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Effect of mu Agonists on Long-Term Survival and Recurrence in Nonsmall Cell Lung Cancer Patients

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Abstract: Opioids are widely used for postoperative analgesia. Morphine may have an effect on cell replication, migration, and cancer recurrence. However, the association of postoperative mu agonists with outcome of nonsmall cell lung cancer (NSCLC) patients has not been fully investigated.

We retrospectively evaluated the impact of postoperative mu agonists on overall survival (OS) and disease-free survival (DFS) in early stage NSCLC patients. Patients and relevant medical information were selected from the Bio-Bank of Shandong Provincial Hospital. Difference of clinicopathologic information in postoperative mu agonists group and no mu agonists group was analyzed by χ^2 test. Univariate and multivariate Cox regression analysis were conducted and represented as hazards ratio and 95% confidence interval form. The primary endpoint was OS and secondary endpoint was DFS.

This retrospective study included 984 consecutive NSCLC patients who underwent surgery between January 2006 and December 2011. No significant difference existed between postoperative mu agonists usage group and no mu agonists usage group in clinicopathologic information except operation type ($P = 0.041$). Postoperative mu agonists usage was related to shorter OS (HR 1.514, 95% CI 1.197–1.916, $P = 0.001$) and shorter DFS (HR 1.415, 95% CI 1.123–1.781, $P = 0.003$) in the multivariate Cox regression model. For the patients who received postoperative chemotherapy or radiotherapy postoperative mu agonists also predict shorter survival (HR 1.437, 95% CI 1.041–1.982, $P = 0.027$). Subgroup analysis showed that administration of postoperative mu agonists was related to shorter OS, especially in males, more smoking, poor differential degree, bilobectomy or pneumonectomy, and stage III subgroup, respectively.

Administration of postoperative mu agonists was related to shorter OS and DFS for the NSCLC patients who underwent surgery.

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Abbreviations: CI = confidence interval, CTC = circulating tumor cell, DFS = disease-free survival, DTC = disseminated tumor cell, EMT = epithelial-to-mesenchymal transition, HPA = hypothalamo–pituitary–adrenal, HR = hazards ratio, IV = intravenous injection, MOR = mu-opioid receptor, NKCC = nature killer cell cytotoxicity, NSCLC = non-small cell lung cancer, OS = overall survival, PCA = patient control analgesics, PO = Peros (Oral intake), ROC = receiver-operating characteristic, SC = subcutaneous injection, SD = standard difference, SI = smoking index, TENS = transcutaneous electrical nerve stimulation.

INTRODUCTION

Lung cancer remains an intractable problem which affects the health and survival of the humans.[1] According to the latest data from the World Health Organization, lung cancer was the most frequently diagnosed cancer (1.8 million, 13.0% of the total) and the leading cause of cancer-related death (1.6 million, 19.4% of the total) all over the world in 2012.[2] NSCLC accounts for 78% of all types of lung cancer.[3] Surgery remains the most effective treatment for the early-stage patients.[4] In total, 71% of the early-stage NSCLC patients undergo surgery and the 1-year related survival rate of lung cancer patients rises by a considerable extent as a result of operation.[5] Postoperative pain, as one of the common complications and reasons for a medical visit, needs physicians to deal with.[3] As the most common used analgesics for postoperative pain, opioids play a role through binding to their receptor including mu, delta, kappa opiate receptor.[6] Apart from analgesic effect, opioids have their side effects such as constipation and nausea.[7] What is more, it has been reported that morphine may promote cell cycle progression, angiogenesis, and metastasis, and inhibit apoptosis through binding to mu-opioid receptor (MOR).[8] Otherwise, opioids also depress host immunity and alter neuroendocrine system function.[9,10]

The relation between perioperative mu agonists and long-term outcome remains controversial. Recent researches revealed that cancer recurrence might be related to intraoperative intravenous opioids anesthesia in breast cancer,[11] prostate cancer,[12] laryngeal, hypo-pharyngeal cancer,[13] and ovarian cancer.[14] However, irrelevance was obtained in colorectal cancer,[15] and major abdominal cancer[16] researches. Maher et al[17] showed postoperative opioids could increase cancer recurrence and reduce DFS of 99 stage I and IIa NSCLC patients. However, Cata[18] found no difference between postoperative intravenous group and epidural analgesia group in the long-term outcome for NSCLC patients. Our study indicated that postoperative mu

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agonists could reduce overall survival and disease-free survival in early-stage NSCLC patients.

