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ORIGINAL RESEARCH

Impact of Intraoperative Dexamethasone on Postoperative Complications and Long-Term Survival in Patients with Non-Small Cell Lung Cancer: A retrospective Propensity Score-Matched Study

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Objective: This study investigated the impact of intraoperative dexamethasone on postoperative complications and long-term survival in patients with non-small cell lung cancer (NSCLC) undergoing surgery.

Methods: Patients with NSCLC who underwent lung resection between January 1, 2006, and December 31, 2009, were included. Patients receiving dexamethasone formed the dexamethasone (DXM) group, while those who did not were assigned to the non-dexamethasone (non-DXM) group. Propensity score matching (PSM) was applied to minimize confounding bias. The primary endpoint was the incidence of postoperative complications.

Results: Of the 579 patients included, 224 received intraoperative DXM, while 355 did not. PSM produced a matched cohort of 400 patients (200 in each group). After matching, the DXM group had significantly lower incidences of postoperative pneumonia ($P < 0.05$), reduced intensive care unit (ICU) ICU occupancy, and shorter postoperative hospital stays (PHS) compared with the non-DXM group ($P < 0.05$). No significant differences were observed in overall survival (OS) or recurrence-free survival (RFS) between the groups.

Conclusion: Intraoperative DXM use reduced the incidence of postoperative pneumonia, ICU occupancy, and PHS. However, no clear association was found between intraoperative DXM use and long-term survival outcomes in NSCLC patients.

Keywords: dexamethasone, postoperative complications, survival, NSCLC

Introduction

Lung cancer remains the second most prevalent and the deadliest type of cancer worldwide.[1] In 2024, it is estimated that 234,580 new cases (116,310 in males and 118,270 in females) of lung and bronchial cancer will be diagnosed, with 125,070 deaths (65,790 males and 59,280 females).[2] Clinically, non-small cell lung cancer (NSCLC) is the predominant pathological type of lung cancer and constitutes 85% of all cases.[3] Despite significant advances in NSCLC treatment such as targeted therapy or immunotherapy over the past decade, surgical resection remains the cornerstone for curative treatment in early-stage cases.[4] Understanding the prognosis of lung cancer following surgery is critical for guiding clinical decisions and optimizing patient management.[5]

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Although the existing data-driven prognostic prediction models displayed the associations between perioperative management and the postoperative outcomes for NSCLC patients, concerns have been raised regarding the effects of certain intraoperative drugs, such as dexamethasone, on patient prognosis.[6,7] Dexamethasone is a synthetic steroid widely used in clinical practice for its anti-allergic and anti-emetic properties as an anesthetic adjunct. While its efficacy in mitigating anesthesia-related complications is well documented, its role in NSCLC perioperative care remains unclear, particularly regarding the balance between anti-inflammatory benefits and immunosuppressive risks specific to oncologic outcomes. In our previous study, we also found that perioperative glucocorticoids were associated with the delayed recurrence in patients with lung cancer.[8] However, unfortunately, we did not conduct in-depth analysis and discussion on this aspect. Therefore, the purpose of this study was to retrospectively analyze the relationship between intraoperative dexamethasone use and postoperative complications as well as long-term survival in NSCLC patients and investigate the potential prognostic implication of intraoperative dexamethasone use.

Methods

Study Population

This retrospective cohort with propensity score-matching was approved by the Institutional Review Board of Peking University Cancer Hospital & Institute, Beijing (approval No. 2019YJZ22-GZ02). The requirement for informed consent was waived thanks to the retrospective design. This study adhered to the Declaration of Helsinki (as revised in 2013). The electronic medical records system of Peking University Cancer Hospital was used to screen eligible patients who were diagnosed by pathological examination and underwent surgical resection for NSCLC from January 1, 2006, to December 31, 2009. Exclusion criteria included: (1) combined with other primary malignant tumors; (2) recurrent lung tumor; (3) incomplete follow-up data or missing information.

Anesthesia, Surgery, and Perioperative Management

General anesthesia with double-lumen endobronchial tube intubation was performed for all patients. Induction agents included propofol and opioids (fentanyl or sufentanil), while maintenance utilized inhalational anesthetics (sevoflurane or isoflurane) combined with opioids. Epidural anesthesia was applied in some cases, depending on anesthesiologist preferences. Lung resections were conducted via posterolateral thoracotomy, tailored to tumor characteristics and surgical requirements. Postoperative analgesia was administrated with patient-controlled pumps delivering ropivacaine (epidural) or sufentanil (intravenous) according to the analgesic protocol chosen.

Data Collection

Data collected included demographics [age, gender and body mass index (BMI)], preoperative information [comorbidity, lab test, American Society of Anesthesiologists classification (ASA), tumor-node-metastasis (TNM) stage, smoking and drinking history], intraoperative details (anesthesia technique, fluid intake, transfusion, DXM administration, surgical procedure, mediastinal lymph node dissection, surgery duration and estimated blood loss), and postoperative information (pathology, differentiation, tumor size, complications, chemotherapy and radiotherapy).

Follow-Up and Endpoints

All patients were followed up by specially assigned personnel through telephone inquiry or outpatient review. Patients were followed up every 6 months within the first postoperative year, then annually. Recurrence and death dates were recorded. The termination of follow-up was death, loss of follow-up or completed follow-up of 10 years.

