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Perioperative Management May Improve Long-term Survival in Patients After Lung Cancer Surgery: A Retrospective Cohort Study

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BACKGROUND: Surgical resection is the main treatment for patients with non–small-cell lung cancer (NSCLC), but patients' long-term outcome is still challenging. The purpose of this study was to identify predictors of long-term survival in patients after lung cancer surgery.

METHODS: Patients who underwent surgery for NSCLC from January 1, 2006, to December 31, 2009, were enrolled into this retrospective cohort study. The primary outcome was the survival length after surgery. Predictors of long-term survival were screened with the multivariable Cox proportional hazard model.

RESULTS: Postoperative follow-up was completed in 588 patients with a median follow-up duration of 5.2 years (interquartile range, 2.0–6.8). Two hundred ninety-one patients (49.5%) survived at the end of follow-up with median survival duration of 64.3 months (interquartile range, 28.5–81.6). The overall survival rates were 90.8%, 70.0%, and 57.1% at the end of the first, third, and fifth year after surgery, respectively. Limited resection (hazard ratio [HR], 1.46; 95% confidence interval [CI], 1.08–1.98; $P = .013$) and large tumor size (HR, 1.29; 95% CI, 1.17–1.42; $P < .001$) were associated with short survival; whereas high body mass index grade (HR, 0.82; 95% CI, 0.69–0.97; $P = .021$), highly differentiated tumor (HR, 0.59; 95% CI, 0.37–0.93; $P = .024$), dissection of mediastinal lymph node during surgery (HR, 0.45; 95% CI, 0.30–0.67; $P < .001$), and perioperative use of dexamethasone (HR, 0.70; 95% CI, 0.54–0.90; $P = .006$) were associated with long survival. No association was found between perioperative use of flurbiprofen axetil and long survival (HR, 0.80; 95% CI, 0.62–1.03; $P = .086$). However, combined administration of dexamethasone and flurbiprofen axetil was associated with longer survival (compared to no use of both: adjusted HR, 0.57; 95% CI, 0.38–0.84; $P = .005$).

CONCLUSIONS: Certain factors in particular perioperative dexamethasone and flurbiprofen axetil therapy may improve patients' long-term survival after surgery for NSCLC. Given the small sample size, these findings should be interpreted with caution, and randomized clinical trials are needed for further clarification. (Anesth Analg 2018;126:1666–74)

KEY POINTS

- **Question:** Does perioperative management affect long-term outcomes in patients after lung cancer surgery?
- **Findings:** Certain factors in particular perioperative dexamethasone and flurbiprofen axetil therapy may improve patients' long-term survival after surgery for non–small-cell lung cancer.
- **Meaning:** Further studies to determine whether combined use of perioperative dexamethasone and nonsteroid anti-inflammatory drugs improves patients' long-term survival after lung cancer surgery are urgently needed.

Cancer is the leading cause of death worldwide. Global cancer statistics[1] showed that about 14.1 million new cancer cases were diagnosed in 2012; among them 1.8 million were lung cancer cases, accounting for 13% of the total cancer diagnosis. Lung cancer is the primary cause of cancer deaths among men globally and among women in the developed countries. According to China's cancer statistics,[2] 733,300 new lung cancer cases (509,300 men

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and 224,000 women) were diagnosed in 2015, accounting for 17.1% of all new cancer diagnosis; 610,200 lung cancer patients (432,400 men and 177,800 women) died during the same period, accounting for 21.7% of all cancer deaths. The incidence and mortality of lung cancer are among the highest of all malignant tumors; it has the highest incidence and mortality in men and the second incidence (lower than breast cancer) but the highest mortality in women.[2] The 5-year survival rate after lung cancer surgery remains low.[3]

Surgical resection is the first-line treatment for non–small-cell lung cancer (NSCLC). However, it is unavoidable that some tumor cells will be disseminated into the blood or the lymphatic systems during surgery. The outcome depends on the balance between tumor-promoting factors and immune function of the body during the perioperative period. Studies showed that stress response induced by surgery attenuates the cytotoxic effect of natural killer cells and the reaction of T cells, and thus inhibits the cell-mediated immunity.[4] Indeed, immunosuppression occurs within hours after surgery and lasts for several days, depending on the severity of surgical trauma.[5] In addition to surgery per se, the anesthesia management during perioperative period, including type of anesthesia, anesthetic drugs, blood transfusion, and hypothermia, can all affect the immune function of patients; for example, volatile anesthetics and opioids might aggravate the immunosuppression and potentially worsen long-term outcome, whereas regional anesthesia and nonsteroidal anti-inflammatory drugs (NSAIDs) might attenuate the immunosuppression and exert protective effects.[6,7] These indicate that perioperative management may contribute to the long-term outcome of patients after lung cancer surgery. The purpose of this study was, therefore, to identify factors that were closely related to perioperative management and beyond in affecting patients' long-term survival after surgery for NSCLC.