METHODS

Ethic Permission

The study acquired the permission by the ethic community of Shandong Provincial Hospital afflicted to Shandong University. Informed consent for the use of clinical data was obtained at the time of surgery.

Setting and Participants

We conducted a retrospective analysis of patients diagnosed with NSCLC who underwent operation (Sublobar resection, Lobectomy, Bilobectomy, or Pneumonectomy) at Shandong Provincial Hospital affiliated to Shandong University between January 2006 and December 2011. Of all 1273 patients, 289 patients were excluded for the following reasons: over 80 years old (n = 6); incomplete clinical data (n = 49); prior diagnosis of cancer (n = 7); other lung cancer histology (Bronchioloalveolar carcinoma, small cell lung cancer, sarcomatoid carcinoma, carcinoid, n = 175); positive margin (n = 19); death in hospital during postoperative period (n = 1); stage-IV disease, or unstaged cancers (n = 32). Thus 984 patients enrolled in the ultimate analysis. Follow-up data were obtained from telephone contact with the patients or their families. Patients were evaluated every 3 months by thorax CT and abdomen ultrasonography for the first 2 years after operation and adjuvant treatment, and annual thereafter according to schedule. One hundred sixty-three patients were lost during follow-up and the lost rate was 16.57%. The histology and TNM stage was determined according to the classification criteria for lung tumors of the World Health Organization and International Association for the Study of Lung Cancer (WHO/IASLC).

Variables and Endpoints

Demographic, oncologic, and operative characteristics were collected. Continuous clinicopathologic variables included age, smoking index, pathologic size, and operation duration, and categorical variables included sex, postoperative analgesics, cancer location, operation type, histology, adjuvant therapy, differential degree, and pathological stage. All patients received general anesthesia (intravenous inhalational anesthesia) during surgery and the intraoperative analgesics amount was due to same criteria calculated by the body weight of each patient and choice of postoperative analgesic regiment was due to nature, duration, degree of pain; side effect of analgesics; body tolerance; concomitant symptoms, etc. Long-term outcomes referred to disease-free survival (DFS) and overall survival (OS). Overall survival was defined as the time from operation to death (any reason). For the patients alive, OS was defined as the time between operation and the date of last follow-up. Disease-free survival was defined as the time from operation to recurrence (local recurrence or distant metastasis). For those patients without recurrence, DFS was defined as the time between operation and the date of last follow-up or death.

Statistics

Continuous clinicopathologic variables were reported as median and categorical variables were reported as counting form. Each continuous clinicopathologic variable was transformed into dichotomy to make the further analysis and the cut-off value was defined when the log-rank statistical value was maximum and identified by receiver operating characteristic (ROC) curves. To examine the association between each clinicopathologic variable and postoperative analgesics, the χ^2 test was used for each fourfold table. Univariate Cox proportional hazards regression (P value, hazards regression, 95% confidence interval) and multivariate Cox proportional hazards regression were performed to assess the association between OS and variables. The relation between OS or DFS and postoperative analgesics was assessed with Kaplan–Meier survival estimates. The proportional hazards assumption of Cox analysis was tested through both Kaplan–Meier survival curve and log-minus-log plot methods. The whole sample was split into a training (67%) and a testing sample (33%) randomly and then the internal cross-validation procedure was applied. The process was repeated 10 times and the best-fitting model was estimated for each training sample. All reported P values were 2-sided, and less than 0.05 were considered to be statistically significant. All statistical calculations were performed by SPSS 19.0 for Windows (SPSS Inc, Chicago, IL).

RESULTS

Baseline Clinicopathologic Information

The demographic, oncologic, and operative characteristics are shown in Table 1. The median follow-up was 49 months varying from 1 to 92 months. Three hundred forty-three patients suffered recurrence. The patients were composed of 698 (70.9%) males and 286 (29.1%) females. The age of patients enrolled varied from 20 to 79 with the median 60. After operation, all patients had chosen intravenous patient control analgesics (PCA) for primary postoperative pain control, and 682 (69.3%) did not have any additional analgesics, with others having pethidine (PO, SC, IV,4.0%), fentanyl (Transdermal Patch, IV, 0.2%), dihydrocodeine (PO, 3.3%), morphine (PO, SC, IV, 13.8%), tramadol (PO, 2.9%), codeine (PO,5.0%), bucinnazine (PO, SC, 1.4%). Moderate postoperative pain occurred and an analgesic (dihydrocodeine, tramadol, bucinnazine, or codeine) was applied. Strong opioid analgesic (morphine, pethidine, or fentanyl) was used to treat acute and severe postoperative pain. On-time and individualized drug administration was carried out, and amount and duration applied was safety and pain disappearance as the standard.

