Association between intraoperative administration of dexamethasone and survival after curative resection for non-small cell lung cancer (NSCLC): A propensity score matching analysis

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Abstract

Background: Few studies have suggested the correlation between intraoperative dexamethasone and oncological outcomes in non-small cell lung cancer (NSCLC) patients with radical resection. The existing data are inconsistent and inadequate, and more evidence is needed. We therefore undertook a propensity-matched cohort study to investigate the correlation. Methods: 832 patients with stage I to IIIa NSCLC who went through a curative resection between January 2008 and December 2013 were enrolled in our study. Propensity-score matching analysis created a population of 206 patients in the non-DEX group and 103 patients in the DEX group. Cox regression analyses were applied to compare the disease-free survival (DFS) and overall survival (OS) between patients who did not and did receive dexamethasone in the propensity score-matched cohort, as well as in the certain patients with high-risk factors of postoperative nausea and vomiting. Results: After propensity score matching, intraoperative dexamethasone was not significantly associated with DFS (HR: 1.014, 95%CI: 0.786-1.309, P = 0.913) and OS (HR: 1.221, 95%CI: 0.905-1.647, P = 0.191). Multivariable cox regression analysis revealed that intraoperative dexamethasone was not still associated with DFS and OS after curative resection for NSCLC. In the subgroup analysis, intraoperative dexamethasone was significantly associated with improved DFS (HR: 0.20, 95%CI: 0.04-0.92, P = 0.038) in the group of anesthetic time less than 2 hours. In the subgroup of VATS, intraoperative dexamethasone was significantly associated with prolonged OS (HR: 0.53, 95%CI: 0.30-0.92, P = 0.023). Conclusion: There was no correlation between intraoperative administration of dexamethasone and survival in NSCLC patients after curative surgery. While patients given intraoperative dexamethasone had better disease-free survival compared with patients not given intraoperative dexamethasone in the subgroup of anesthetic time less than 2 hours. Intraoperative administration of dexamethasone may improve overall survival in the subgroup of VATS. Our results indicate that intraoperative administration of dexamethasone is probably favorable in the aforementioned populations.

Background

Disease recurrence and metastasis are the fatal hallmark of cancer[1]. Several factors, such as cancer surgery, subsequent therapy and host immune function, affect risk of recurrence and metastasis[2–4]. Major operations may facilitate tumor to release more tumor cells into circulatory system and increase the chance of metastasis[5], but host immune defense system plays an important role in killing tumor cells[6]. Experimental results show that perioperatively damaged immune function augments the possibility of cancer recurrence[7]. Therefore, perioperative period may be crucial.

Many perioperative managements, such as blood transfusion, epidural analgesia and decreased opioid intake, affect cancer outcomes[8–10]. Dexamethasone can decrease the risk of postoperative nausea and vomiting, especially for patients who meet the high-risk factors including female, nonsmoking status, long duration of anesthesia, thoracoscope, laparoscopy, inhaled anesthetics and so on[11, 12]. Dexamethasone as an immunosuppressive drug may have a deleterious effect on cancer recurrence or

patient overall survival after radical surgery[13]. Depression of natural killer cell function have been supposed to be the mechanism by which dexamethasone can depress host immune defense system[14].

One previous study noted that perioperative dexamethasone may have an advantageous impact on the long-term survival for non-small-cell lung cancer (NSCLC) patients with cancer radical surgery[15]. Another study showed that perioperative dexamethasone was not associated with recurrence-free survival and overall survival after curative surgery for NSCLC[16]. However, these data are inconsistent and inadequate, and more scientific studies are needed. As numerous patients who have lung cancer resection receive intraoperative dexamethasone for prevention of postoperative nausea and vomiting, the effect of dexamethasone on survival is a vital clinical problem.

To address this issue, we undertook a propensity score matching analysis, which was adjusted for strong prognostic factors, to assess the correlation between intraoperatively administration of dexamethasone and survival in NSCLC patients undergoing surgical resection. Specifically, the aim of subgroup analysis was to investigate whether intraoperatively administration of dexamethasone was associated with better or poorer prognosis in the certain patients with high-risk factors of postoperative nausea and vomiting.

Methods

The study was approved by the research data declaration (RDD) of Sun Yat-sen University cancer Center.

Study participants

Clinicopathological characteristics of all patients who had lung cancer resection were collected from electronic medical records at Sun Yat-sen University cancer Center between January 2008 and December 2013. The exclusion criteria were as follows: benign lung tumor or small cell lung cancer, metastatic lung cancer, other malignancy, history of lung surgery, bilateral lung cancer, American Society of Anesthesiologists (ASA) physical status equal to or greater than IV, receiving corticosteroids due to chronic obstructive pulmonary disease (COPD)/asthma exacerbation/ inflammatory bowel disease, TNM stage a or , severe perioperative complications and those who lacked histologic confirmation or clinical details[17, 18]. All enrolled patients were divided into two groups on the basis of whether they received dexamethasone during lung cancer resection. Whether patients receive dexamethasone depends on the preference of anesthesiologists. Patients in the dexamethasone group (DEX group) received dexamethasone, and those in the non-dexamethasone group (non-DEX group) didn't receive dexamethasone.