METHODS

This was a retrospective cohort study of prospectively collected data. The study protocol was approved by the Clinical Research Ethics Committee of Beijing University Cancer Hospital (ethics approval number 2014[074]). Considering that the study was observational and that patients who would be enrolled in this study underwent surgery years ago and lived in different regions nationwide, the Ethics Committee agreed to exempt the written informed consent, but all enrolled patients had verbally agreed to participate for long-term outcome follow-up. This manuscript adheres to the applicable Enhancing the QUAlity and Transparency Of health Research (EQUATOR) guidelines.

Patients

Patients who underwent lung cancer surgery from January 1, 2006, to December 31, 2009, in Beijing University Cancer Hospital were screened using the electronic medical records system. The inclusion criteria were as follows: (1) age ≥18 years; and (2) the diagnosis of NSCLC was confirmed by postoperative pathological examination. Patients were excluded if they met any of the following criteria: (1) complicated with primary malignant tumor in other place; (2) recurrent metastatic lung tumor; (3) long-term steroid exposure; or (4) impossible follow-up due to incomplete information.

Anesthesia, Surgery, and Perioperative Management

General anesthesia with double-lumen endobronchial tube intubation was performed for all patients. Anesthesia was induced with intravenous anesthetics (propofol and/or etomidate) and opioids (fentanyl or sufentanil), and maintained with inhalational anesthetics (sevoflurane or isoflurane, with or without nitrous oxide) and opioids (fentanyl and/or sufentanil). Epidural anesthesia with local anesthetics (lidocaine and/or ropivacaine) was also performed in some patients (combined with general anesthesia) according to the preference of anesthesiologists. For some patients, dexamethasone (5–10 mg) was administered for the prevention of postoperative nausea and vomiting (PONV), and flurbiprofen axetil (50–100 mg) was administered as a supplemental analgesia according to the decision of anesthesiologists during anesthesia.

Lung resections were performed through a standard posterolateral thoracotomy. Lobectomy with mediastinal lymph node dissection was the standard procedure, but other surgical procedures (such as pneumonectomy, wedge resection, bronchial sleeve resection, or even tumor resection/sampling, with or without mediastinal lymph node dissection) were also performed according to the situations of tumor and decisions of surgeons.

Postoperative analgesia was provided with patient-controlled analgesia pumps, which were established with ropivacaine (with or without fentanyl) for epidural analgesia or opioids (morphine or sufentanil) for intravenous analgesia. For some patients, flurbiprofen axetil (100–200 mg) was added into the intravenous analgesia pump according to the decision of anesthesiologists. PONV were treated with dexamethasone (5–10 mg), 5-hydroxytryptamine-3 receptor antagonists, or metoclopramide. Other perioperative managements were performed according to routine practice.

Data Collection

Data were collected using the medical record system and included demographic characteristics (age, gender, height, and weight), preoperative information (surgical diagnosis, comorbidity, American Society of Anesthesiologists classification, tumor location, and history of chemotherapy for cancer), anesthesia-related information (type of anesthesia, uses of anesthetic drugs, intraoperative blood infusion, uses and doses of glucocorticoids, and NSAIDs), surgery-related information (type of surgical procedure, duration of surgery, performance of mediastinal lymph node dissection), and postoperative information (occurrence of complications, maximal tumor size, pathological diagnosis, grade of tumor cell differentiation, chemotherapy, and/or radiotherapy). The maximal tumor size was the results reported by the pathologists by measuring the resected tumor specimens. The total consumption of opioids during and after surgery was converted into fentanyl equivalents (1 μg fentanyl equals to sufentanil 0.1 μg or morphine 110 μg).[8]

