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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Research

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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 lung tumor resection between January 2008 and December 2013 were enrolled in our study. Propensity-score matching analysis created a population of 260 patients in the non-DEX group and 130 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 (PONV).

Results: After propensity score matching, intraoperative dexamethasone was not significantly associated with DFS (HR: 0.944, 95%CI: 0.720-1.237, *P* = 0.655) and OS (HR: 1.210, 95%CI: 0.927-1.581, *P* = 0.486). Multivariable cox regression analysis revealed that intraoperative dexamethasone was not independent prognostic factor for DFS and OS in NSCLC patients undergoing surgical resection. In the subgroup analysis, including female subgroup, nonsmoking subgroup, long anesthetic time subgroup, VATS subgroup and inhaled anesthetics subgroup, intraoperative dexamethasone was not significantly associated with DFS and OS.

Conclusion: There was no correlation between intraoperative administration of dexamethasone and survival in NSCLC patients after curative surgery. In the high-risk subgroups of PONV, that is, female, nonsmoking, long anesthetic time, VATS and inhaled anesthetics, patients given intraoperative dexamethasone had no better or poorer prognosis compared with patients not given intraoperative dexamethasone.

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 anesthetic time, 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 uploading the raw data onto the research data deposit (RDD) public platform, with the approval RDD number as RDDA2020001408.

Study participants

Clinicopathological characteristics of all patients who had lung tumor 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 □b 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 tumor resection. Whether patients receive dexamethasone depends on the preference of anesthesiologists. Patients in the dexamethasone group (DEX group) received intraoperatively dexamethasone, and those in the non-dexamethasone group (non-DEX group) didn't receive intraoperatively dexamethasone.

Patient characteristics and Outcome

The following data were extracted from electronic medical records: age, gender, height, weight, smoking status, smoking index, co-morbid illness, Karnofsky performance score (KPS), TNM stage, histology type, tumor size, American Society of Anesthesiologists (ASA) score, type of anesthesia, anesthetic time,

operation methods, dexamethasone, NSAIDS, transfusion, type of postoperative pain control, date of surgery, postoperative complications, chemotherapy and radiotherapy. Co-morbid illnesses consisted of coronary heart disease, heart failure, cerebrovascular disease, hemiplegia, diabetes mellitus, hypertension, hepatitis B, hyperthyroidism or hypothyroidism, nephropathy, peptic ulcer, asthma, chronic obstructive pulmonary disease and connective tissue diseases. Smoking index is the number of cigarettes per day times years of smoking. Tumor size was the largest diameter of tumor mass. Charlson comorbidity index was a tool to calculate the cumulative prognostic burden of co-morbid illnesses in an objective method. Type of postoperative pain control consisted of intravenous analgesia and epidural analgesia; Core component of intravenous analgesia was fentanyl or sufentanil; While core component of epidural analgesia was morphine. The Clavien-Dindo classification was based on the therapy which was used to rectify a specific postoperative complication.

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, which was performed using the IBM SPSS Statistics 22.0 (SPSS Inc, Armonk, NY, USA). Propensity score was the possibility of covariates and calculated by logistic regression analysis. The propensity score for each individual was measured by incorporating the covariates of age, sex, BMI, smoking index, Charlson comorbidity index, KPS, TNM stage, histological type, tumor size, American Society of Anesthesiologists (ASA) score, anesthetic time, type of anesthesia, NSAIDS, operation method, Clavien-Dindo classification, blood transfusion, postoperative pain control, chemotherapy and radiotherapy using logistic regression analysis. A propensity score-matched cohort of patients receiving vs. not receiving dexamethasone was generated at a ratio of 1:2. For each patient in the DEX group, two patients not receiving dexamethasone were matched using the nearest neighbor method. We tested multiple caliper in 0.1, 0.01 or 0.001 of standard deviation (SD) of the logit of the estimated propensity score, which meant the maximum distance of two units was 0.1, 0.01 or 0.001. Ultimately, the caliper of 0.1 met the appropriateness of matching with preferable homogeneity and minimum loss of sample size. We evaluated the efficiency of matching to balance baseline characteristics by using standard differences [19, 20]. Standardized differences less than 10% was regarded as homogeneity of baseline characteristics between two groups.