The primary endpoint was postoperative complications defined as postoperative pulmonary complications (PPCs) (eg, pneumonia, pleural effusion, pneumothorax, pulmonary embolism, atelectasis and respiratory failure) and non-PPCs (eg, new-onset arrhythmia, myocardial ischemia, heart failure, cerebral infarction and deep venous thrombosis of lower extremity). All postoperative complications were diagnosed according to the Society of Thoracic Surgeons and European Society of Thoracic Surgeons joint definitions.[9]

The secondary endpoint included intensive care unit (ICU) occupancy, duration of drainage catheter indwelling, postoperative hospital stay (PHS) which was defined as the length of hospital stay after surgery, recurrence-free survival (RFS) which was defined as the duration in years from surgery to recurrence or death, whichever happened first, and overall survival (OS) which is defined as the duration in years from surgery to death from any cause.

Statistical Analysis

Continuous data were presented as mean (±SD) or median (interquartile range [IQR]) on the basis of normal or abnormal distribution. Categorical data are presented as number (%). Continuous variables were compared using the independent samples *t*-test or Mann–Whitney *U*-test. Categorical variables were analyzed using Pearson's chi-squared test or Fisher's exact test as appropriate.

A propensity score matching (PSM) approach was employed to account for potential confounding factors between the patients with intraoperative DXM (DXM group) and patients without intraoperative DXM (non-DXM group). Baseline characteristics and perioperative data were analyzed, including age, gender, BMI, ASA classification, comorbidities, history of smoking and drinking, preoperative lab test, preoperative chemotherapy, TNM stage, pathological type, differentiation grade, maximum tumor size, surgical procedure, mediastinal lymph node dissection, duration of surgery, anesthesia technique, estimated blood loss, blood transfusion, fluid intake, postoperative radiotherapy and chemotherapy. Patients were matched in a 1:1 ratio using the nearest-neighbor matching with caliper widths equal to 0.02 of the standard deviation of the logit of the propensity score.

Univariate analyses were performed by the Kaplan–Meier survival analysis with Log rank tests. Variables with a p-value <0.2 in the univariate analysis were included in the Cox proportional hazard model for multivariable analysis to identify the final predictors for RFS or OS. In terms of continuous variables, the cut-off points were chosen according to clinical significance, mean or median values.

All statistical analyses were performed using IBM Statistics SPSS Version 26 (SPSS, Inc, Chicago, IL). A 2-tailed P-value of <0.05 was considered significant.

Results

In total, 622 patients, undergoing NSCLC resection, were recruited in this study between January 1, 2006, and December 31, 2009. After review, 43 patients were excluded, including 10 combined with other primary malignant tumors, 6 with recurrent lung tumor, 8 combined with infectious diseases and respiratory infections and 19 with incomplete data (3 no TNM stage, 2 no differentiation grade and 14 lost to follow-up) (Figure 1). Therefore, 579 patients were included in the final analysis. Among these patients, 224 received intraoperative DXM and 335 did not. Before matching, there were significant variations in COPD, ASA grade, TNM stage, anesthesia technique between the two groups (Table 1), and after matching, there were no significant differences in demographic characteristics or perioperative data between the two groups (Table 1).

After PSM, there was no significant difference in overall postoperative complications between DXM group and non-DXM group (33.0% vs 30.5%, P = 0.591) (Table 2). The incidence of pneumonia, among major PPCs, was significantly lower in the DXM group than that in non-DXM group (3.5% vs 8.5%, P = 0.035), while the occurrences of other postoperative complications did not differ significantly between the two groups (P > 0.05) (Table 2). Compared with the non-DXM group, the DXM group had lower ICU occupancy (15.5% vs 23.5%, P = 0.043) and shorter PSH [12.0 (9.0–14.0) days vs 12.5 (10.0–15.0) days, P = 0.038] (Table 3).

After matching, in the DXM group, the median duration of RFS was 63.4 months (IQR, 14.1–122.0), and the median duration of OS was 81.4 months (IQR, 26.4–122.2), and the 5-year RFS and OS rate were 50.9% (95% CI 44.0–57.9) and 61.5% (95% CI 54.7–68.2); in the non-DXM group, the median duration of RFS was 56.9 months (IQR, 13.9–121.6), and the median duration of OS was 78.4 months (IQR, 26.4–122.2), and the 5-year RFS and OS rate were 48.0% (95% CI 41.1–54.9) and 59.0% (95% CI 52.2–65.8), respectively (Tables 3 and 4).

In the match cohort, 14 factors were included in multivariable Cox proportional hazard model for RFS, including 13 factors with P < 0.20 in univariable analyses and intraoperative DXM. Multivariable analysis identified 5 independent factors. Of them, preoperative Hemoglobin >136 g/L and mediastinal lymph node dissection were associated with