Postoperative Follow-up

All patients were followed up by specially assigned personnel from the Department of Medical Records and Statistics of Peking University Cancer Hospital. Follow-up

was performed in the way of outpatient review, telephone inquiry, or letter communication. Patients were followed up every 6 months within the first year after surgery, and once a year thereafter. The living status and the recurrence of tumor were confirmed during each follow-up. In case of tumor recurrence, the time of diagnosis was recorded; in case of patient death, the time of death was also documented. Tumor recurrence including local recurrence or distant recurrence/metastasis was confirmed by imagological examination.[9] The time of recurrence was the earliest date of clinical diagnosis made by surgeons or radiologists according to imagological evidence. The time of death was the date appeared in the medical certificate of death. Follow-up was terminated when patients died or were lost to follow-up. The recurrence-free survival (RFS) and overall survival (OS) were calculated according to the follow-up results. Data assignment was performed according to a previous published study similar to the current one.[10]

The primary outcome was OS, which is defined as the duration from the date of surgery to the date of death from any cause. The secondary outcome was RFS, which is defined as the duration from the date of surgery to the date of recurrence or death for any cause, whichever happened first.

Statistical Analysis

Numeric data with abnormal distribution were presented as median (interquartile range [IQR]). Categorical data were presented as numbers (%). Patients with missing data were presented as numbers (%). Univariate analyses were performed using the Kaplan–Meier survival analysis against outcomes (RFS or OS), with comparisons between layers of baseline and perioperative variables performed with log-rank tests. For continuous variables, the choices of cut-off points between layers were made according to clinical significance, literatures, or median values.[11–13] Factors that were possibly associated with the outcomes (set as $P < .20$ in log-rank tests or were regarded as clinically important) were included in the Cox proportional hazard model for multivariable analysis to identify independent factors that were associated with outcomes ($P < .05$). The survival curves in patients with 3 combinations of perioperative flurbiprofen axetil and/or dexamethasone were compared to a reference group (no use of both) by log-rank test, and the criterion of significance was adjusted with Bonferroni correction ($P < .05/3 = .0167$). All tests were 2-sided. Statistical analysis was performed using the SPSS version 14.0 (SPSS, Inc, Chicago, IL).

Although no formal sample size calculation was performed beforehand, the high number of events (nearly 300 deaths) compared with the number of Cox model variables (15 or 16) indicated that the "ten events per variable" rule was exceeded, implying the reliability of the regression estimates.[14]

RESULTS

Patient Recruitment

A total of 676 patients underwent lung cancer surgery between January 1, 2006, and December 31, 2009; 632 patients met the inclusion/exclusion criteria; 588 patients completed long-term follow-up and were included in the final statistical analysis (Figure 1). The postoperative follow-up was ended on December 31, 2015.

Results of Follow-up

Baseline, perioperative, and follow-up data were presented in Supplemental Digital Content, Tables A–E, http://links.lww.com/AA/C285. The median interval from the date of surgery to the last follow-up was 5.2 years (IQR, 2.0–6.8). At the time of the last follow-up, 297 patients (50.5%) died. Among survivors, 32 patients had tumor recurrence; resulting an overall recurrence/death rate of 56.0%. The median duration of RFS was 53.5 months (IQR, 14.9–78.1), and the median duration of OS was 64.3 months (IQR, 28.5–81.6).

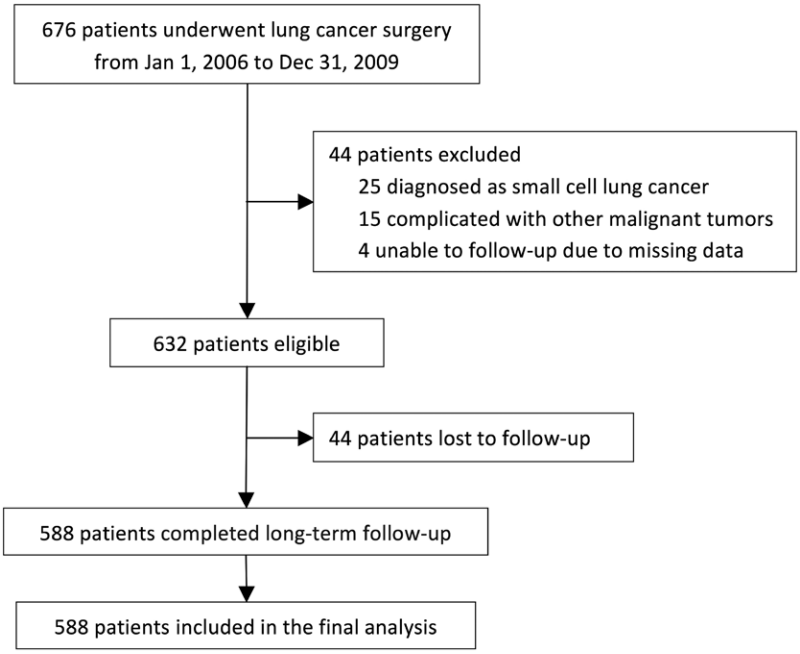

Figure 1. Flowchart of the study.