Survival Analysis and Subset Analysis

Kaplan–Meier survival curves for overall survival and disease-free survival according to whether using postoperative mu agonists or not are provided in Figure 1. There was significant separation between 2 groups in both OS ($P = 0.001$) and DFS curves ($P = 0.004$). Table 2 shows that there was no significant difference between the 2 groups for sex, age, smoking index, operation duration, cancer location, histology, stage, differential degree, and adjuvant therapy except operation type ($P = 0.041$).

Subgroup analysis is seen in Figure 2. Postoperative mu agonists group presented a worse survival in males; small and large smoking index; moderate and poor differential degree; bilobectomy or pneumonectomy; and stage III subgroups. For the patients who received adjuvant therapy, survival difference between 2 groups was also significant ($P = 0.003$).

Univariate and Multivariate Cox Regression

Results of univariate and multivariate Cox regression of prognostic factors for overall survival in NSCLC are shown in

TABLE 1. Demographic, Oncologic, and Operative Characteristics; Association With Postoperative Analgesics

Clinicopathologic Factors	Counting Form or Median	No pp Opioids	Pp Opioids	*P*
Sex				
Male	698	506	192	0.187
Female	286	219	67	
Age, y	60			
≤60		340	138	0.078
≥60		385	121	
Smoking index	400			
≤430		507	191	0.270
≥430		216	68	
Pp analgesics*				
No use	682			
Pethidine	40			
Fentanyl	2			
Dihydrocodeine	32			
Morphine	136			
Tramadol	29			
Codeine	49			
Bucinnazine	14			
Cancer location				
Left	459	330	129	0.235
Right	525	395	130	
Operation type				
Sublobar resection or lobectomy	745	561	184	0.041
Bilobectomy or pneumonectomy	239	164	75	
Operation duration, h	2.80			
≤3		411	135	0.204
≥3		314	124	
Histology				
Adenocarcinoma	554	411	143	0.681
Nonadenocarcinoma	430	314	116	
pathological size, cm	3.5			
≤4		394	157	0.081
≥4		331	102	
Stage				
I	437	330	107	0.117
II	262	198	64	
III	285	197	88	
Differential degree				
Well	135	98	37	0.911
Moderate	698	514	184	
Poor	151	113	38	
Adjuvant therapy				
Yes	499	372	127	0.530
No	485	353	132	

Adjuvant therapy = chemotherapy or radiotherapy; Pp = analgesics; Pp = postoperative.
* Refer to the analgesics usage apart from PCA, not analgesics in PCA. Sublobar resection: segmentectomy or wedge resection.

Table 3. After testing the proportional hazards assumption, variables including age, operation duration, smoking index, postoperative analgesics, operation type, pathological size, stage, and differential degree met the inclusion criteria of the Cox analysis. Due to Univariate Cox Regression Analysis, elder age, larger smoking index, postoperative mu agonists, larger tumor, worse pathological stage, longer operation time, and worse differential stage predicted shorter OS. And for operation type, compared with sublobar resection or lobectomy, the bilobectomy or pneumonectomy group was related to a poor prognosis ($P < 0.001$). However, after adjusting for smoking index, operation duration, and operation type, only age ($P < 0.001$), postoperative mu agonists ($P = 0.001$), pathological size ($P = 0.015$), pathological stage ($P < 0.001$), and differential stage ($P < 0.01$) were left and statistically significant. Univariate and multivariate analysis results of DFS are listed in Table 4. After being adjusted for smoking index, operation duration, and operation type, postoperative mu agonists could increase 12.3% to 78.1% risk of recurrence. In summary, postoperative mu agonists were associated with increased risk