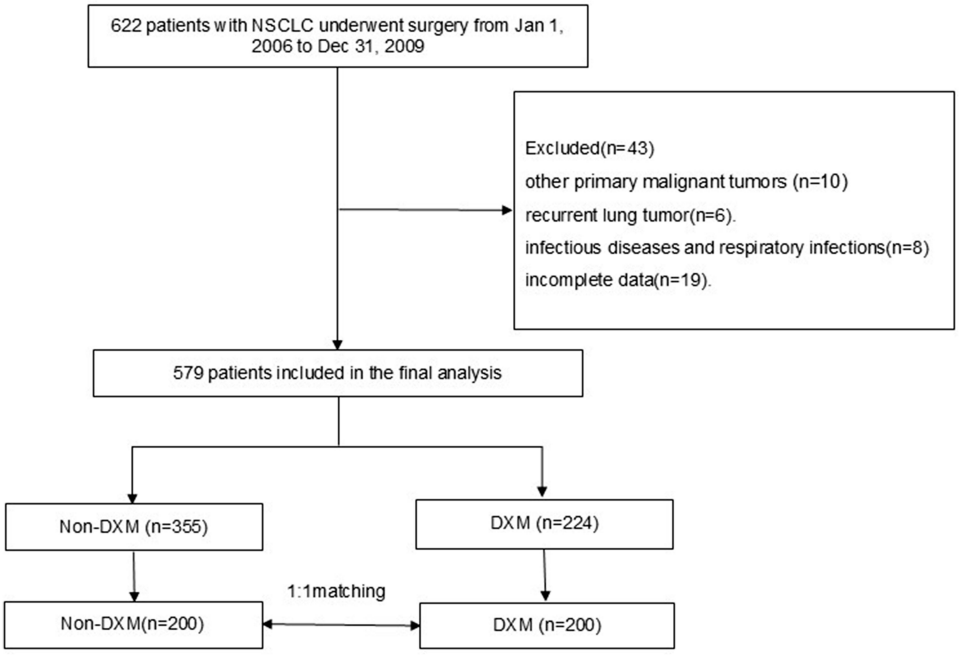

Figure 1 Flowchart of the study.
Abbreviations: NSCLC, non-small cell lung cancer; DXM, dexamethasone.

delayed recurrence; postoperative complications, postoperative radiotherapy, and chemotherapy were associated with early recurrence (Tables 5 and 6). In the case of OS, after PSM, 13 factors were included in multivariable Cox proportional hazard model, including 12 factors with P <0.20 in univariable analyses and intraoperative DXM. Multivariable analysis identified 5 independent factors. Among them, preoperative Hemoglobin >136 g/L and mediastinal lymph node dissection were associated with prolonged survival; maximal tumor size >3.0cm, postoperative complications, postoperative radiotherapy and chemotherapy were associated with shortened survival (Tables 5 and 6).

Table 1 Baseline and Perioperative Characteristics Before and After Propensity Score-Matching

Characteristics	All Patients (n=579)	Prematching (n=579)			Postmatching (n=400)		
		Non-DXM group (n=355)	DXM group (n=224)	P value	Non-DXM group (n=200)	DXM group (n=200)	P value
Age, years	59.8±10. 3	60.3±10. 9	59.2±9.3	0.196	59.0±11.0	59.9±9.7	0.358
Gender, male	370(69.3)	231(65.1)	139(62.1)	0.462	112(56.0)	130(65.0)	0.066
BMI, kg/m^2	24.2±3.1	24.2±3.1	24.2±3.1	0.822	23.9±3.1	24.2±3.3	0.356
Preoperative comorbidities							
Coronary heart disease	26(6.2)	26(7.3)	10(4.5)	0.165	9(4.5)	11(5.5)	0646
Arrhythmia	41(7.1)	31(8.7)	10(4.5)	0.051	10(5.0)	11(5.5)	0.823
Hypertension	154(26.6)	92(25.9)	62(27.7)	0.640	55(27.5)	60(30.0)	0.581
Diabetes mellitus	187(32.3)	120(33.8)	67(29.9)	0.329	58(29.0)	62(31.0)	0.663
Previous stroke	20(3.5)	12(3.4)	8(3.6)	0.902	7(3.5)	9(4.5)	0.610
Hyperlipidemia	5(0.9)	2(0.6)	3(1.3)	0.294	0(0.0)	4(1.0)	0.062
COPD	18(3.1)	7(2.0)	11(4.9)	0.047	5(2.5)	11(5.5)	0.126
Smoking history	310(53.5)	190(53.5)	120(53.6)	0.991	97(48.5)	113(56.5)	0.109
Drinking history	134(23.1)	90(25.4)	44(19.6)	0.113	39(19.5)	35(17.5)	0.607
ASA grade				0.008			0.761
I	212(36.6)	115(32.4)	240(67.6)		84(42.0)	81(40.5)	
II	367(63.4)	97(43.3)	127(56.7)		116(58.0)	119(59.5)	

(*Continued*)

Table 1 (Continued).