The RFS and OS rates at the first, third, and fifth year after surgery were 81.6% (standard error, ±1.6%), 59.2% (±2.0%), 48.1% (±2.1%), and 90.8% (±1.2%), 70.0% (±1.9%), 57.1% (±2.0%), respectively.

Risk Factor Analysis

Recurrence-Free Survival. Fifteen factors that were identified by univariate analysis ($P < .20$) (Table 1) or considered clinically important were included in the multivariable Cox proportional hazard model. Multivariable analysis identified 7 independent factors; among them increasing tumor size (hazard ratio [HR], 1.23; 95% confidence interval [CI], 1.12–1.34; $P < .001$), postoperative radiotherapy (HR, 1.72; 95% CI, 1.06–2.78; $P = .027$), and postoperative chemotherapy (HR, 1.60; 95% CI, 1.27–2.02; $P < .001$) were associated with early recurrence, whereas high body mass index (BMI) grade (HR, 0.85; 95% CI, 0.72–1.00; $P = .046$), highly differentiated tumor (HR, 0.61; 95% CI, 0.40–0.92; $P = .019$), mediastinal lymph node dissection during surgery (HR, 0.52; 95% CI, 0.35–0.77; $P = .001$), and perioperative use of dexamethasone (HR, 0.70; 95% CI, 0.55–0.89; $P = .004$) were associated with delayed recurrence (Table 2).

Overall Survival. Sixteen factors that were identified by univariate analysis ($P < .20$) (Table 1) or considered clinically important were included in the multivariable Cox proportional hazard model. Multivariable analysis identified 6 independent factors; among them limited resection (HR, 1.46; 95% CI, 1.08–1.98; $P = .013$) and increasing tumor size (HR, 1.29; 95% CI, 1.17–1.42; $P < .001$) were associated with shortened survival, whereas high BMI grade (HR, 0.82; 95% CI, 0.69–0.97; $P = .021$), highly differentiated tumor (HR, 0.59; 95% CI, 0.37–0.93; $P = .024$), mediastinal lymph node dissection during surgery (HR, 0.45; 95% CI, 0.30–0.67; $P < .001$), and perioperative use of dexamethasone (HR, 0.70; 95% CI, 0.54–0.90; $P = .006$) were associated with prolonged survival. Perioperative use of flurbiprofen axetil (HR, 0.80; 95% CI, 0.62–1.03; $P = .086$) was not associated with prolonged survival (Table 2).

Joint Effects of Perioperative Flurbiprofen Axetil and Dexamethasone

The survival curves in patients with 4 combinations of perioperative flurbiprofen axetil (yes, no) and dexamethasone (yes, no) showed a possible additive effect in improving survival (Figure 2). Patients who received both flurbiprofen axetil and dexamethasone had a better survival than those who did not received both ($\chi^2 = 11.494$; $P = .001$), with the estimated 5-year survival rates of 68.0% and 46.1%, respectively (Table 3). After adjustment with confounding factors, administrating both flurbiprofen axetil and dexamethasone was associated with prolonged OS when compared to no use of both (adjusted HR, 0.57; 95% CI, 0.38–0.84; $P = .005$) (Table 4).

Table 1. Predictors of Survival (Kaplan–Meier Univariate Analyses)