Patient characteristics and Outcome

The following data were extracted from electronic medical records: age, gender, height, weight, smoking status, co-morbid illness, TNM stage, histology type, tumor size, ASA physical status, type of anesthesia, anesthetic time, operation methods, transfusion, type of postoperative pain control, date of surgery, chemotherapy and radiation therapy. Co-morbid illnesses consist of coronary heart disease, diabetes

mellitus (DM), hypertension, hepatitis B, hyperthyroidism or hypothyroidism and chronic obstructive pulmonary disease (COPD). Tumor size was the largest diameter of tumor mass.

The primary endpoint of our study was disease-free survival (DFS) and overall survival (OS). DFS was the interval between the date of surgery and the date of relapse of lung cancer, metastasis or death. Relapse of lung cancer was defined as locoregional new occurrences of tumor mass and confirmed by imaging or histopathological examination. Metastasis of lung cancer was defined as the dissemination of lung cancer from lung to another part of the body, and confirmed by imaging or histopathological examination. OS was the interval between the date of surgery and the date of death. We recorded the dates of death from the hospital information system (HIS) of Sun Yat-sen University cancer Center. The final follow-up was December 31, 2018. The follow-up period was at least 5 years. Patients lost to follow-up during the study period were censored.

Statistical Analysis

Propensity score matching was conducted to balance baseline characteristics between two groups by reducing the potential confounding factors. Propensity score was the possibility of receiving dexamethasone treatment and calculated by logistic regression analysis. Thereafter, a propensity score-matched cohort of patients receiving vs. not receiving dexamethasone was generated at a ratio of 1:2 by using the nearest neighbor method with caliper less than 0.01. We evaluated the efficiency of matching to balance baseline characteristics by using standard differences [19, 20]. Categorical variables were presented as the number. Continuous variables were presented as the mean or median. The Student's t test or the Mann-Whitney U test were used for comparisons of continuous variables. The chi-square test or the Fisher's exact test were used to compare categorical variables. In the propensity score-matched cohort, disease-free survival (DFS) and overall survival (OS) were compared between the non-DEX and DEX groups, and calculated using the Kaplan–Meier method. Multivariable cox proportional hazards models were conducted to identify other potential confounding factors associated with intraoperatively administration of dexamethasone. Potential confounding factors consisted of age, tumor size, type of anesthesia, transfusion, year of diagnosis, TNM stage, postoperative radiotherapy and chemotherapy. All variables were entered into multivariable cox proportional hazards regression analysis to compare the hazards ratio between the two groups by using the "enter" method. Multivariable cox proportional hazards regression model was then to assess the association between anesthetic variables and survival after lung cancer resection for NSCLC patients. Associations between intraoperatively administration of dexamethasone and high-risk factors of postoperative nausea and vomiting (PONV) for disease-free survival and overall survival was calculated by cox proportional hazard regression analysis and presented as forest plot[21]. Univariable and multivariable analyses were performed using the IBM SPSS Statistics 23.0 (SPSS Inc, Armonk, NY, USA). Propensity score matching analysis was carried out using R software version 3.5.3 (R Project for Statistical Computing, Austria). A two-tailed $P < 0.05$ was considered statistically significant.

Results

A total of 2480 patients who underwent lung cancer resection at Sun Yat-sen University cancer Center were enrolled during the study period (2008–2013). Of these, 823 patients catered to inclusion criteria and were finally brought into our study (Fig. 1). 823 patients fell into two groups: the non-DEX group (N = 675, 82%), and the DEX group (N = 148, 18%). Among 148 patients with intraoperative dexamethasone therapy, 21 (14.2%) received 5 mg of dexamethasone, 6 (4.0%) received 7.5 mg of dexamethasone and 121(81.8%) received 10 mg of dexamethasone. All patients in the non-DEX group didn't receive any intraoperative glucocorticoids.

The comparisons of patients' characteristics, tumor-related characteristics, anesthetic variables and surgical variables between non-DEX and DEX groups in the entire cohort are illustrated in Table 1. Smoking status, perioperative blood transfusion, postoperative analgesia and chemotherapy were significantly different between two groups ($P < 0.05$). Variables associated with intraoperatively administration of dexamethasone ($P < 0.2$) as presented in Table 1 were entered into multivariable cox proportional regression analysis. The independent risk factors of intraoperatively administration of dexamethasone, including smoking status ($P < 0.001$), blood transfusion ($P = 0.005$), postoperative analgesia ($P = 0.001$) and chemotherapy ($P = 0.037$), were shown in Table 2. The variables used for matching were smoking status, blood transfusion, postoperative analgesia and postoperative adjuvant chemotherapy.

Table 1
Comparison of baseline characteristics between the intraoperative dexamethasone (DEX) and non-DEX groups in the entire cohort.