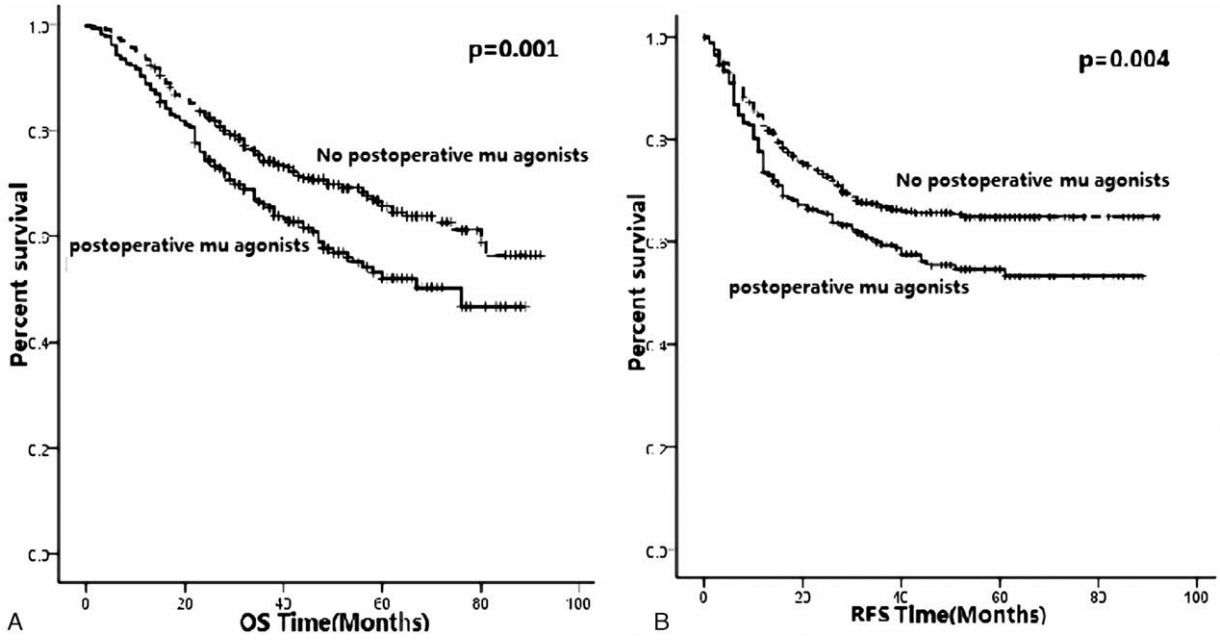

FIGURE 1. A, Kaplan–Meier survival curve for overall survival between 725 no postoperative mu agonists patients and 259 postoperative mu agonists patients after surgery. The 5-year survival rate of no postoperative mu agonists group is 65.6%, while the 5-year survival rate of postoperative mu agonists group is only 52.0%. The long-rank value (Mantel–Cox) is 11.60 and the *P* value is 0.001. B, Kaplan–Meier survival curve for disease-free survival between 725 no postoperative mu agonists patients and 259 postoperative mu agonists patients after radical operation. The long-rank value (Mantel–Cox) is 8.19 and the *P* value is 0.004.

of recurrence (adjusted HR 1.415, 95% CI 1.123–1.781, $P = 0.003$) and higher mortality (adjusted HR 1.514, 95% CI 1.197–1.916, $P = 0.001$).

Cross Validation

Table 4 shows the result of 10 repeated times 3-fold internal cross validation. Hazard ratio and *P* value of both training and testing samples in each repeated time suggested postoperative mu agonists credibly predicted a shorter OS.

DISCUSSION

Resembling the conclusion of Maher et al,[17] our result suggested that postoperative mu agonists may be related to higher recurrence possibility and shorter overall survival compared with no mu agonists, especially in males; large or small tumor size; small or large smoking index; poor differential degree; and bilobectomy or pneumonectomy subgroups. There were fewer researches focusing on postoperative opioids and prognosis than intraoperative opioids. Gupta et al[19] studied the relation between perioperative opioids (epidural or intravenous anesthesia and analgesics) and colorectal cancer recurrence and acquired a statistically significant result in rectal but not colonic cancer. And he proposed that the reason for this difference might be associated with specific type of tumor, age, and cancer location. Another retrospective research showed no effect on long-term survival in ovarian cancer.[20] Moreover, a perspective study on perioperative analgesia concluded that use of epidural analgesia for abdominal cancer surgery could not improve OS and DFS.[21] Results of clinical researches emphasizing on postoperative opioids and cancer recurrence remain controversial and that may be due to specific type of tumor. Bimonte in his review summarized that contrasting resulting in vivo and in vitro studies might be due to different concentration and/or time of use of morphine; low daily doses and single dose of morphine could enhance tumor progression.[22] Administration of postoperative mu agonists, other than daily opioids used for terminal cancer pain, is more likely to be single dose or low regular doses in hospitals. In contrast, the usage of opioids for advanced NSCLC patients without operation and suffering from terminal cancer pain might be chronic high doses.