		Recurrence-Free Survival		Overall Survival	
Variable	**n**	**n (%)**	***P* Value**	**n (%)**	***P* Value**
Age (y)			.330		.179
<60	258	122 (47.3)		138 (53.5)	
≥60	330	137 (41.5)		153 (46.4)	
Gender			.531		.029
Female	214	99 (46.3)		119 (55.6)	
Male	374	160 (42.8)		172 (46.0)	
BMI (kg·m^{-2})			.028		.015
<18.5	19	7 (36.8)		8 (42.1)	
18.5–24.9	343	142 (41.4)		160 (46.6)	
25.0–27.9	170	77 (45.3)		87 (51.2)	
≥28.0	56	33 (58.9)		36 (64.3)	
Coronary heart disease			.198		.604
No	551	239 (43.4)		271 (49.2)	
Yes	37	20 (54.1)		20 (54.1)	
Hypertension			<.001		.005
No	432	171 (39.6)		199 (46.1)	
Yes	156	88 (56.4)		92 (59.0)	
Arrhythmia			.375		.266
No	546	244 (44.7)		274 (50.2)	
Yes	41	15 (36.6)		17 (41.5)	
Diabetes			.259		.288
No	526	228 (43.3)		257 (48.9)	
Yes	62	31 (50.0)		34 (54.8)	
ASA classification			.392		.597
I	215	92 (42.8)		104 (48.4)	
II	354	158 (44.6)		178 (50.3)	
III	19	9 (47.4)		9 (47.4)	
Preoperative chemotherapy			.037		.009
No	523	233 (44.6)		264 (50.5)	
Yes	60	21 (35.0)		22 (36.7)	
Anesthetic technique			.246		.493
General anesthesia	448	194 (43.3)		221 (49.3)	
Combined epidural–general anesthesia	140	65 (46.4)		70 (50.0)	

(*Continued*)

Table 1. Continued

Variable	n	Recurrence-Free Survival n (%)	Recurrence-Free Survival *P* Value	Overall Survival n (%)	Overall Survival *P* Value
Style of surgery			<.001		<.001
Lobectomy	424	197 (46.5)		226 (53.3)	
Pneumonectomy	21	12 (57.1)		12 (57.1)	
Wedge resection	49	20 (40.8)		21 (42.9)	
Bronchial sleeve resection	34	15 (44.1)		16 (47.1)	
Local resection/sampling	60	15 (25.0)		16 (26.7)	
Mediastinal lymph node dissection			<.001		<.001
No	61	15 (24.6)		16 (26.2)	
Yes	527	244 (46.3)		275 (52.2)	
Duration of surgery (h)			.821		.910
≤4.0	365	158 (43.3)		177 (48.5)	
>4.0	220	98 (44.5)		111 (50.5)	
Maximal tumor size (cm)			<.001		<.001
≤1.0	41	26 (63.4)		27 (65.9)	
1.1–2.0	143	82 (57.3)		93 (65.0)	
2.1–3.0	143	57 (39.9)		68 (47.6)	
3.1–4.0	91	38 (41.0)		43 (47.3)	
≥4.1	170	56 (32.9)		60 (35.3)	
Grade of tumor cell differentiation			.045		.010
Undifferentiated	81	40 (49.4)		43 (53.1)	
Poorly differentiated	75	22 (29.3)		24 (32.0)	
Moderately differentiated	364	154 (42.3)		176 (48.4)	
Highly differentiated	68	43 (63.2)		48 (70.6)	
Intraoperative blood transfusion			.150		.070
No	579	257 (44.7)		289 (49.9)	
Yes	9	2 (22.2)		2 (2.2)	
Perioperative fentanyl equivalents (μg/kg)			.201		.106
<38.9	297	119 (40.1)		133 (44.8)	
≥38.9	291	140 (48.1)		158 (54.3)	
Perioperative dexamethasone administration			.008		.013
No	256	103 (40.2)		116 (45.3)	
Yes	332	156 (47.0)		175 (52.7)	
Perioperative flurbiprofen axetil administration			.359		.091
No	267	107 (40.1)		116 (43.4)	
Yes	321	152 (47.4)		175 (54.5)	
Occurrence of postoperative complications[a]			.079		.138
No	175	89 (50.9)		96 (54.9)	
Yes	413	170 (41.2)		195 (47.2)	
Postoperative radiotherapy			<.001		.090
No	564	256 (45.4)		284 (50.4)	
Yes	24	3 (12.5)		7 (29.2)	
Postoperative chemotherapy			<.001		<.001
No	303	168 (55.4)		175 (57.8)	
Yes	285	91 (31.9)		116 (40.7)	

Results are presented as number (%).

Abbreviations: ASA, American Society of Anesthesiologists; BMI, body mass index.

[a]Include pneumothorax, pleural effusion, atrial arrhythmia, atelectasis, myocardial ischemia, pneumonia, and others.

DISCUSSION

In this retrospective cohort study, 588 patients with primary NSCLC after surgical resection were followed up for a median of 5.2 years. The OS rates were 90.8%, 70.0%, and 57.1% at the first, third, and fifth year after surgery. Multivariable Cox proportional hazard analysis showed that limited resection and increasing tumor size were associated with shortened survival, whereas high BMI grade, highly differentiated tumor, mediastinal lymph node dissection, and perioperative use of dexamethasone were related to longer survival after surgery. Perioperative use of flurbiprofen axetil was not associated with longer survival; however, combined administration of dexamethasone and flurbiprofen axetil showed additive effect in prolonging survival.