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. 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 clinicopathological variables and survival after lung cancer resection for NSCLC patients. Associations between intraoperatively administration of dexamethasone and disease-free survival and overall survival in the high-risk factor subgroups of postoperative nausea and vomiting (PONV) were calculated by cox proportional hazard regression analysis and presented as forest plot[21]. Univariable, multivariable analyses and propensity score matching analysis were carried out using the IBM SPSS Statistics 22.0 (SPSS Inc, Armonk, NY, USA). A two-tailed $P < 0.05$ was considered statistically significant.

Results

A total of 2480 patients who underwent lung tumor 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 (Figure 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 10mg 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 index, Charlson comorbidity index, blood transfusion, NSAIDS, 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 index ($P = 0.001$), blood transfusion ($P = 0.019$), NSAIDS ($P = 0.001$), postoperative analgesia ($P = 0.011$), radiotherapy ($P = 0.008$) and chemotherapy ($P = 0.015$), were shown in Table 2. Propensity score matching analysis generated a cohort of 260 patients in the non-DEX group and 130 patients in the DEX group. The comparison of baseline characteristics after propensity score matching analysis between the non-DEX group and the DEX group was illustrated in Table 3. All baseline characteristics between two groups were balanced ($P > 0.05$, SD > 0.1).

The median follow-up period was 52.00 (interquartile range, 31.00 to 76.25) months for all the matched patients. In the non-DEX group and the DEX group, the median follow-up period was 54.00 (interquartile range, 30.00 to 73.75) months and 49.00 (interquartile range, 31.75 to 83.00) months, respectively. There was no significant difference in the follow-up period among two groups (P = 0.711). 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 74.6%, 49.4%, 42.3% and 83.0%, 52.5%, 40.3%, respectively; While 1-yr, 3-yr and 5-yr overall survival rates in the non-DEX and DEX groups were 92.7%, 73.5%, 65.2% and 94.6%, 73.3%, 55.1%, respectively. There was no significant difference between the non-DEX group and the DEX group in disease-free survival (P = 0.655) or overall survival (P = 0.486) (Figure 2A and 2B). Then, we undertook multivariable cox proportional hazards regression analysis to validate whether intraoperative dexamethasone was independent prognostic factors for NSCLC patients with radical resection. Multivariable cox regression model revealed no statistically significant association between intraoperative dexamethasone and disease-free survival (HR: 1.027, 95% CI: 0.807-1.305, P = 0.831) (Table 4). Then, multivariable cox proportional regression analysis for overall survival was performed and revealed that intraoperative dexamethasone was not associated with better or poorer overall survival (HR: 1.183, 95% CI: 0.849-1.648, P = 0.322) (Table 5). We also conducted cox proportional regression analyses to identify risk factors for disease-free survival and overall survival. High KPS, advanced TNM stage, tumor size more than 4cm, intraoperatively administration of NSAIDS and usage of radiotherapy were significantly associated with poorer disease-free survival; While advanced TNM stage, tumor size more than 4cm, and ASA □ were associated with poorer overall survival.

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. In order to balance baseline characteristics between non-DEX group and DEX group, propensity score matching was carried out in the high-risk subgroups of postoperative nausea and vomiting (Table S1-S5). Figure 3A reported that there was no correlation between intraoperatively administration of dexamethasone and disease-free survival in female subgroup, nonsmoking subgroup, long anesthetic time subgroup, VATS subgroup and inhaled anesthetics subgroup, respectively. Figure 3B showed no association between intraoperatively administration of dexamethasone and overall survival in female subgroup, nonsmoking subgroup, long anesthetic time subgroup, VATS subgroup and inhaled anesthetics subgroup, respectively.

Discussion

Our study found no correlation between intraoperatively administration of dexamethasone and survival in NSCLC patients after lung cancer resection. In the high-risk subgroups of PONV, that is, female, nonsmoking, long anesthetic time, VATS and inhaled anesthetics, patients given intraoperative dexamethasone had no better or poorer prognosis compared with patients not given intraoperative dexamethasone. Our results indicate that intraoperative dexamethasone, commonly used for prevention of postoperative nausea and vomiting (PONV), do not affect cancer recurrence and overall survival in non-small cell lung cancer patients having lung cancer resection.