Characteristics	All Patients (n=579)	Prematching (n=579)			Postmatching (n=400)		
		Non-DXM group (n=355)	DXM group (n=224)	P value	Non-DXM group (n=200)	DXM group (n=200)	P value
Preoperative chemotherapy	59(10.2)	40(11.3)	19(8.5)	0.281	15(7.5)	19(9.5)	0.473
TNM stage				0.002			0.652
I	256(44.6)	141(39.7)	117(52.2)		101(50.5)	107(53.5)	
II	113(19.5)	65(18.3)	48(21.4)		44(22.0)	34(17.0)	
III	160(27.6)	116(32.7)	44(19.6)		43(21.5)	47(23.5)	
IV	48(8.3)	33(9.3)	15(6.7)		12(6.0)	12(6.0)	
Pathological type				0.275			0.754
Adenocarcinoma	370(63.9)	233(65.6)	137(61.2)		130(65.0)	127(63.5)	
Non-adenocarcinoma	209(36.1)	122(34.4)	87(38.8)		70(35.0)	73(36.5)	
Differentiation grade				0.957			0.137
Undifferentiation	80(13.8)	48(13.5)	32(14.3)		30(15.0)	26(13.0)	
Low	73(12.6)	43(12.1)	30(13.4)		23(11.5)	260(13.0)	
Moderate	358(61.8)	222(62.5)	136(60.7)		128(64.0)	114(57.0)	
High	68(11.7)	42(11.8)	26(11.6)		19(9.5)	34(17.0)	
Preoperative lab test							
Preoperative blood glucose, mmol/L	5.8±1.9	5.8±1.9	5.7±1.7	0.576	5.8±1.7	5.6±1.8	0.320
WBC count, $\times 10^9$/L	7.2±2.8	7.1±2.5	7.3±3.3	0.353	7.0±2.9	7.3±3.0	0.324
Hemoglobin, g/L	136±16.1	135±16.3	137±15.9	0.299	135±17.1	138±14.0	0.084
PLT count, $\times 10^9$/L	229.9±77.1	229.4±81.4	230.7±69.8	0.838	232.8±75.9	223.5±66.4	0.191
Surgical procedure				0.790			0.803
Segmentectomy/Wedge resection	129(22.3)	82(23.1)	47(21.0)		41(20.5)	44(22.0)	
Lobectomy	429(74.1)	261(73.5)	168(75.0)		152(76.0)	147(73.5)	
Total pneumectomy	21(3.6)	12(3.4)	9(4.0)		7(3.5)	9(4.5)	
Mediastinal lymph node dissection	518(89.5)	314(88.5)	204(91.1)	0.317	184(92.0)	181(90.5)	0.596
Maximal tumor size, cm	3(2–4)	3(2–4)	2(1–3)	0.365	3(2–4)	3(2–4)	0.633
Anesthesia technique				0.001			0.086
General	464(80.1)	300(84.5)	164(73.2)		165(82.5)	151(75.5)	
Combined epidural-general	115(19.9)	55(15.5)	60(26.8)		35(17.5)	49(24.5)	
Duration of surgery, min	3.8(3.1–4.4)	3.7(3.1–4.4)	3.9(3.2–4.5)	0.203	3.9(3.2–4.6)	3.8(3.1–4.4)	0.428
Intraoperative blood loss, mL	200(100–200)	200(100–200)	200(100–200)	0.638	200(100–200)	200(100–200)	0.468
Total fluid intake, mL	2000(1600–2500)	2000(1600–2500)	1600(2000–2500)	0.217	2000(1600–2338)	2000(1600–2500)	0.259
Crystalloids, mL	1300(1100–1600)	1350(1100–1600)	1250(1100–1600)	0.914	1400(1100–1600)	1250(1025–1600)	0.505
Colloid, mL	500(500–1000)	500(500–1000)	500(500–1000)	0.150	500(500–1000)	500(500–1000)	0.326
Intraoperative transfusion	8(1.4)	6(1.7)	2(0.9)	0.423	2(1.0)	2(1.0)	1.000
Postoperative chemotherapy	280(48.4)	175(49.3)	105(46.9)	0.570	92(46.0)	96(48.0)	0.689
Postoperative radiotherapy	23(4.0)	13(3.7)	10(4.5)	0.630	7(3.5)	10(5.0)	0.457

Notes: Data are presented as median (interquartile range), mean ± standard deviation, or n (%) and compared with the independent-samples *t*-test, the Mann–Whitney *U*-test, the Pearson's chi-squared test or Fisher's exact test as appropriate. P<0.05 was considered statistically significant.

Abbreviations: DXM, dexamethasone; BMI, body mass index; COPD, chronic obstructive pulmonary disease; ASA, American Society of Anesthesiologists; TNM, tumor-node-metastasis stage; WBC, white blood cell; PLT, platelets.

There were no significant differences in overall survival (OS) and recurrence-free survival (RFS) between the two groups. Intraoperative administration of dexamethasone was lack of association with RFS (HR, 0.789; 95% CI, 0.608–1.024; P = 0.075) and OS (HR, 0.885; 95% CI, 0.677–1.158; P = 0.374) (Table 6, Figures 2 and 3).

Discussion

Surgical trauma, including thoracic surgery, induces a stress response that leads to the activation of physiological responses, which promote wound healing and organ recovery, and participate in systemic inflammatory responses and angiogenesis[10,11] In lung cancer surgery, systemic inflammation has two important aspects, namely, postoperative

Table 2 Occurrences of Postoperative Complications Requiring Treatment During Hospital Stay

Variables	Non-DXM Group (n=200)	DXM Group (n=200)	χ^2	P value
PPCs				
Pneumonia	17(8.5)	7(3.5)	4.433	0.035
Pleural effusion	18(9.0)	17(8.5)	0.031	0.860
Pneumothorax	20(10.0)	22(11.0)	0.106	0.744
Pulmonary embolism	0(0.0)	2(1.0)	2.010	0.249
Atelectasis	4(2.0)	8(4.0)	1.375	0.241
Respiratory failure	2(1.0)	2(1.0)	0.000	1.000
Non-PPCs				
New-onset arrhythmia	15(7.5)	7(3.5)	3.078	0.079
Myocardial ischemia	9(4.5)	13(6.5)	0.770	0.380
Heart failure	0(0.0)	1(0.5)	1.003	0.500
Cerebral infarction	0(0.0)	1(0.5)	1.003	0.500
Deep venous thrombosis of lower extremity	1(0.5)	0(0.0)	1.003	0.500
Total postoperative complications	61(30.5)	66(33.0)	0.288	0.591

Notes: Data are showed as numbers (%). P<0.05 was considered statistically significant.
Abbreviations: PPCs, postoperative pulmonary complications; DXM, dexamethasone; ARDS, acute respiratory distress syndrome.