Long-term survival remains low in patients after lung cancer surgery. In a systematic review by Whitson et al,[15] the mean 5-year OS rate was 65.6% (95% CI, 56.7–74.4) in patients after thoracotomy lobectomy for early-stage NSCLC. A later systematic review showed that the 5-year survival ranged from 58% to 97% after thoracotomy for lung cancer.[16] In our patients, the 5-year survival rate (57.1%) was slightly lower than the previously reported mean results, but it was in accord with results in Chinese patients, that is, a 5-year survival rate of 54.0% after surgery for stage I lung cancer.[17]

It is reported that BMI is inversely proportional to the risk of lung cancer.[12] Indeed, a previous study[18] reported that higher BMI was associated with improved OS after

Table 2. Predictors of Survival (Multivariate Cox Proportional Hazard Model)

	Recurrence-Free Survival[a]		Overall Survival[a]	
Variable	**HR (95% CI)**	***P* Value**	**HR (95% CI)**	***P* Value**
Age ≥60 y	…	…	1.25 (0.98–1.60)	.079
Male gender	…	…	1.03 (0.80–1.34)	.817
BMI (each grade increase)[b]	0.85 (0.72–1.00)	.046	0.82 (0.69–0.97)	.021
Preoperative coronary heart disease	0.90 (0.54–1.48)	.667	…	…
Preoperative hypertension	0.77 (0.58–1.02)	.069	0.80 (0.60–1.08)	.145
Preoperative chemotherapy	1.11 (0.78–1.59)	.564	1.40 (0.97–2.01)	.070
Limited resection[c]	1.22 (0.91–1.63)	.190	1.46 (1.08–1.98)	.013
Highly differentiated tumor	0.61 (0.40–0.92)	.019	0.59 (0.37–0.93)	.024
Tumor size (each grade increase)[d]	1.23 (1.12–1.34)	<.001	1.29 (1.17–1.42)	<.001
Mediastinal lymph node dissection	0.52 (0.35–0.77)	.001	0.45 (0.30–0.67)	<.001
Intraoperative blood transfusion	1.31 (0.60–2.84)	.497	1.60 (0.73–3.43)	.246
Combined with epidural anesthesia[e]	0.95 (0.72–1.25)	.698	0.98 (0.74–1.32)	.916
Perioperative dexamethasone administration	0.70 (0.55–0.89)	.004	0.70 (0.54–0.90)	.006
Perioperative flurbiprofen axetil administration	0.94 (0.74–1.19)	.587	0.80 (0.62–1.03)	.086
Occurrence of postoperative complications[f]	1.19 (0.93–1.54)	.172	1.15 (0.88–1.50)	.319
Postoperative radiotherapy	1.72 (1.06–2.78)	.027	1.12 (0.66–1.90)	.678
Postoperative chemotherapy	1.60 (1.27–2.02)	<.001	1.22 (0.96–1.56)	.110

Abbreviations: BMI, body mass index; CI, confidence interval; HR, hazard ratio.
[a]Factors with $P < .20$ in the Kaplan–Meier univariate analyses and were considered clinically important were included.
[b]Divided into 4 grades, that is, underweight (<18.5 kg·m^{-2}), normal (18.5–24.9 kg·m^{-2}), overweight (25.0–28.0 kg·m^{-2}), and obesity (> 28.0 kg·m^{-2}).
[c]Including wedge resection, bronchial sleeve resection and local resection/sampling, compared to lobectomy or pneumonectomy.
[d]Divided into 5 grades, that is, ≤1.0, 1.1–2.0, 2.1–3.0, 3.1–4.0, and ≥4.1.
[e]Perioperative fentanyl equivalent was not included because of significant correlation with the combined use of epidural anesthesia.
[f]Include pneumothorax, pleural effusion, atrial arrhythmia, atelectasis, myocardial ischemia, pneumonia, and others.