In our research, mu agonists include morphine, pethidine, fentanyl, codeine, and dihydrocodeine. PCA is widely used for postoperative analgesia[23] and all patients enrolled chose intravenous postoperative PCA with butorphanol (10 mg), nefopam (200 mg), and antiemetic drugs as basic postoperative analgesia. Postoperative mu agonists referred to the mu agonists applied when PCA was used up. Analgesics in PCA including nefopam (non-mu agonists analgesics) and butorphanol (mainly kappa opioid receptor) were also postoperative, but none of them were MOR agonists analgesics.[24] Thus analgesics in PCA were not included in the category of postoperative mu agonists for the reason that they were not MOR agonists.

Administration of mu agonists has a higher incidence of recurrence through 2 feasible ways: immune inefficiency and residuals survival progression. Vitro studies and animal models indicated that opioids could cause immune modulation in innate and adaptive immunity such as inducing macrophages and T lymphocytes apoptosis, reducing primary antibody response of B lymphocytes, and suppressing T helper cell function.[9] More significantly, mu agonists decrease Natural Killer cell cytotoxicity (NKCC) which plays a part in preventing metastases[25] and have been proven as a prognostic predictor of NSCLC.[26] What is more, opioids may affect immune function by altering

TABLE 2. Uni-Variate and Multivariate Cox Regression of Prognostic Factors for OS in NSCLC

Characteristics	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	*P*	Adjusted HR (95% CI)	*P*
Age, y				
≤60	1		1	
≥60	1.280 (1.027–1.595)	0.028	1.577 (1.260–1.975)	<0.001
Smoking index				
≤430	1		1	
≥430	1.376 (1.094–1.729)	0.006	1.157 (0.914–1.464)	0.225
Postoperative analgesics				
No pp mu agonists	1		1	
Pp mu agonists	1.489 (1.181–1.877)	0.001	1.514 (1.197–1.916)	0.001
Operation duration, h				
≤3	1		1	
≥3	1.491 (1.197–1.857)	<0.001	1.151 (0.916–1.448)	0.228
Pathological size, cm				
≤4	1		1	
≥4	1.987 (1.594–2.477)	<0.001	1.347 (1.060–1.711)	0.015
Stage				
I	1		1	
II	3.216 (2.350–4.402)	<0.001	2.513 (1.806–3.496)	<0.001
III	5.463 (4.074–7.326)	<0.001	4.176 (3.031–5.753)	<0.001
Operation type				
Sublobar resection or lobectomy	1		1	
Bilobectomy or pneumonectomy	2.006 (1.597–2.519)	<0.001	1.245 (0.970–1.598)	0.085
Differential degree				
Well	1		1	
Moderate	4.641 (2.537–8.492)	<0.001	2.661 (1.428–4.958)	0.002
Poor	5.958 (3.137–11.316)	<0.001	2.927 (1.508–5.683)	0.002

CI = confidence interval; HR = hazard ratio; Pp = postoperative.