Table 3 Other Postoperative Outcomes and Long-Term Outcomes

Variables	Non-DXM Group (n=200)	DXM Group (n=200)	Z/χ^2	P value
ICU occupancy	47(23.5)	31(15.5)	4.077	0.043
Drainage catheter indwelling, days	9.0(6.0–11.0)	9.0(6.0–10.8)	1.290	0.197
PHS	12.5(10.0–15.0)	12.0(9.0–14.0)	2.075	0.038
Recurrence-free survival, months	56.9(13.9–121.6)	63.4(14.1–122.0)	0.608	0.436
Overall survival, months	78.4(33.9–121.8)	81.4(26.4–122.2)	0.085	0.061

Notes: Data are showed as medians (interquartile range) or numbers (%). P<0.05 was considered statistically significant.
Abbreviations: DXM, dexamethasone; ICU, intensive care unit; PHS, postoperative hospital stay.

Table 4 The Survival Status of Patients After Surgery

Variables	RFS		OS	
	Non-DXM group (n = 200)	DXM group (n = 200)	Non-DXM group (n = 200)	DXM group (n = 200)
Survival rate at 3y (95% CI)	57.0(50.1–63.9)	59.5(52.7–66.3)	73.5(67.4–79.2)	69.0(62.6–75.4)
Survival rate at 5y (95% CI)	48.0(41.8–54.9)	50.9(44.0–57.9)	59.0(52.2–65.8)	61.5(54.7–68.2)
Survival rate at 10y (95% CI)	38.1(31.3–44.9)	41.8(34.8–48.7)	40.8(33.5–48.1)	44.6(37.4–57.8)

Note: Data are showed as mean (95% confidence interval).
Abbreviations: RFS, recurrence-free survival; OS, overall survival; DXM, dexamethasone; CI, confidence interval.

morbidity and control of tumor cell spread, which play a crucial role in postoperative tumor prognosis.[12] Many factors, such as tissue injury, perioperative medications, and perioperative management (transfusion, fluid intake, and so forth), modulate the inflammatory response in lung cancer surgery.[6] Prior study reported that glucocorticoids may attenuate surgical stress-induced inflammatory responses both directly by suppressing the release of proinflammatory cytokines and by inducing IL-10 synthesis.[13] In this study, the intraoperative glucocorticoid used was dexamethasone, which was routinely administrated to prevent postoperative nausea and vomiting (PONV), usually at a dose of 5–10mg.

Table 5 Kaplan-Meier Univariable Analyses for Survival

Variable	N	RFS		OS	
		n (%)	P value	n (%)	P value
Age, years			0.631		0.707
≤65	277	164(59.2)		154(55.6)	
>65	123	74(60.2)		68(55.3)	
Gender			0.538		0.464
Female	158	92(58.2)		84(53.2)	
Male	242	146(60.3)		138(57.0)	
BMI, kg/m^2			0.282		0.304
<18.5	15	10(66.7)		10 (66.7)	
18.5–24.9	217	127(58.5)		120(55.3)	
25–27.9	137	79(57.7)		77(56.2)	
≥28	31	22(71.0)		15(48.4)	
Coronary heart disease			0.147		0.206
No	380	223(58.7)		208(54.7)	
Yes	20	15(75.0)		14(70.0)	
Hypertension			0.700		0.764
No	285	171(60.0)		159(55.8)	
Yes	115	67(58.3)		63(54.8)	
Arrythmia			0.476		0.232
No	379	224(59.1)		208(57.8)	
Yes	21	14(66.7)		14(66.7)	
Diabetes mellitus			0.093		0.860
No	280	165(58.9)		155(55.4)	
Yes	120	73(60.8)		67(55.8)	
Previous stroke			0.466		0.645
No	384	227(59.1)		212(55.2)	
Yes	16	11(68.7)		10(62.5)	
Hyperlipidemia					
No	396	236(59.6)	0.473	220(55.6)	0.640
Yes	4	2(50.0)		2(50.0)	
COPD			0.446		0.745
No	384	227(59.1)		212(55.2)	
Yes	16	11(68.7)		10(62.5)	
Smoking history			0.138		0.135
No	190	106(55.8)		98(51.6)	
Yes	210	132(62.9)		124(59.0)	
Drinking history			0.704		0.988
No	326	190(59.2)		182(55.8)	
Yes	74	45(60.8)		40(54.1)	
Preoperative chemotherapy			0.888		0.652
No	366	219(59.8)		203(55.5)	
Yes	34	19 (55.9)		19(55.9)	
ASA grade			0.142		0.169
I	165	91(55.2)		86(52.1)	
II	235	147(62.6)		135(57.9)	
Tumor stage			0.051		0.135
I	208	129(62.0)		119(57.2)	
II	78	37(47.4)		35(44.9)	
III	90	53(58.9)		52(57.8)	
IV	74	69(79.2)		68(66.7)	

(*Continued*)

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Table 5 (Continued).