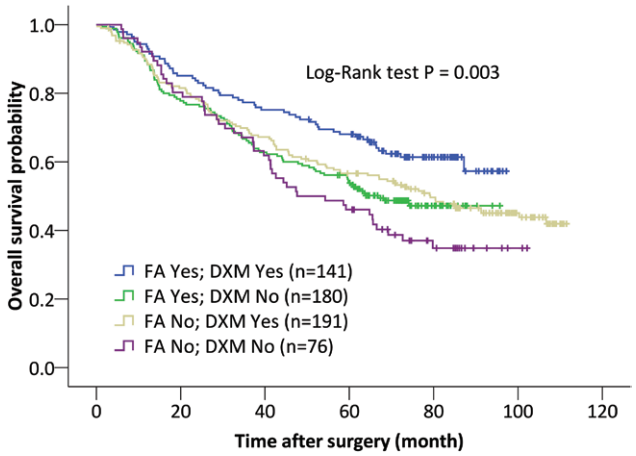

Figure 2. Survival curves of patients with or without the perioperative administration of FA and DXM alone or in combination. Patients who received both FA and DXM showed survival better than those who received none of them ($P = .001$). The criterion of significance after Bonferroni correction was $P < .0167$. DXM indicates dexamethasone; FA, flurbiprofen axetil.

Table 3. The Overall Survival Rates of Patients With 4 Combinations of Perioperative FA and DXM

	Overall Survival Rate After Surgery		
	First Year	**Third Year**	**Fifth Year**
FA: no; DXM: no	92.1% (86.0–98.1)	65.8% (55.2–76.4)	46.1% (34.9–57.3)
FA: yes; DXM: no	88.9% (84.4–93.4)	65.6% (58.7–72.5)	53.8% (46.5–61.0)
FA: no; DXM: yes	88.9% (84.4–93.5)	68.8% (62.1–75.5)	56.6% (49.5–63.7)
FA: yes; DXM: yes	93.6% (89.5–97.7)	77.3% (70.4–84.2)	68.0% (60.4–75.6)

Results are presented as mean (95% CI).
Abbreviations: DXM, dexamethasone; FA, flurbiprofen axetil.

surgical resection of NSCLC patients. In young patients with advanced NSCLC, BMI <25 kg·m^2 was a negative prognostic factor.[19] Our results also showed that high BMI grade was associated with delayed recurrence and longer OS. Histological grade has been known to be a significant prognostic factor for survival of NSCLC patients.[20] In line with previous studies, we found that highly differentiated tumor was associated with a low risk of recurrence and a long OS. Tumor size is also a well-known prognostic factor for many cancers including NSCLC, with larger size predicting a worse prognosis in most cases.[11] In the present study, tumor size was stratified into 5 grades (ie, ≤1.0, 1.1–2.0, 2.1–3.0, 3.1–4.0, and ≥4.1 cm), and we found that each grade increase was associated with significant higher risks of both recurrence and death.

Intraoperative lymph node scavenge is closely related to postoperative outcome; complete mediastinal lymph node dissection reduces the risk of recurrence and death after surgery.[21] However, for patient with lymph node stages N0 or N1 (less than hilar) NSCLC, complete lymphadenectomy during pulmonary resection did not improve survival.[22] The present study enrolled patients with various stages of NSCLC. Our results showed that mediastinal lymph node dissection during surgery was associated with delayed recurrence and prolonged survival. Lobectomy or greater resection remains the treatment of choice for patients with early-stage NSCLC and is associated with better outcome.[23] Our results also showed that, compared to lobectomy or pneumonectomy, limited resection was associated with short survival. Other reasons that might have lead to our results were that limited resection was usually performed in patients with more severe comorbidity (such as decreased pulmonary function) or advanced-stage NSCLC.

Dexamethasone is frequently used to prevent PONV.[24] High-dose dexamethasone (30 mg·kg^{-1}) can cause significant

Table 4. Joint Effects of Perioperative FA and/or DXM on Overall Survival (Cox Proportional Hazard Model)

	Unadjusted		Adjusted[a]	
Variable	**HR (95% CI)**	***P* Value**	**HR (95% CI)**	***P* Value**
FA: no; DXM: no	Reference		Reference	
FA: yes; DXM: no	0.82 (0.58–1.16)	.265	0.87 (0.61–1.25)	.457
FA: no; DXM: yes	0.76 (0.54–1.07)	.117	0.76 (0.53–1.09)	.131
FA: yes; DXM: yes	0.52 (0.35–0.77)	.001	0.57 (0.38–0.84)	.005

Abbreviations: DXM, dexamethasone; FA, flurbiprofen axetil; HR, hazard ratio.