hypothalamo–pituitary–adrenal (HPA) axis activity in the neuroendocrine system.[9] CTCs are the tumor cells that primary tumor release into peripheral blood no matter at early or advanced stages that are associated with the cancer recurrence and metastasis.[27,28] Surgery is beneficial to the survival of NSCLC, especially for the early-stage patients, but paradoxically more circulating tumor cells are released after surgery compared with preoperative period.[29] The majorities of these CTCs are eliminated by apoptosis, necrosis, and immune system during perioperative period and reduce to be at an undetectable level a few days after operation.[30,31] Similarly, disseminated tumor cells (DTC) refer to the CTCs circulating into the bone marrow, considered to be related to the bone metastasis.[32] When the immune system is insufficient, CTCs and DTCs may cause unwilling consequence. Postoperative mu agonists, playing the role as both ''fertilizer'' and ''pesticide'' for the ''seed'' CTCs, can protect and enhance the proliferation and function of CTCs during perioperative period.[8] Vitro studies indicated that mu agonists could increase the number of CTCs by accelerating cell cycle progression and cancer cell replication and by inhibiting apoptosis.[33] Moreover, mu agonists could promote CTCs on the function of invasiveness and metastasis. Mu agonists may facilitate epithelial-to-mesenchymal transition (EMT) procedure of CTCs;[34] promote the tumor angiogenesis and secondary growth;[35] and promote CTCs invasion by disrupting vascular endothelial barrier, increasing its permeability thus facilitating CTCs adherence and extraction from blood vessel to target tissue to form a secondary growth especially in bone and brain.[36,37] Through the above, we put forward the hypothesis that the interaction and relationship among postoperative mu agonists, CTCs and immune system may be a potential mechanism of cancer recurrence. With the assistance of mu agonists, CTCs have more opportunities to survive, proliferate, metastasize, and colonize in a new target organ such as brain, bone, or local recurrence after the removal of primary tumor. As a result, when using postoperative mu agonists to release the postoperative pain, the immune system may not play its function of surveillance and eliminating the residuals in the blood after operation.

It was reported that nicotine and mu agonists share several similar properties and biological behaviours, and repeated smoking can result in increased MOR expression.[38,39] An obvious upregulation of the MOR in both NSCLC patients and NSCLC cell lines can be observed.[40] And samples from metastatic lung cancer patients have higher MOR expression compared with nonmetastatic ones.[41] Moreover, there is an association between shorter overall survival and increased MOR expression.[42] These point out that the relation between mu agonists and NSCLC prognosis may be more evident than other types of cancers because of smoking. According to ''Smoking or Never'' layer, Kaplan–Meier survival analysis shows that postoperative mu agonists attenuate overall survival