Variable	N	RFS		OS	
		n (%)	P value	n (%)	P value
Pathological type			0.935		
Adenocarcinoma	257	155(60.3)		144(56.0)	
Non-adenocarcinoma	143	83(58.0)		78(54.5)	
Differentiation grade			0.870		0.878
Undifferentiation	56	35(62.5)		32(57.1)	
Low	49	27(55.1)		25(51.0)	
Moderate	242	142(58.7)		134(55.4)	
High	53	34(64.2)		22(58.5)	
Preoperative blood glucose, mg/dL			0.380		0.503
≤180	296	173(59.4)		162(54.7)	
>180	104	65(62.5)		60(57.7)	
WBC count, $\times 10^9$/L			0.949		0.697
≤7.2	252	149(59.1)		141(56.0)	
>7.2	148	89(60.1)		81(54.7)	
Hemoglobin, g/L			0.025		0.038
≤136	192	124(64.4)		115(59.9)	
>136	208	114(54.8)		107(51.4)	
PLT count, $\times 10^9$/L			0.174		0.126
≤229.9	229	142(62.0)		134(58.5)	
>229.9	171	96(56.1)		88(51.5)	
Surgical procedure			0.010		0.005
Segmentectomy/Wedge	85	59(69.3)		57(67.1)	
Lobectomy	299	170(56.9)		156(52.2)	
Total pneumectomy	16	9(56.2)		9(56.2)	
Mediastinal lymph node dissection			0.003		0.003
No	35	27(77.1)		26(74.3)	
Yes	365	211(57.8)		196(53.7)	
Anesthesia technique			0.168		0.956
General anesthesia	316	189(59.8)		176(55.7)	
Combined epidural-general anesthesia	84	49(58.3)		46(54.8)	
Duration of surgery, h			0.425		0.381
≤3.0	82	52(63.4)		50(61.0)	
>3.0	318	186(58.5)		172(45.1)	
Total fluid intake, mL			0.643		0.871
≤2000	212	127(59.9)		116(54.7)	
>2000	188	111(59.0)		106(56.4)	
Crystalloids, mL			0.773		0.809
≤1300	196	117(59.7)		107(54.6)	
>1300	204	121(59.3)		115(56.4)	
Colloid, mL			0.746		0.404
≤500	272	161(59.2)		148(54.4)	
>500	128	77(60.2)		74(57.8)	
Intraoperative blood loss, mL			0.044		0.068
≤200	329	188(57.1)		176(53.5)	
>200	71	50(70.4)		46(64.8)	
Intraoperative blood transfusion			0.685		0.563
No	396	235(59.3)		219(55.3)	
Yes	4	3(75.0)		3(75.0)	

(*Continued*)

Table 5 (Continued).

Variable	N	RFS		OS	
		n (%)	P value	n (%)	P value
Intraoperative DXM			0.436		0.805
No	200	123(61.5)		114(57.0)	
Yes	200	115(57.5)		108(54.0)	
Maximal tumor size, cm			0.425		<0.001
≤3.0	236	126(53.4)		114(48.3)	
>3.0	164	112(68.3)		108(65.9)	
Postoperative complications			0.069		0.039
No	273	154(56.4)		143(52.4)	
Yes	127	84(66.1)		79(62.2)	
Postoperative radiotherapy			<0.001		0.017
No	383	222(58.0)		208(54.3)	
Yes	17	16(94.1)		14(82.4)	
Postoperative chemotherapy			<0.001		<0.001
No	212	101(47.6)		99(46.7)	
Yes	188	137(72.9)		123(65.3)	

Note: Results are presented as number (%). P<0.05 was considered statistically significant.
Abbreviations: RFS, recurrence-free survival; OS, overall survival; BMI, body mass index; COPD, chronic obstructive pulmonary disease; ASA, American Society of Anesthesiologists; TNM, tumor-node-metastasis stage; WBC, white blood cell; PLT, platelets; DXM, dexamethasone.

Table 6 Multivariable Cox Proportional Hazard Model for Survival

Variable	RFS		OS	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Coronary heart disease	1.248(0.713–2.184)	0.438	-	-
Smoking history	1.249(0.963–1.621)	0.093	1.175(0.898–1.538)	0.241
ASA grade II	1.211(0.931–1.576)	0.154	1.252(0.953–1.644)	0.107
TNM stage [a]	1.025(0.893–1.177)	0.723	1.054(0.917–1.212)	0.460
Preoperative Hemoglobin>136 g/L	0.757(0.584–0.980)	0.035	0.706(0.540–0.923	0.011
Preoperative PLT count> 229.9×10^9/L	0.832(0.640–1.081)	0.169	0.835(0.637–1.095)	0.193
Surgical procedure [b]	0.947(0.696–1.287)	0.726	0.849(0.622–1158)	0.300
Mediastinal lymph node dissection	0.621(0.413–0.934)	0.022	0.548(0.363–0.828)	0.004
Combined epidural-general anesthesia	0.948(0.688–1.306)	0.745	-	-
Intraoperative blood loss>200mL	1.351(0.985–1.852)	0.062	1.229(0.936–1.802)	0.118
Maximal tumor size>3.0cm	-	-	1.647(1.252–2.166)	<0.001
Postoperative complications	1.341(1.022–1.759)	0.034	1.336(1.008–1.770	0.044
Postoperative radiotherapy	2.234(1.314–3.799)	0.003	1.590(0.909–2.781)	0.104
Postoperative chemotherapy	2.095(1.600–2.743)	<0.001	1.481(1.128–1.945)	0.005
Intraoperative DXM	0.789(0.608–1.024)	0.075	0.885(0.677–1.158)	0.374