Variable	Non-DEX group (N = 675)	DEX group (N = 148)	P value
Age, years	60.21	59.31	0.58
Sex			0.388
Male	382	78	
Female	293	70	
BMI, kg/m2	23.02	23.12	0.05
Smoking status			0.001 *
Never	363	116	
Ever	312	32	
Co-morbid illness			0.191
No	441	105	
Yes	234	43	
TNM stage			0.326
	157	23	
	122	33	
	374	87	
Histology type			0.876
Adenocarcinoma	530	113	
Squamous cell carcinoma	96	24	
Large cell carcinoma	6	2	
Others	43	9	
Tumor size, cm	3.30	3.42	0.813
ASA score			0.939
≤2	608	133	
2	67	15	
Duration of anesthesia	3.64	4.15	0.39

Variable	Non-DEX group (N = 675)	DEX group (N = 148)	P value
Type of anesthesia			0.138
Inhalation	643	145	
Intravenous	32	3	
Operative approach			0.938
Thoracotomy	463	102	
VATS	212	46	
Blood transfusion			0.001*
No	573	141	
Yes	102	7	

Table 1

Comparison of baseline characteristics between the intraoperative dexamethasone (DEX) and non-DEX groups in the entire cohort. (Continued)

Variable	Non-DEX group (N = 675)	DEX group (N = 148)	P value
Postoperative analgesia			0.001*
No	43	9	
PCIA	433	128	
PCEA	152	11	
Radiotherapy			0.119
No	539	110	
Yes	134	38	
Chemotherapy			0.012*
No	323	54	
Yes	352	94	
Year of diagnosis			0.777
2006–2010	445	104	
2011–2015	230	44	

ASA, American Society of Anesthesiologists; BMI, body mass index; Dex, dexamethasone; PCIA, patient controlled intravenous analgesia; PCEA, patient controlled epidural analgesia; VATS, video-assisted thoracic surgery.

*P-value less than 0.05 was considered statistically significant.

Table 2
Multivariable analysis of independent predictive factors of intraoperative dexamethasone.

Independent predictive factor	Wald	P value	HR (95% CI)
BMI	0.110	0.740	0.936(0.635–1.380)
Smoking status	20.561	< 0.001*	2.716(1.764–4.184)
Co-morbid illness	0.999	0.318	1.232(0.818–1.854)
Type of anesthesia	2.411	0.120	2.653(0.774–9.090)
Blood transfusion	8.032	0.005*	3.194(1.431–7.130)
Postoperative analgesia	11.386	0.001*	1.973(1.330–2.928)
Radiotherapy	2.171	0.141	0.716(0.459–1.117)
Chemotherapy	4.345	0.037*	0.661(0.448–0.976)

A comparison of baseline characteristics after propensity score matching analysis between the non-DEX group and the DEX group is illustrated in Table 3. Propensity score matching analysis generated a cohort of 206 patients in the non-DEX group and 103 patients in the DEX group. All baseline characteristics between two groups were balanced (P > 0.1). The median follow-up period was 44 (interquartile range, 25.5 to 62) months for all the matched patients. In the non-DEX group and the DEX group, the median follow-up period was 46 (interquartile range, 25 to 64) months and 42 (interquartile range, 26 to 59) months, respectively. There was no significant difference in the follow-up period among two groups (P = 0.401). The Kaplan-Meier survival curves demonstrated 1-yr, 3-yr and 5-yr disease-free survival rates in the non-DEX and DEX groups were 70.9%, 31.3%, 19.6% and 72.8%, 30.1%, 15.1%, respectively; While 1-yr, 3-yr and 5-yr overall survival rates in the non-DEX and DEX groups were 91.2%, 65.4%, 48.1% and 92.2%, 63.5%, 34.5%, respectively. There was no significant difference between the non-DEX group and the DEX group in disease-free survival (P = 0.913) or overall survival (P = 0.191) (Fig. 2). Multivariable cox proportional hazards regression model for disease-free survival was carried out and revealed no statistically significant association between intraoperative dexamethasone and disease-free survival (HR: 1.057, 95% CI: 0.809–1.381, P = 0.686) (Table 4). Then, multivariable cox proportional regression analysis for overall survival was performed and revealed that intraoperative dexamethasone was not associated with poorer overall survival (HR: 0.205, 95% CI: 0.893–1.690, P = 0.191) (Table 5). We also conducted cox proportional regression analyses to identify risk factors for disease-free survival and overall survival. Age over 60 years, advanced TNM stage and usage of chemotherapy were significantly associated with poorer disease-free survival; While age over 60 years, advanced TNM stage and tumor size more than 4 cm were associated with poorer overall survival.

Table 3
Comparisons of baseline characteristics between the intraoperative dexamethasone (DEX) and non-DEX groups in the propensity score-matched sample.

Variable	Non-DEX group (N = 206)	DEX group (N = 103)	P value
Age, years	60.2	59.3	0.889
Sex			0.374
Male	117	53	
Female	89	50	
BMI, kg/m2	23.10	23.26	0.32
Smoking status			0.84
Never	166	82	
Ever	40	21	
Co-morbid illness			0.129
No	128	73	
Yes	78	30	
TNM stage			0.459
	32	11	
	46	22	
	128	70	
Histology type			0.669
Adenocarcinoma	169	79	
Squamous cell carcinoma	27	19	
Large cell carcinoma	2	1	
Others	8	4	
Tumor size, cm	3.49	3.48	0.626
ASA score			0.415
≤2	188	91	
2	18	12	

Variable	Non-DEX group (N = 206)	DEX group (N = 103)	P value
Duration of anesthesia	3.77	3.98	0.459
Type of anesthesia			0.122
Inhalation	191	100	
Intravenous	15	3	
Operative approach			1.0
Thoracotomy	138	69	
VATS	68	34	
Blood transfusion			0.311
No	202	99	
Yes	4	4	
Postoperative analgesia			0.626
No	15	7	
PCIA	168	88	
PCEA	23	8	

Table 3

Comparisons of baseline characteristics between the intraoperative dexamethasone (DEX) and non-DEX groups in the propensity score-matched sample. (Continued)

Variable	Non-DEX group (N = 206)	DEX group (N = 103)	P value
No	150	71	
Yes	56	32	
Chemotherapy			0.397
No	74	32	
Yes	132	71	
Year of diagnosis			0.129
2006–2010	128	73	
2011–2015	78	30	
ASA, American Society of Anesthesiologists; BMI, body mass index; Dex, dexamethasone; PCIA, patient controlled intravenous analgesia; PCEA, patient controlled epidural analgesia; VATS, video-assisted thoracic surgery.			
P-value less than 0.05 was considered statistically significant.			