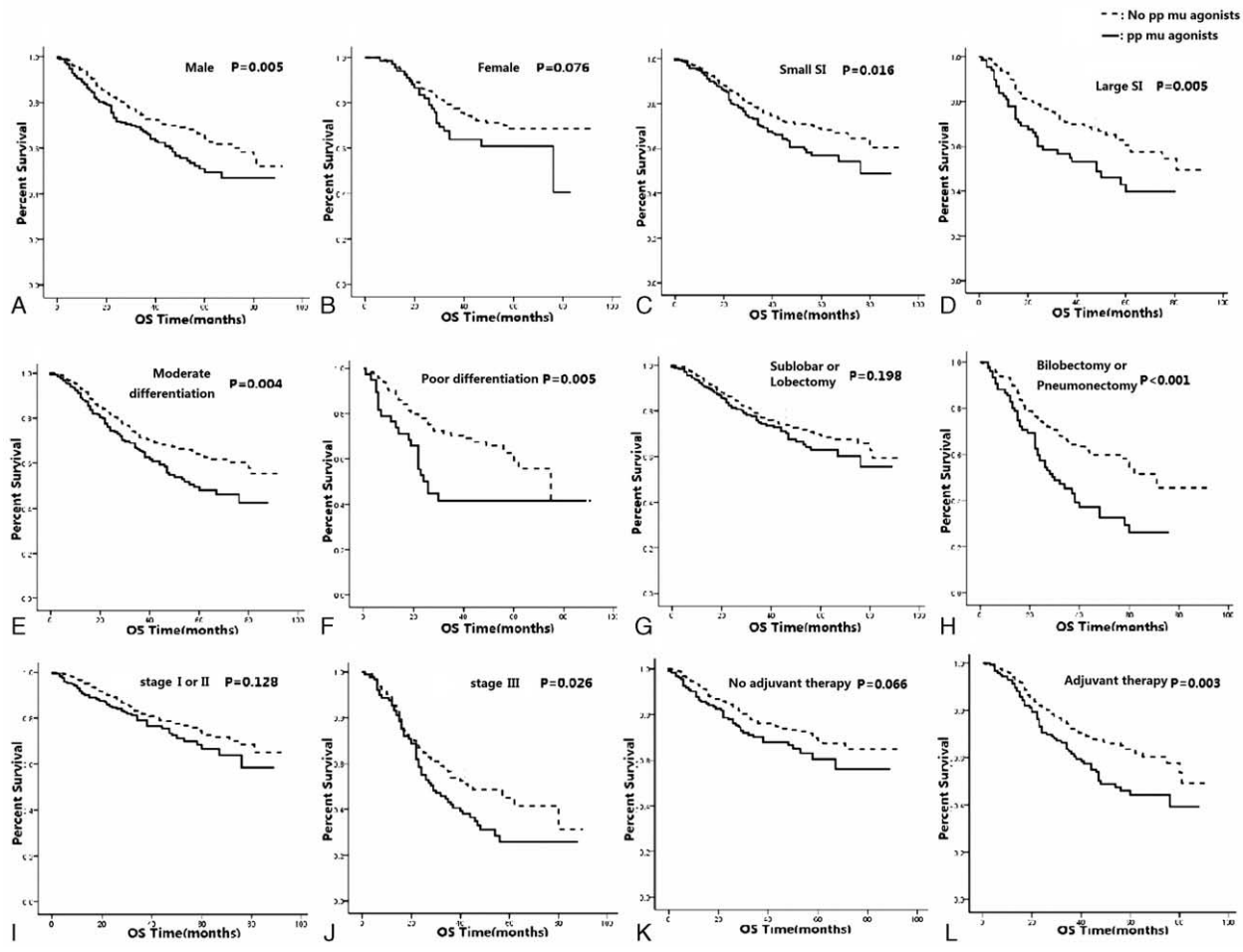

FIGURE 2. Subgroups analysis of overall survival between no postoperative mu agonists group () and postoperative mu agonists groups (). Charts A and B show OS difference between 2 groups in males and females, respectively. Data show OS difference is significant in males ($P = 0.005$) and not so significant in females ($P = 0.076$). Charts C and D show significant OS difference between 2 groups in small (≤430) smoking index ($P = 0.016$) and large (>430) smoking index ($P = 0.005$). It can be seen that no significant difference exists in well differential degree ($P = 0.849$, data not shown) and significant difference in both moderate (chart E, $P = 0.004$) and poor (chart F, $P = 0.005$) differential degree. Compared with Sublobar or Lobectomygroup (chart G, $P = 0.198$), Bilobectomy or Pneumonectomy group has obvious OS difference between 2 groups (chart H, $P < 0.001$). No statistical significance is observed in OS difference between 2 groups in stage I or II (chart I, $P = 0.128$). And chart J shows the OS difference between 2 groups in stage III ($P = 0.026$). Kaplan–Meier survival curves for overall survival between 2 groups in no adjuvant therapy and adjuvant therapy patients are shown in chart K ($P = 0.066$) and chart L ($P = 0.003$), respectively.

significantly in Smoking layer ($P = 0.002$, data not shown). In the Never Smoking layer, that may not be so significant ($P = 0.169$, data not shown).

The statistically significant difference of postoperative analgesics in two operation-type subgroups may be due to longer duration (Crosstab between operation type and duration, $P < 0.001$) and more hurt for the bilobectomy or pneumonectomy patients. Thus, more CTCs are released into blood and survive with the help of mu agonists, and result in higher recurrence. In subgroups analysis, males have significant overall survival difference between 2 groups ($P = 0.005$) while females do not ($P = 0.076$). The reason may be associated with more smoking males did (Crosstab between smoking index and sex, $P < 0.001$). For the patients who received adjuvant therapy, the postoperative mu agonists predict a shorter overall survival ($P = 0.003$, data not shown). When the patients received postoperative mu agonists, more CTCs left than no postoperative mu agonists patients due to our previous hypothesis. And Androulakis et al[43] showed that CTCs before front-line chemotherapy were related to long-term outcomes. That interprets the reason for significantly prognostic difference between postoperative and no postoperative mu agonists groups in adjuvant therapy layer. In subgroups analysis, the survival difference between 2 groups is not significant in well differential degree ($P = 0.849$), and appears significant in moderate ($P = 0.004$) and poor ($P = 0.005$) differential degrees. Compared with sublobar resection or lobectomy group ($P = 0.198$), survival difference in bilobectomy or pneumonectomy group seems much more significant ($P < 0.001$). The reason may be that bilobectomy or pneumonectomy has higher possibility of releasing more tumor cells into circulation due to larger surgical trauma and region. Furthermore, bilobectomy or pneumonectomy is related to poorer pathological stages and more possible occult microresiduals in lung or lymph nodes. And significant