Notes: P<0.05 was considered statistically significant. [a]TNM stage was divided into four stages: I, II, III and IV. The next stage was compared to the last stage. [b]Surgical procedure was divided into three categories: segmentectomy/wedge, lobectomy and total pneumectomy. Total pneumectomy was compared to lobectomy or segmentectomy/wedge.
Abbreviations: RFS, recurrence-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval; ASA, American Society of Anesthesiologists; TNM stage, tumor-node-metastasis stage; PLT, platelets; DXM, dexamethasone.

Postoperative complications are particularly common in patients with lung cancer, and the influence of postoperative complications after surgery is complicated.[14] So far, postoperative complications have been reported to be associated with an exaggerated systemic inflammatory response following surgery.[15] With regard to early postoperative

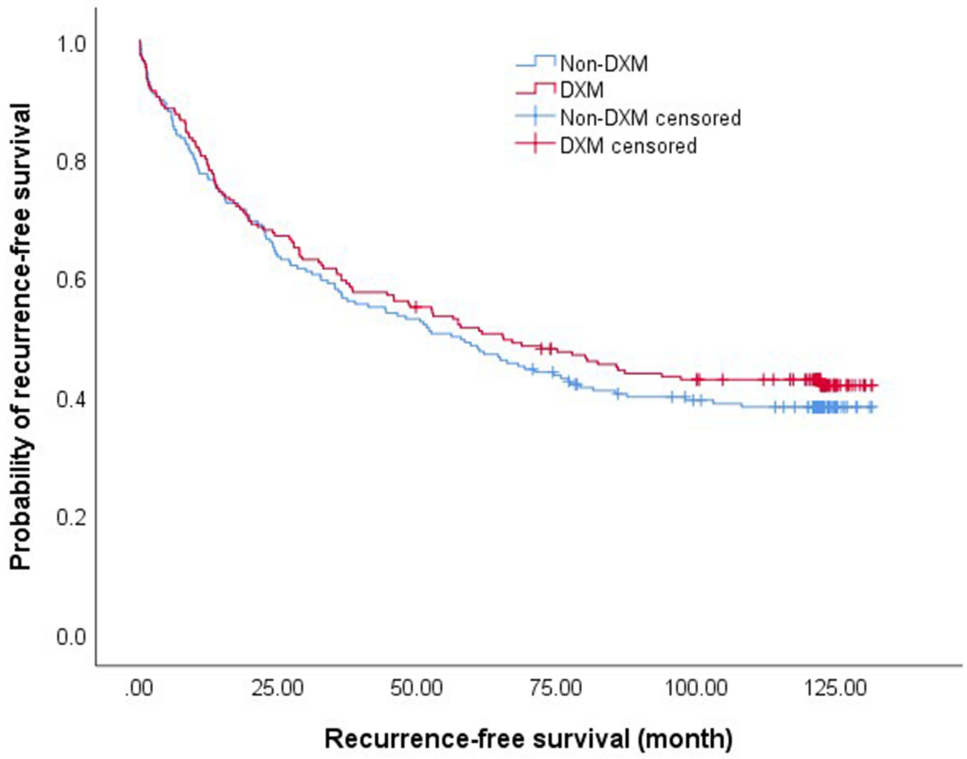

Figure 2 Kaplan-Meier curves showing RFS for intraoperative DXM use (HR, 0.789; 95% CI, 0.608–1.024; P = 0.075).
Abbreviations: RFS, recurrence-free survival; DXM, dexamethasone; HR, hazard ratio; CI, confidence interval.