[a]Factors entered in the multivariate Cox proportional hazard model included age ≥60 years, male gender, body mass index (each grade increase), preoperative hypertension, preoperative chemotherapy, limited resection, highly differentiated tumor, tumor size (each grade increase), mediastinal lymph node dissection, intraoperative blood transfusion, combined with epidural anesthesia, occurrence of postoperative complications, postoperative radiotherapy, and postoperative chemotherapy.

immunosuppression,[25] but the dose of dexamethasone for the purpose of PONV prevention is usually 8–10 mg or less. Glucocorticoids have long been used to treat hematological malignancies via apoptotic pathway.[26] However, data from cancer cell lines derived from various "solid" tumors suggested that glucocorticoids, for example, dexamethasone, can inhibit chemo-induced cancer apoptosis and promote cancer cell growth.[27] The underlying molecular mechanisms of these phenomena remain unknown but may be somehow attributed to the functional loss or less expression of glucocorticoid receptor depending on certain cancer type.[28] For example, in patients after colorectal cancer surgery, perioperative dexamethasone was associated with an increased risk of recurrence[29,30]; in patients with endometrial cancer, the administration of dexamethasone was not associated with an increased risk of recurrence.[31] In contrast, in patients with pancreatic cancer, perioperative dexamethasone was associated with improved long-term survival.[32] Our results showed that the use of dexamethasone was associated with a prolonged RFS and OS after lung cancer surgery.

NSAIDs are commonly used during the perioperative period to improve analgesia and reduce opiate consumption by inhibiting the activity of cyclooxygenase (COX) and the synthesis of prostaglandins. Prostaglandin E2 can selectively inhibit the activity of macrophage, neutrophils, T-helper cells, and natural killer cells,[33] whereas blocking prostaglandins synthesis with COX inhibitors decreases tumor angiogenesis and induces tumor cell apoptosis.[4] Retrospective studies showed that intraoperative use of ketorolac or diclofenac was associated with better outcome in patients undergoing breast cancer surgery.[34,35] In lung cancer patients, the observational study by Forget et al[35] showed that NSAIDs use at the beginning of the surgery was independently associated with a lower metastases risk; the retrospective study by Choi et al[36] found that ketorolac administration was slightly associated with better OS (P = .05) in univariate analysis. In this study, flurbiprofen axetil (a nonselective COX inhibitor with high binding affinity to the site of lesion) was the only NSAID administrated during the perioperative period. Although the use of flurbiprofen axetil was not associated with long-term survival, we found an additive effect of dexamethasone and flurbiprofen axetil in prolonging postoperative survival, possibly due to relieved immunosuppression action in patients after cancer surgery.[37–39] Considering the widespread use of these 2 drugs during the perioperative period, their effects in particular long-term effects on lung cancer patients indeed need to be explored further.

Our results also showed that postoperative radiotherapy and chemotherapy were associated with short RFS. We attributed the phenomena to the use of these therapies in patients with advanced-stage NSCLC,[40] a common practice during the study period.

Except the retrospective nature of our study, several other limitations also exist. First, cancer stage was not included in the analyses because these data were lacking in many patients. However, we included tumor size and differentiation grade in the regression model, which are closely related with cancer staging and patients' outcomes. Second, some perioperative data such as intraoperative body temperature and blood glucose level were not included because these parameters were not routinely monitored during that period of time when surgeries were performed. Third, as a monocenter study, our results may not be extrapolated to patients in other centers. Nevertheless, our results showed for the first time that perioperative dexamethasone and flurbiprofen axetil in combination might produce a synergic effect in improving survival although these observational findings require further clarification with randomized clinical trials.

CONCLUSIONS

Our results showed that, for NSCLC patients, the OS rates at the first, third, fifth year after surgery were 90.8%, 70.0%, and 57.1%, respectively. Limited resection and increasing tumor size were associated with a shortened OS, whereas high BMI grade, highly differentiated tumor, mediastinal lymph node dissection during surgery, and perioperative use of dexamethasone were associated with a prolonged OS after surgery. Although no association was found between perioperative use of flurbiprofen axetil and long survival, combined administration of dexamethasone and flurbiprofen axetil showed an additive effect in prolonging survival. Considering the small sample size and retrospective nature of the study, the aforementioned findings should be interpreted with caution. Further studies in particular to determine whether combined use of perioperative dexamethasone and NSAIDs therapy improves patients' long-term survival after lung cancer surgery are urgently needed. ■

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DISCLOSURES

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