Table 4
Univariable and multivariable Cox regression analyses for disease-free survival in the propensity matched cohort.

Variable	Univariable			Multivariable		
	HR	95% CI	P value	HR	95% CI	P value
Dexamethasone						
No	Reference			Reference		
Yes	1.014	0.786–1.309	0.913	1.065	0.814–1.391	0.647
Age, years						
Age ≤ 60	Reference			Reference		
Age□60	1.206	0.947–1.535	0.129	1.362	1.049–1.770	0.021
Sex						
Female	Reference			Reference		
Male	0.859	0.674–1.095	0.219	0.886	0.678–1.157	0.374
BMI, kg/m^2						
≤ 24	Reference			Reference		
□24	0.988	0.771–1.268	0.926	0.998	0.767–1.298	0.988
Smoking status						
Never	Reference			Reference		
Ever	0.971	0.720–1.310	0.847	0.898	0.648–1.245	0.519
Co-morbid illness						
No	Reference			Reference		
Yes	0.948	0.742–1.211	0.668	0.900	0.688–1.178	0.444
TNM stage						
□	Reference			Reference		

Variable	Univariable			Multivariable		
□	0.485	0.331–0.710	□0.001	0.510	0.334–0.778	0.008
□	0.741	0.548-1.000	0.051	0.879	0.636–1.217	0.002
Histology type						
Adenocarcinoma	Reference			Reference		
Squamous cell carcinoma	0.898	0.490–1.646	0.727	0.816	0.430–1.550	0.535
Large cell carcinoma	0.640	0.327–1.253	0.193	0.614	0.309–1.219	0.163
Others	1.646	0.459–5.906	0.445	1.536	0.392–6.014	0.538
Tumor size, cm						
≤ 4	Reference			Reference		
□4	1.017	0.768–1.346	0.907	1.006	0.732–1.382	0.972
ASA score						
≤ 2	Reference			Reference		
□2	1.002	0.781–1.285	0.986	1.023	0.783–1.337	0.868

Table 4

Univariable and multivariable Cox regression analyses for disease-free survival in the propensity matched cohort. (Continued)

Variable	Univariable			Multivariable		
	HR	95% CI	P value	HR	95% CI	P value
Anesthetic time, hr						
≤ 2	Reference			Reference		
2	0.667	0.407–1.092	0.107	0.737	0.432–1.258	0.263
Type of anesthesia						
Inhalation	Reference			Reference		
Intravenous	0.861	0.493–1.505	0.600	0.987	0.535–1.818	0.966
Operative approach						
Thoracotomy	Reference			Reference		
VATS	0.802	0.617–1.041	0.097	0.813	0.611–1.082	0.156
Blood transfusion						
No	Reference			Reference		
Yes	1.306	0.645–2.643	0.459	0.990	0.471–2.081	0.979
Postoperative analgesia						
No	Reference			Reference		
PCIA	1.200	0.657–2.192	0.554	1.236	0.668–2.288	0.500
PCEA	1.226	0.804–1.868	0.344	1.160	0.751–1.791	0.503
Radiotherapy						
No	Reference			Reference		

ASA, American Society of Anesthesiologists; BMI, body mass index; CI, confidence index; Dex, dexamethasone; HR, hazard ratio; PCIA, patient controlled intravenous analgesia; PCEA, patient controlled epidural analgesia; VATS, video-assisted thoracic surgery.

P-value less than 0.05 was considered statistically significant.

Variable	Univariable			Multivariable		
Yes	1.418	1.090–1.844	0.009	1.309	0.987–1.736	0.062
Chemotherapy						
No	Reference			Reference		
Yes	1.489	1.153–1.923	0.002	1.417	1.073–1.871	0.014
Year of diagnosis						
2006–2010	Reference			Reference		
2011–2015	0.987	0.925–1.054	0.698	0.916	0.674–1.243	0.573
ASA, American Society of Anesthesiologists; BMI, body mass index; CI, confidence index; Dex, dexamethasone; HR, hazard ratio; PCIA, patient controlled intravenous analgesia; PCEA, patient controlled epidural analgesia; VATS, video-assisted thoracic surgery.						
P-value less than 0.05 was considered statistically significant.						

Table 5
Univariable and multivariable Cox regression analyses for overall survival in the propensity matched cohort.