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 260 patients in the non-DEX group and 130 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

Intraoperative dexamethasone, commonly used for prevention of postoperative nausea and vomiting (PONV), do not affect cancer recurrence and overall survival in non-small cell lung cancer patients having lung cancer resection. In the high-risk subgroups of PONV, patients given intraoperative dexamethasone had no better or poorer prognosis compared with patients not given intraoperative dexamethasone. 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.

Tables

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	0.580
Sex			0.388
Female	382	78	
Male	293	70	
BMI, kg/m2	23.02	23.11	0.05
Smoking index			0.001*
≤400	451	120	
400	224	28	
Charlson comorbidity index	3.80	3.64	0.046*
KPS	90.67	91.622	0.054
TNM stage			0.326
	157	23	
	122	33	
	374	87	
Histology type			0.642
Adenocarcinoma	536	113	
Nonadenocarcinoma	139	35	
Tumor size, cm	3.30	3.42	0.813
ASA score			0.939
	608	133	
	67	15	
Duration of anesthesia	3.64	4.15	0.290
Type of anesthesia			0.138
Inhalation	643	145	
Intravenous	32	3	
Operative approach			0.938
Thoracotomy	463	102	

VATS	212	46	
Clavien-Dindo			0.068
□	588	139	
□	57	2	
□a	13	4	
□b	9	1	
□a	7	2	
□b	1	0	
□	0	0	

Variable	Non-DEX group (N=260)	DEX group (N=130)	*P* value
Blood transfusion			0.001*
No	573	141	
Yes	102	7	
NSAIDS			0.015*
No	259	41	
Yes	416	107	
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	

ASA, American Society of Anesthesiologists; BMI, body mass index; Dex, dexamethasone; KPS, Karnofsky performance score; 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	0.049	0.825	1.004(0.969-1.040)
Smoking index	9.381	0.001	1.939(1.880-3.387)
Charlson comorbidity index	0.112	0.738	0.943(0.668-1.331)
KPS	1.117	0.291	0.978(0.939-1.019)
Type of anesthesia	2.812	0.094	0.499(0.222-1.124)
Clavien-Dindo	0.443	0.506	0.994(0.978-1.011)
Blood transfusion	7.889	0.019	3.246(1.911-6.704)
NSAIDS	10.240	0.001	1.486(1.166-1.894)
Postoperative analgesia	11.707	0.011	1.542(1.369-2.395)
Radiotherapy	7.101	0.008	1.407(1.095-1.809)
Chemotherapy	5.954	0.015	1.334(1.058-1.681)

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=260)	DEX group (N=130)	*P* value	*Standardized differences*
Age, years	60.43	59.29	0.738	-0.087
Sex			0.666	-0.056
Female	116	61		
Male	144	69		
BMI, kg/m2	23.15	23.13	0.210	0.032
Smoking index			0.805	-0.026
≤400	229	114		
400	31	16		
Charlson comorbidity index	3.79	3.65	0.193	-0.089
KPS	90.423	91.769	0.157	0.092
TNM stage			0.444	-0.018
	49	22		
	49	33		
	162	75		
Histology type			0.610	-0.083
Adenocarcinoma	198	102		
Nonadenocarcinoma	62	28		
Tumor size, cm	3.45	3.39	0.885	-0.058
ASA score			0.495	-0.081
	231	120		
	29	10		
Duration of anesthesia	3.83	3.83	0.949	-0.009
Type of anesthesia			1.000	0.000
Inhalation	254	127		
Intravenous	6	3		
Operative approach			0.820	0.000
Thoracotomy	174	85		

VATS	86	45		
Clavien-Dindo			0.762	0.047
□	243	122		
□	8	2		
□a	4	4		
□b	2	0		
□a	3	2		
□b	0	0		
□	0	0		

Variable	Non-DEX group (N=260)	DEX group (N=130)	*P* value	*Standardized differences*
Blood transfusion			0.871	0.017
No	247	123		
Yes	13	7		
NSAIDS			0.938	-0.024
No	79	39		
Yes	181	91		
Postoperative analgesia			0.888	0.019
No	38	7		
PCIA	178	112		
PCEA	44	11		
Radiotherapy			0.932	0.024
No	201	100		
Yes	59	30		
Chemotherapy			0.771	0.073
No	108	52		
Yes	152	78		

