	–	–
Preoperative diabetes	0.962 (0.659–1.403)	0.839	–	–
Smoking	1.697 (1.188–2.424)	0.004	1.136 (0.683–1.889)	0.622
Drinking	1.941 (1.219–3.091)	0.005	1.454 (0.859–2.461)	0.163
Preoperative chemotherapy	2.007 (1.017–3.959)	0.044	1.456 (0.722–2.936)	0.293
ASA II	0.838 (0.578–1.215)	0.350	–	–
Tumor stage[‡]	1.236 (1.034–1.477)	0.020	1.205 (1.002–1.448)	0.047
Surgical procedure[§]	1.347 (0.929–1.951)	0.116	–	–
Combined epidural-general anesthesia	1.239 (0.809–1.897)	0.324	–	–
Duration of surgery >3 h	1.079 (0.706–1.648)	0.726	–	–
Total intraoperative fluid volume (mL)	1.340 (0.938–1.913)	0.107	–	–
Intraoperative blood transfusion	1.491 (0.307–7.252)	0.620	–	–
Mediastinal lymph node dissection	1.493 (0.861–2.591)	0.154	–	–
Perioperative fentanyl equivalents >28.2 µg/kg	1.556 (1.089–2.223)	0.015	1.623 (1.123–2.346)	0.010
Perioperative NSAIDs administration	1.160 (0.814–1.654)	0.411	–	–
Perioperative glucocorticoids administration	0.994 (0.696–1.420)	0.972	–	–
Grade of tumor cell differentiation[¶]	1.219 (0.992–1.498)	0.059	–	–
Maximal tumor size >3 cm	1.582 (1.100–2.275)	0.013	1.323 (0.898–1.950)	0.157

[†], BMI was divided into four classes: underweight (<18.5 kg/m^2), normal (18.5–24.9 kg/m^2), overweight (25–28 kg/m^2) and obesity (>28 kg/m^2). The next class was compared to the last level. [‡], tumor stage was divided into four stages: I, II, III and IV. The next stage was compared to the last stage. [§], surgical procedure was divided into three categories: segmentectomy, lobectomy and total pneumectomy. Total pneumectomy was compared to lobectomy or segmentectomy. [¶], grade of tumor cell differentiation was divided into four grades: undifferentiation, poor differentiation, moderate differentiation and high differentiation. The next grade was compared to the last grade. P<0.05 was considered statistically significant. OR, odd ratio; CI, confidence interval; BMI, body mass index; ASA, American Society of Anesthesiologists; NSAIDs, non-steroid anti-inflammatory drugs.

are also different voices in recent studies. An in vitro and human lung tissue study suggested that lung cancer tissues and cell lines express opioid growth factor receptor (OGFR), a negative regulator of cell proliferation, was a binding site of morphine and involved in subsequent morphine-induced lung cancer growth suppression (46). Oh *et al.* investigated 1,009 medical records of patients and found intraoperative and postoperative use of opioid does not affect the risk of recurrence or death due to lung cancer (47). Hasegawa *et al.* drew a similar conclusion in a prospective cohort study of patients with NSCLC and suggested opioid dose does not shorten the survival of patients with advanced NSCLC (48). In this study, the association between perioperative fentanyl equivalents and OS, RFS and PPCs for NSCLC

was evaluated and the median of perioperative fentanyl equivalents was selected as the cut-off value referring to the previous study (8). The results revealed that perioperative fentanyl equivalents >28.2 µg/kg prolonged the OS and improved long-term patient outcomes (HR =0.779, 95% CI: 0.619–0.980, P=0.033). In the case of small sample size and retrospective nature, the value of exceeding 28.2 µg/kg for perioperative fentanyl equivalent needed to be confirmed by prospective studies, but it suggested a trend that to some extent, increasing perioperative opioid dosage might be beneficial for the survival of patients. The effects of opioids probably varied according to cancer subtype, because the different expression of opioid receptors in lung cancer cells would be a crucial factor for opioid effects on oncologic outcomes. For example, lung adenocarcinoma showed a higher OGFR expression than squamous cell carcinoma (46). Additionally, unlike other retrospective data, sufentanil accounted for the majority of opioids in this cohort, therefore we hypothesized the biological effects that opioid drugs had on tumors were possibly related to the different drug type, dose and mode of administration (49-51). What's more, previous evidence for the use of opioids impact on long-term survival of lung cancer cells are retrospective, and follow-up rarely exceeds 5 years in these studies (49,50). Hence, it is reasonable to speculate that different conclusions may be drawn with the extension of follow-up time, and further studies should be conducted to confirm the conclusions of those aforementioned literatures.