Variable	Univariable			Multivariable		
	HR	95% CI	P value	HR	95% CI	P value
Dexamethasone						
No	Reference			Reference		
Yes	1.221	0.905–1.647	0.191	1.219	0.887–1.677	0.223
Age, years						
Age ≤ 60	Reference			Reference		
Age 60	1.437	1.076–1.920	0.014	1.423	1.035–1.956	0.030
Sex						
Female	Reference			Reference		
Male	1.057	0.791–1.414	0.706	1.017	0.739-1.400	0.918
BMI, kg/m^2						
≤ 24	Reference			Reference		
24	0.997	0.740–1.343	0.983	1.013	0.732–1.402	0.938
Smoking status						
Never	Reference			Reference		
Ever	1.367	0.975–1.919	0.07	1.278	0.881–1.855	0.196
Co-morbid illness						
No	Reference			Reference		
Yes	0.878	0.651–1.183	0.392	0.846	0.611–1.171	0.313
TNM stage						
	Reference			Reference		

Variable	Univariable			Multivariable		
□	0.754	0.489–1.162	0.200	0.560	0.347–0.904	0.033
□	0.753	0.521–1.088	0.130	0.715	0.482–1.059	0.018
Histology type						
Adenocarcinoma	Reference			Reference		
Squamous cell carcinoma	0.609	0.310–1.196	0.150	0.763	0.369–1.578	0.466
Large cell carcinoma	0.741	0.353–1.553	0.427	0.693	0.323–1.487	0.347
Others	2.359	0.635–8.759	0.200	1.799	0.425–7.624	0.425
Tumor size, cm						
≤ 4	Reference			Reference		
□4	1.784	1.303–2.444	□0.001	1.630	1.131–2.349	0.009
ASA score						
≤ 2	Reference			Reference		
□2	1.263	0.943–1.693	0.118	1.125	0.824–1.534	0.459

Table 5

Univariable and multivariable Cox regression analyses for overall survival in the propensity matched cohort. (Continued)

Variable	Univariable			Multivariable		
	HR	95% CI	P value	HR	95% CI	P value
Anesthetic time, hr						
≤ 2	Reference			Reference		
2	0.735	0.409–1.321	0.303	0.590	0.312–1.114	0.104
Type of anesthesia						
Inhalation	Reference			Reference		
Intravenous	0.344	0.128–0.928	0.035	0.470	0.165–1.332	0.155
Operative approach						
Thoracotomy	Reference			Reference		
VATS	0.755	0.547–1.041	0.086	0.935	0.657–1.332	0.711
Blood transfusion						
No	Reference			Reference		
Yes	2.257	1.057–4.815	0.035	2.151	0.947–4.885	0.067
Postoperative analgesia						
No	Reference			Reference		
PCIA	1.034	0.489–2.187	0.931	0.984	0.457–2.121	0.968
PCEA	1.189	0.711–1.989	0.510	1.065	0.626–1.814	0.816
Radiotherapy						
No	Reference			Reference		

ASA, American Society of Anesthesiologists; BMI, body mass index; CI, confidence index; Dex, dexamethasone; HR, hazard ratio; PCIA, patient controlled intravenous analgesia; PCEA, patient controlled epidural analgesia; VATS, video-assisted thoracic surgery.

P-value less than 0.05 was considered statistically significant.

Variable	Univariable			Multivariable		
Yes	0.944	0.686–1.298	0.723	0.821	0.581–1.160	0.264
Chemotherapy						
No	Reference			Reference		
Yes	1.183	0.873–1.601	0.279	1.060	0.760–1.479	0.730
Year of diagnosis						
2006–2010	Reference			Reference		
2011–2015	0.894	0.825–0.968	0.006	0.693	0.471–1.020	0.063
ASA, American Society of Anesthesiologists; BMI, body mass index; CI, confidence index; Dex, dexamethasone; HR, hazard ratio; PCIA, patient controlled intravenous analgesia; PCEA, patient controlled epidural analgesia; VATS, video-assisted thoracic surgery.						
P-value less than 0.05 was considered statistically significant.						

These propensity score-matched patients were stratified according to the high-risk factors of postoperative nausea and vomiting. Subgroup analysis was performed to explore whether intraoperative dexamethasone affected survival in some certain subgroup. Figure 3 reported a significant correlation between intraoperatively administration of dexamethasone and improved disease-free survival in the subgroup of anesthetic time less than 2hrs (HR: 0.20, 95% CI: 0.04–0.92, P = 0.038). Meanwhile, there was a significant association between intraoperatively administration of dexamethasone and longer overall survival in the subgroup of VATS (HR: 0.53, 95% CI: 0.30–0.92, P = 0.023).

Discussion

Our study found no correlation between intraoperatively administration of dexamethasone and survival in NSCLC patients after lung cancer resection. While patients given dexamethasone had better disease-free survival in the subgroup of anesthetic time less than 2 hours. Intraoperative administration of dexamethasone may improve overall survival in the subgroup of VATS. Our results indicate that intraoperative dexamethasone, commonly used for prevention of postoperative nausea and vomiting (PONV), do not augment cancer recurrence and affect overall survival in non-small cell lung cancer patients having lung cancer resection. However, intraoperative administration of systemic dexamethasone is probably favorable in the aforementioned populations.