ASA, American Society of Anesthesiologists; BMI, body mass index; Dex, dexamethasone; KPS, Karnofsky performance score; 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	0.944	0.720-1.237	0.655	1.027	0.807-1.305	0.831
Age, years						
Age≤60	Reference			Reference		
Age>60	1.007	0.994-1.019	0.293	1.008	0.990-1.027	0.365
Sex						
Female	Reference			Reference		
Male	0.829	0.641-1.071	0.151	1.050	0.858-1.285	0.634
BMI, kg/m^2						
≤24	Reference			Reference		
>24	0.990	0.950-1.031	0.622	0.985	0.955-1.016	0.348
Smoking index						
≤400	Reference			Reference		
>400	0.976	0.727-1.311	0.873	0.974	0.802-1.184	0.794
Charlson comorbidity index						
>3	Reference			Reference		
≥3	0.948	0.742-1.211	0.668	0.716	0.499-1.028	0.070
KPS						
>70	Reference			Reference		
≥70	0.991	0.979-1.004	0.164	0.959	0.926-0.993	0.019
TNM stage						
	Reference			Reference		

	0.355	0.239-0.529	0.001	0.459	0.350-0.601	0.001
	0.604	0.430-0.848	0.004	0.739	0.573-0.954	0.020
Histology type						
Adenocarcinoma	Reference			Reference		
Nonadenocarcinoma	0.653	0.471-0.906	0.011	0.813	0.625-1.056	0.121

Variable	Univariable			Multivariable		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Tumor size, cm						
≤4	Reference			Reference		
4	1.017	0.768-1.346	0.907	1.062	1.009-1.117	0.021
ASA score						
	Reference			Reference		
	1.024	0.955-1.099	0.500	1.040	0.853-1.267	0.701
Duration of anesthesia						
≤2	Reference			Reference		
2	0.966	0.887-1.051	0.418	0.940	0.880-1.003	0.062
Type of anesthesia						
Inhalation	Reference			Reference		
Intravenous	0.703	0.289-1.707	0.436	0.824	0.518-1.310	0.413
Operative approach						
Thoracotomy	Reference			Reference		
VATS	0.925	0.707-1.212	0.573	0.918	0.743-1.134	0.426
Clavien-Dindo						
≤2	Reference			Reference		
2	1.008	0.988-1.029	0.417	0.998	0.984-1.012	0.727
Blood transfusion						
No	Reference			Reference		
Yes	0.549	0.291-1.035	0.064	1.053	0.798-1.391	0.715
NSAIDS						

No	Reference			Reference		
Yes	1.404	1.053-1.872	0.021	1.254	1.026-1.533	0.027
Postoperative analgesia						
No	Reference			Reference		
PCIA	0.929	0.551-1.564	0.781	0.865	0.610-1.227	0.416
PCEA	1.461	0.997-2.143	0.052	1.098	0.846-1.425	0.482

Variable	Univariable			Multivariable		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Radiotherapy						
No	Reference			Reference		
Yes	1.364	1.028-1.810	0.031	1.309	1.058-1.619	0.013
Chemotherapy						
No	Reference			Reference		
Yes	1.211	0.922-1.590	0.168	1.112	0.908-1.362	0.304

ASA, American Society of Anesthesiologists; BMI, body mass index; CI, confidence index; Dex, dexamethasone; HR, hazard ratio; KPS, Karnofsky performance score; 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	1.210	0.927-1.581	0.486	1.183	0.849-1.648	0.322
Age, years						
Age≤60	Reference			Reference		
Age>60	1.008	0.997-1.019	0.153	1.012	0.979-1.046	0.470
Sex						
Female	Reference			Reference		
Male	1.260	1.010-1.571	0.040	1.028	0.728-1.451	0.876
BMI, kg/m^2						
≤24	Reference			Reference		
>24	1.002	0.968-1.039	0.892	0.979	0.930-1.030	0.414
Smoking index						
≤400	Reference			Reference		
>400	1.078	0.867-1.340	0.499	1.047	0.712-1.540	0.815
Charlson comorbidity index						
>3	Reference			Reference		
≥3	1.115	1.015-1.226	0.023	0.714	0.366-1.394	0.324
KPS						
>70	Reference			Reference		
≥70	0.986	0.975-0.996	0.009	0.966	0.906-1.030	0.293
TNM stage						
□	Reference			Reference		