In contrast, the findings from this study also indicated that perioperative fentanyl equivalents >28.2 µg/kg significantly increased the risk of PPCs, was is related to unfavorable short-term outcomes, and affect the postoperative recovery of patients (OR =1.623, 95% CI: 1.123–2.346, P=0.010). There have been evidences that opioids may have adverse effects on the lungs and increase the risk of PPCs associated with opioid use (52), which may be partly attributed to potential side effects of respiratory depression and increased inhalation risk. In addition, Plein *et al.* and Roy *et al.* reported that opioids damage macrophages and NK cells and reduce migration of macrophages and neutrophils (53,54). Therefore, opioid may inhibit the immune system, and, as a result, increase the risk of postoperative pneumonia and pleural effusion. In general, as noted above, it was prudent to consider that opioids might affect PPCs primarily through indirect effects, including respiratory depression that increases the occurrence of pulmonary atelectasis, and immunosuppression that promotes

inflammatory responses in the lungs and thorax, partly leading to pneumonia and pleural effusion, and further affecting the healing of prolonged air leakage. However, results from the study added evidence for increased risk for PPCs in the patients with opioid exposure alike. Increased perioperative fentanyl equivalents may be detrimental factor for recovery of patients after surgery.

From an evolving perspective, the overall decrease in opioid is not a universal end point, but should be target at specific cancer subtypes or ultimately specific patients. These findings should be considered when formulating perioperative analgesic strategies for patients with NSCLC, and supports the judicious use of opioids to balance the favorable and unfavorable effect.

Perioperative glucocorticoids exposure

In this cohort, results suggested perioperative glucocorticoids (mainly dexamethasone) were associated with delayed recurrence. Dexamethasone is frequently used to prevent postoperative nausea and vomiting (PONV) in doses of 8–10 mg (55). The effect of perioperative glucocorticoids on the outcome of cancer patients is controversial. Previous research showed that perioperative dexamethasone was associated with an increased risk of recurrence in patients after colorectal cancer surgery (56). On the other hand, perioperative dexamethasone was found that it inhibited the proliferation of breast cancer cells (57), and improved the long-term survival of patients with pancreatic cancer (58). In the previous research, the results showed that dexamethasone prolonged RFS and OS after lung cancer surgery, and that perioperative NSAIDs and glucocorticoids might produce a "synergic" effect in improving survival (8). Nevertheless, these effects require further clarification in the future.

Limitations

This study comes with several limitations. Firstly, the data of intraoperative body temperature was not recorded because this parameter was not routinely monitored during operation. Several researches reported intraoperative hypothermia was associated with increased early complications and shortened long-term survival (59). Secondly, in addition to PPCs, postoperative complications also include arrhythmias, myocardial infarction and so on (60). Nevertheless, considering the low incidence of these complications in this study, they were not set as

observation variables. Thirdly, as a mono-center study, the results may not be extrapolated to other patients' population in other centers. Finally, although epidural opioids entered the systemic circulation, the accuracy of this conversion ratio for epidural opioids was unclear (47). Therefore, differences in the blood half-lives of opioids and method of administration (bolus or continuous) might lead to unresolved bias in the analysis.

Conclusions

Taken together, though there were no significant associations observed between other perioperative anesthetic factors such as anesthesia technique with patient's outcomes in this study, the findings suggested that opioid and glucocorticoid exposure may affect the prognosis of patients with NSCLC after surgery anyway. If perioperative fentanyl equivalents were over 28.2 µg/kg, it could be a favorable factor for OS, but a negative factor for short-term rehabilitation of patients with NSCLC undergoing resection. However, these findings need to be validated by further prospective studies and must be interpreted with some caution because of the small cohort size and retrospective design.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-1812/rc

Data Sharing Statement: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-1812/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-1812/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The Clinical Research Ethics Committee of Peking University Cancer Hospital approved the study (No. 2019YJZ22-GZ02) and waived the need for written informed consent given that all patients were operated on many years ago and lived all over the country. But oral consent was obtained from each patient included in the study.

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