Glucocorticoids (GCs), such as dexamethasone, can arrest growth or induce apoptosis in lymphocytes[22]. In leukemia and lymphoma, dexamethasone is the cornerstone of treatment for all lymphatic cancers and hematopoietic malignancies[23]. Moreover, dexamethasone performs a variety of

functions, including preventing postoperative nausea and vomiting, reducing postoperative pain, anti-inflammation, antianaphylaxis, immunosuppression and so on[12, 24, 25]. The administration of dexamethasone during treatment of nonhematologic malignancy is at issue. The effect of dexamethasone on oncological outcomes has been investigated by another researchers. Obradovic MMS et al. reported that glucocorticoids increased the risk of breast cancer metastasis by activating glucocorticoid receptor[26]. Similarly, immunosuppressive dose of dexamethasone might enhance prostate cancer progression[27]. In rectal cancer patients with curative resection, there was an association between low-dose perioperative dexamethasone and poorer survival[28]. On the contrary, glucocorticoids perform a beneficial effect in certain solid tumors. Perioperatively administration of dexamethasone may improve survival in pancreatic adenocarcinoma patients[29]. A retrospective study noted that perioperatively dexamethasone had no effect on ovarian cancer recurrence[30]. The aforementioned studies implied that dosage, timing and frequency of dexamethasone played a decisive role in different oncological outcomes. Histopathological type of tumor and primary site of tumor were equally important. As a consequence, further researches are wanted to verify the effect of dexamethasone on other cancer.

A few studies suggested the correlation between administration of dexamethasone and survival in non-small lung cancer patients with lung cancer resection. One study noted that NSCLC patients treated with lung cancer resection may get survival benefit from perioperatively administration of dexamethasone[15]. A systematic analysis reported that glucocorticoids might have a deleterious effect in NSCLC patients. Another study indicated that dexamethasone was not associated with recurrence-free survival and overall survival after lung cancer resection for NSCLC patients[16]. These results are inconsistent and inadequate, and more studies are necessary. Our study provides more evidence to verify the association between intraoperatively administration of dexamethasone and survival in NSCLC patients as well as in some certain subgroup populations.

Lack of correlation between intraoperatively administration of dexamethasone and survival may be associated with the following several factors. On one hand, two factors may facilitate favorable effect of dexamethasone on survival for NSCLC patients. Dexamethasone reduces stress response which has a detrimental influence on host immune function[31]. In addition, dexamethasone can suppress proliferation of non-small cell lung cancer by inactivating estrogen[32]. On the other hand, intraoperatively administration of dexamethasone augments the risks of cancer recurrence and metastasis through several possible ways. Dexamethasone depresses host immune defense system by inhibiting the function of natural killer cell (NK), which takes part in tumor cytotoxicity[33]. Besides, low concentrations of dexamethasone not only induce proliferation of normal cells, but also induces proliferation of cancer cell in vitro, including glioma and astrocytoma[34]. Meanwhile, dexamethasone, as a long half-life glucocorticoid, may remain stable for 36–72 hours in humans[35]. Thus, the detrimental effects of dexamethasone might persist for a relatively long period of time in non-small cell lung cancer patients. As a consequence, these deleterious effects may be just right to counteract the favorable effects of dexamethasone to generate an overall neutral effect.

This study has some limitations. Firstly, sample size was relatively small. Our study consisted of 148 patients receiving intraoperative dexamethasone and 675 patients who were not given dexamethasone. After propensity score matching, there were only 206 patients in the non-DEX group and 103 patients in the DEX group. Secondly, we performed a propensity score matching analysis to decrease the potential confounding effect of each variable. But we failed to take into consideration those unknown confounding factors. Thirdly, the date of cancer recurrence could be inaccuracy and we may overestimate the date of cancer recurrence. Because relapse may occur before relapse was detected by imaging or histopathological examination. Moreover, our study couldn't collect the details of intraoperative and postoperative opioids administration, so we couldn't assess the effect of opioids on survival. Finally, we couldn't avoid selection bias on account of retrospective analysis. This could be an important reason that we found no association between intraoperative dexamethasone and survival.

Our results show that there was no correlation between intraoperatively administration of dexamethasone and survival in NSCLC patients after lung cancer resection. However, we still don't know whether the correlation between intraoperatively dexamethasone and survival is coincidental. The exact effects of intraoperative dexamethasone on non-small cell lung cancer patients with lung cancer resection should be verified in further researches. An adequately powered randomized control trial (RCT) that has strict inclusion criteria and exclusion criteria will verify the effect of intraoperative dexamethasone on disease-free survival and overall survival for non-small cell lung cancer patients.

Conclusion

There was no correlation between intraoperatively administration of dexamethasone and survival in non-small cell lung cancer (NSCLC) patients. Comparing with patients not receiving dexamethasone intraoperatively, patients receiving dexamethasone had improved disease-free survival in the subgroup of anesthetic time less than 2 hours. Intraoperatively administration of dexamethasone may improve overall survival in the subgroup of VATS.

Our results indicate that intraoperatively administration of dexamethasone has no impact on survival in NSCLC patients with lung cancer resection. In some certain patient populations, intraoperative administration of systemic dexamethasone is probably favorable. However, the effects and mechanisms of dexamethasone on non-small cell lung cancer should be verified in further research.

Abbreviations

ASA: American Society of Anesthesiologists; BMI: Body mass index; CI: Confidence interval; COPD: Chronic obstructive pulmonary disease; DEX: Dexamethasone; DFS: Disease-free survival; GC: Glucocorticoids; HR: Hazards ratio; IV: Intravenous; NSCLC: Non-small cell lung cancer; OS: Overall survival; PCIA: Patient controlled intravenous analgesia; PCEA: Patient controlled epidural analgesia; PONV: Postoperative nausea and vomiting; RCT: Randomized control trial; SD: Standard Deviation; VATS: Video-assisted thoracic surgery.