	0.422	0.316-0.564	0.001	0.295	0.173-0.501	0.001
	0.581	0.429-0.786	0.001	0.532	0.346-0.819	0.004
Histology type						
Adenocarcinoma	Reference			Reference		
Nonadenocarcinoma	1.052	0.815-1.357	0.697	1.109	0.709-1.734	0.652

Variable	Univariable			Multivariable		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Tumor size, cm						
≤4	Reference			Reference		
4	1.179	1.118-1.244	0.001	1.155	1.048-1.272	0.004
ASA score						
	Reference			Reference		
	1.203	0.974-1.487	0.086	1.636	1.138-2.352	0.008
Duration of anesthesia						
≤2	Reference			Reference		
2	0.948	0.884-1.017	0.137	1.008	0.901-1.129	0.885
Type of anesthesia						
Inhalation	Reference			Reference		
Intravenous	0.453	0.202-1.015	0.054	0.401	0.096-1.674	0.210
Operative approach						
Thoracotomy	Reference			Reference		
VATS	0.825	0.645-1.054	0.124	1.034	0.723-1.480	0.853
Clavien-Dindo						
≤2	Reference			Reference		
2	0.996	0.980-1.012	0.643	0.997	0.971-1.024	0.843
Blood transfusion						
No	Reference			Reference		
Yes	01.227	0.903-1.666	0.190	0.910	0.423-1.956	0.809
NSAIDS						

No	Reference			Reference		
Yes	1.420	1.125-1.793	0.003	1.311	0.911-1.885	0.145
Postoperative analgesia						
No	Reference			Reference		
PCIA	0.898	0.597-1.351	0.606	0.779	0.399-1.522	0.465
PCEA	1.094	0.829-1.444	0.525	1.023	0.626-1.670	0.929

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
Radiotherapy						
No	Reference			Reference		
Yes	1.509	1.184-1.923	0.001	1.094	0.760-1.575	0.630
Chemotherapy						
No	Reference			Reference		
Yes	1.374	1.101-1.714	0.005	1.202	0.853-1.692	0.293

ASA, American Society of Anesthesiologists; BMI, body mass index; CI, confidence index; Dex, dexamethasone; HR, hazard ratio; KPS, Karnofsky performance score; 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.

Declarations

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.

Availability of data and material

The study was approved by uploading the raw data onto the research data deposit (RDD) public platform, with the approval RDD number as RDDA2020001408. You will find more detailed information in the RDD public platform (www.researchdata.org.cn).

Competing interests

The authors declare that they have no competing interests.

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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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Figures