TABLE 3. Cross Validation

	Training Group		Testing Group	
Repeated Times	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
1	1.402 (1.043–1.885)	0.025	1.758 (1.211–2.552)	0.003
2	1.374 (1.026–1.839)	0.033	1.708 (1.163–2.507)	0.006
3	1.352 (1.012–1.807)	0.041	1.775 (1.197–2.633)	0.004
4	1.425 (1.069–1.901)	0.016	1.612 (1.090–2.382)	0.017
5	1.387 (1.045–1.842)	0.024	1.757 (1.176–2.625)	0.006
6	1.409 (1.064–1.865)	0.017	1.722 (1.140–2.602)	0.010
7	1.471 (1.107–1.955)	0.008	1.505 (1.009–2.243)	0.045
8	1.355 (1.015–1.809)	0.040	1.825 (1.238–2.691)	0.002
9	1.389 (1.039–1.857)	0.026	1.709 (1.158–2.523)	0.007
10	1.474 (1.112–1.955)	0.007	1.518 (1.011–2.280)	0.044

CI = confidence interval; HR = hazards regression.

difference between 2 groups can be seen in stage III patients ($P = 0.026$) compared with stage I or II ($P = 0.128$).

More importantly, our research has many limitations. First, it is a retrospective analysis with inevitable disadvantages that it is not randomized and a selection bias exists. Although we performed cross validation, the reliability is lower than prospective studies. Second, without complete original postoperative pain records, we cannot exactly exclude or evaluate the influence of pain factor. Zylla et al[44] reported pain was also a prognostic predictor of advanced NSCLC before chemotherapy. Third, the samples that use postoperative non-mu agonists seem a bit few. For this reason, we cannot separate them as an independent group that can be analyzed further and screened the specific non-MOR analgesics beneficial to prognosis.

If our assumption is confirmed by further researches, when the postoperative pain happens and postoperative analgesia is

TABLE 4. Univariate and Multivariate Cox Regression of Prognostic Factors for DFS

	Univariate Analysis		Multivariate Analysis	
Characteristics	**HR (95% CI)**	***P***	**Adjusted HR (95% CI)**	***P***
Age, y				
⩽62.5	1		1	
⩾62.5	1.384 (1.119–1.711)	0.003	1.725 (1.387–2.146)	<0.001
Smoking index				
≤430	1		1	
≥430	1.571 (1.268–1.947)	<0.001	1.148 (0.919–1.435)	0.223
Postoperative analgesics				
No pp mu agonists	1		1	
Pp mu agonists	1.389 (1.106–1.745)	0.005	1.415 (1.123–1.781)	0.003
Operation duration, h				
⩽2.750	1		1	
≥2.750	1.450 (1.171–1.795)	0.001	1.066 (0.852–1.335)	0.576
Pathological size, cm				
⩽3.55	1		1	
≥3.55	2.107 (1.698–2.614)	<0.001	1.377 (1.095–1.731)	0.006
Stage				
I	1		1	
II	4.512 (2.585–7.874)	<0.001	2.616 (1.894–3.613)	<0.001
III	5.754 (3.174–10.431)	<0.001	4.462 (3.271–6.088)	<0.001
Operation type				
Sublobar resection or lobectomy	1		1	
Bilobectomy or pneumonectomy	1.927 (1.542–2.407)	<0.001	1.151 (0.906–1.462)	0.249
Differential degree				
Well	1		1	
Moderate	3.283 (2.416–4.461)	<0.001	2.382 (1.346–4.217)	0.003
Poor	5.426 (4.078–7.219)	<0.001	2.575 (1.395–4.754)	0.002

CI = confidence interval; HR = hazard ratio; Pp = postoperative.

needed, clinicians might try non-mu agonists analgesics, weak MOR agonist analgesics (tramadol), mixed agonist/antagonist of MOR (bucinnazine, dezocine), or other immunostimulatory analgesics. Other alternative analgesic methods such as local anesthesia, TENS, cryoanalgesia, acupuncture are also considered. However, that does not mean NO or Little Analgesics. Clinicians should have a positive attitude to the control of postoperative pain rather than conservative treatment in consideration of the life quality and suppressive effect of pain itself on immune system which may be associated with long-term outcomes.[45] We advocate high life quality on the premise of pain release. Further orientation may focus on the balance between immunosuppression of postoperative mu agonists and immune-enhancement of drugs or natural products. Moreover, a prospective study is needed to confirm the relation between postoperative mu agonists and long-term outcome and screen common mu agonists or other analgesics beneficial to long-term outcomes.

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