Declarations

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Not applicable.

Authors' contributions

All authors had full access to all the data and take responsibility for the integrity of the data and accuracy of the data analysis. DTC, WAZ and FY helped design the study. HQZ, WX and QL helped conduct of the study and data collection. FY, GC and JDX helped conduct of the study, data analysis, interpretation of the results and manuscript preparation as co-authors. All authors have read and approved the final manuscript.

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Availability of data and materials

The datasets used or presented during this study are available from the corresponding author upon reasonable request.

Ethics approval and consent to participate

The medical study was approved by the Clinical Research Ethics Committee of Sun Yat-sen University Cancer Center. The informed consent was waived because of the retrospective nature of this study and no risk for the patients in this study.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figures

Figure 1

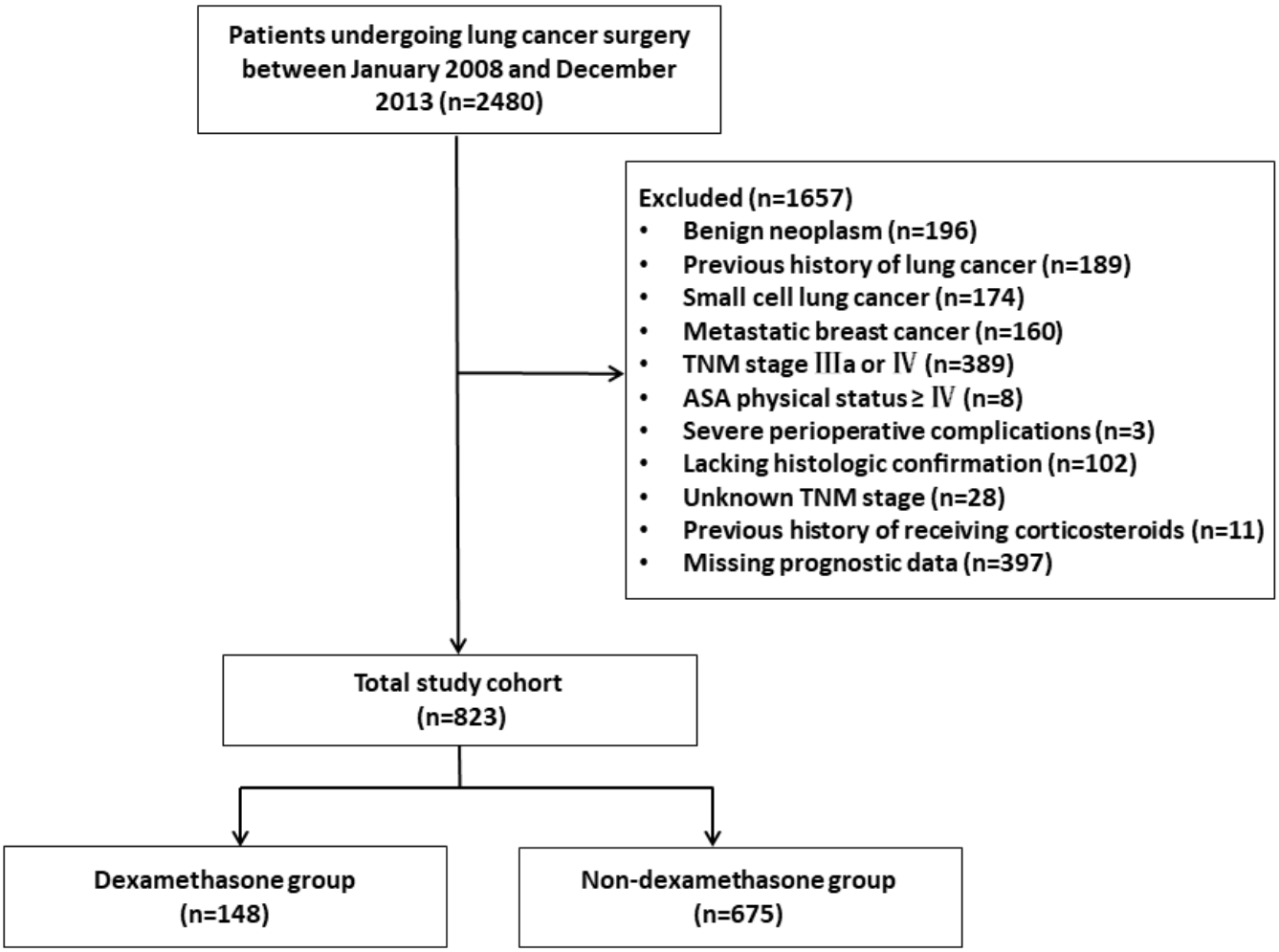

Figure 1

Flowchart of study selection.