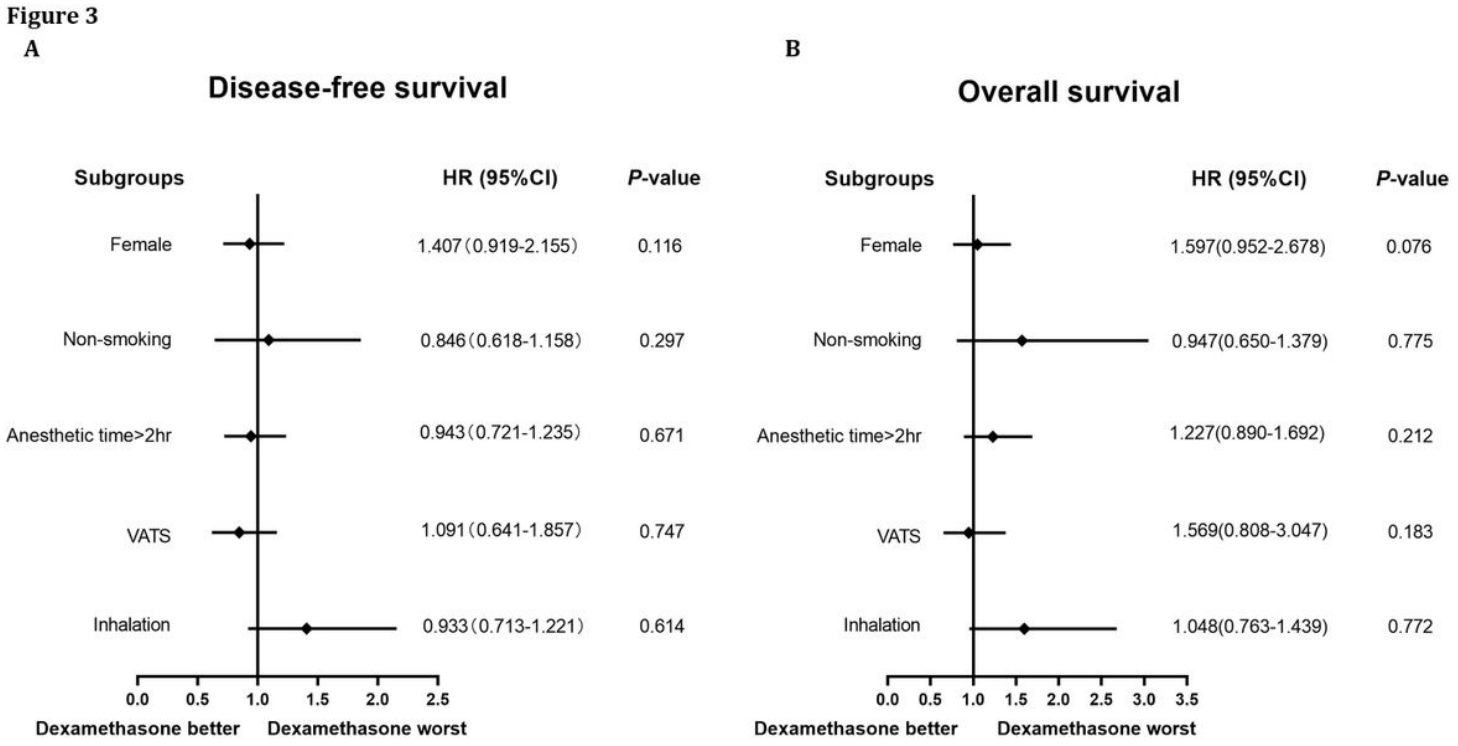

Figure 2

Flowchart of study selection.

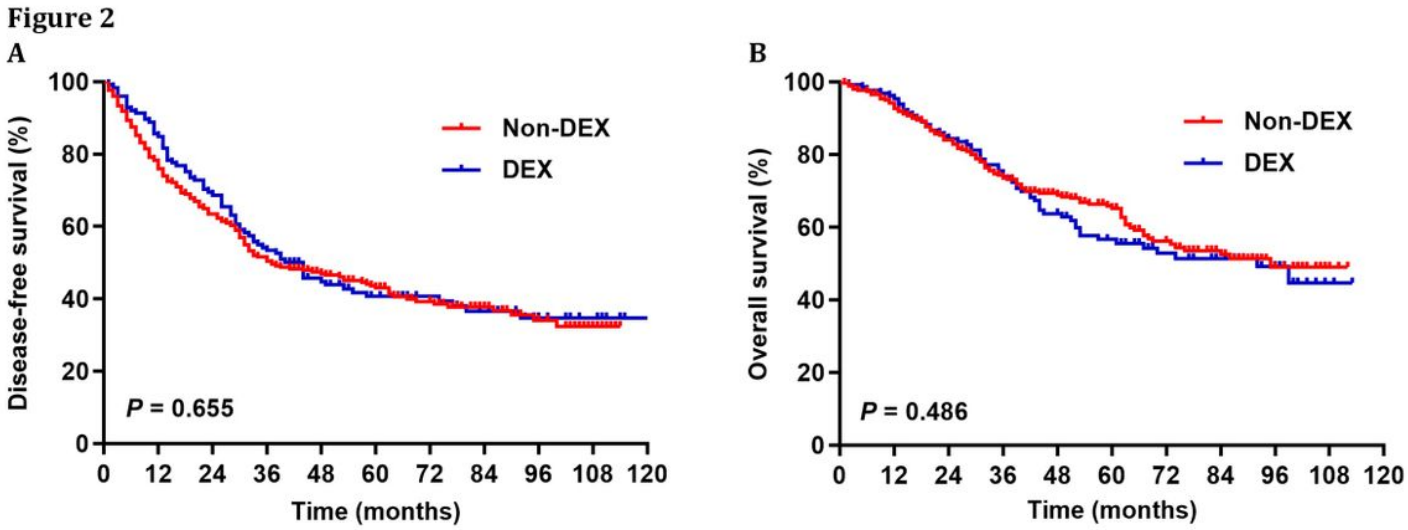

Figure 3

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.

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