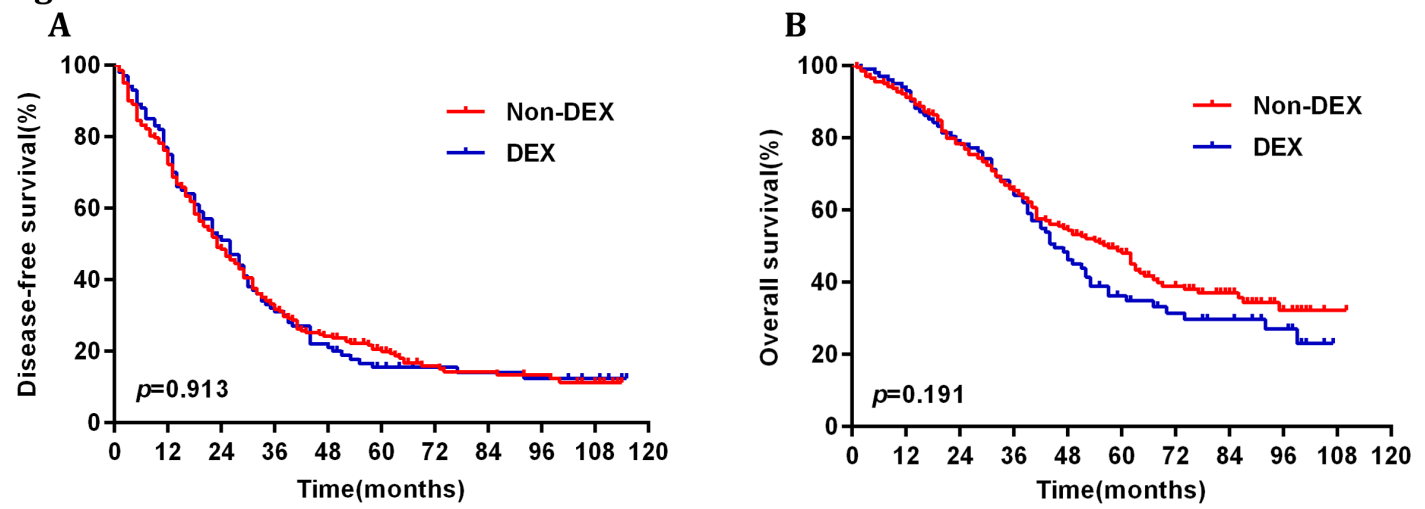

Figure 2

The Kaplan-Meier curves of the intraoperative dexamethasone (DEX) and non-DEX groups in the propensity matched cohort. (A) Disease-free survival. (B) Overall survival. DEX, dexamethasone.

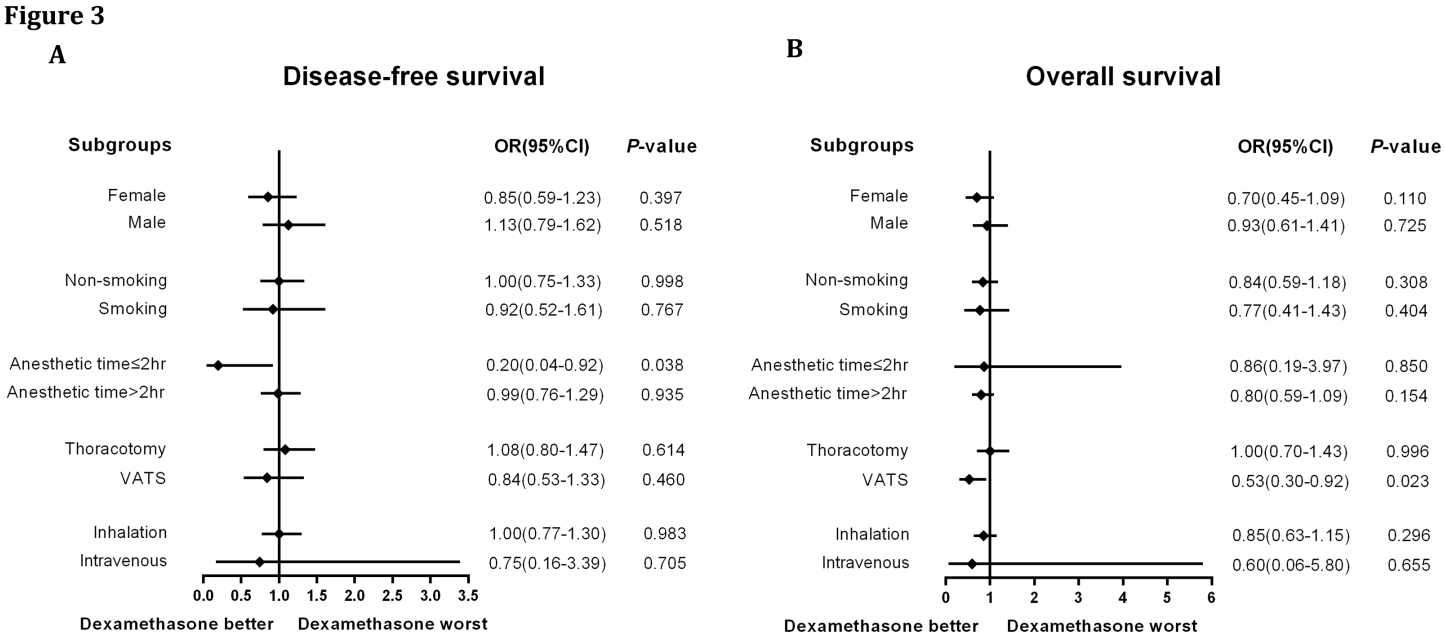

Figure 3

Subgroup analysis of disease-free survival (A) and overall survival (B) according to the risk factors of postoperative nausea and vomiting. CI, confidence interval; OR, odd ratio; VATS, video-assisted thoracic surgery.