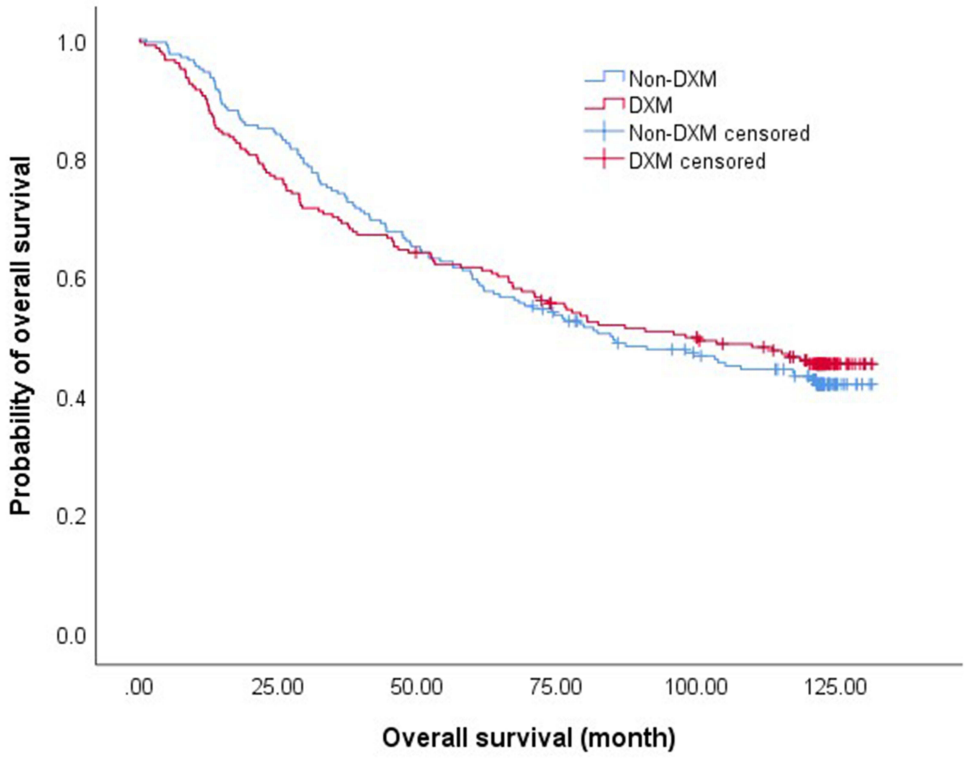

Figure 3 Kaplan-Meier curves showing OS for intraoperative DXM use (HR, 0.885; 95% CI, 0.677–1.158; P = 0.374).
Abbreviations: OS, overall survival; DXM, dexamethasone; HR, hazard ratio; CI, confidence interval.

complications, reduced levels and function of lymphocytes and NK cells can cause weakened cellular defense function, which may manifest in clinical practice as postoperative pneumonia, wound infection, or other inflammation.[16] In the present matched cohort, there were no significant difference in total postoperative complications between the DXM group and non-DXM group. It seemed to imply a lack of connection between intraoperative dexamethasone and postoperative complications. However, in the matter of PPCs, the result showed the occurrence of postoperative pneumonia (POP) in the DXM group was lower than that in the non-DXM group (3.5% vs 8.5%, P = 0.035) and suggested that a low dose of dexamethasone during operation for prophylaxis of PONV might have the salutary effect on patients with NSCLC after surgery. According to previous studies, POP is one of prevalent postoperative inflammatory-related complications after lung cancer surgery, the incidence of which ranges from 2.1% to 40%.[17,18] Dexamethasone is a synthetic glucocorticoid with potent anti-inflammatory effects in addition to its antiemesis.[19] In a prospective double-blind trial, Corcoran et al found dexamethasone 4mg administered during surgery mitigate systematic inflammatory response after surgery, as detected using the C-reactive protein (CRP), which has been increasingly recognized as a reliable indicator of systemic inflammatory response and attenuated the changes in counts of all cells, apart from basophils and natural killer cells.[20,21] Likewise, in another in-vivo experiment, Bain et al observed a significant decrease in classical monocytes, a major source of pro-inflammatory cytokines, within 2h of dexamethasone administration, and confirmed rapid effects of 8 mg dexamethasone on innate immune cells with the potential to alter the inflammatory response to surgery.[22] To our best knowledge, no studies have specifically elucidated the effect of intraoperative dexamethasone on postoperative pneumonia after lung cancer. Based on our results, we speculated that the decrease in the occurrence of POP was partly attributed to the anti-inflammatory properties of dexamethasone in the DXM group. Moreover, POP has been reported to be associated with significant increases in intensive care unit stays, postoperative hospital stay, and hospitalization cost.[23] In the current study, there were lower ICU occupancy (15.5% vs 23.5%, P = 0.043) and shorter PSH [12.0 days (IQR, 9.0–14.0) vs 12.5 days (IQR,10.0–15.0), P = 0.038] in the DXM group compared with the non-DXM group. We suspected that POP was responsible for these two outcomes in some degree. The reduced ICU occupancy and shortened PHS will greatly reduce the hospitalization cost and the financial burden of patients. It is of great clinical significance. Generally, postoperative complications after lung cancer resection remain a complicated challenge and mostly unpredictable. The link between intraoperative DXM use and POP deserves further study to develop more patient-friendly clinical management strategies.

Another concern of this study was the long-term survival status of patients with NSCLC. In the matched cohort, the median duration of RFS was 63.4 months (IQR, 14.1–122.0), and the median duration of OS was 81.4 months (IQR, 26.4–122.2) in the DXM group, while the median duration of RFS was 56.9 months (IQR, 13.9–121.6), and the median duration of OS was 78.4 months (IQR, 33.9–121.8) in the non-DXM group. Although there was a trend of prolonged RFS and OS in the DXM group, the difference was not significant between two groups after Kaplan–Meier analysis. Cox proportional hazard model revealed that intraoperative DXM was not the independent predictor for RFS (HR, 0.789; 95% CI, 0.608–1.024; P = 0.075) and OS (HR, 0.885; 95% CI, 0.677–1.158; P = 0.374). As far as the impact of corticosteroids on tumors are concerned, the available retrospective data have shown mixed results. Oliveira et al found there was no evidence for an association between perioperative systemic dexamethasone administration and ovarian cancer recurrence after primary cytoreductive surgery.[24] Similarly, Newhook et al found intraoperative dexamethasone failed to confer any long-term survival benefit for patients with resected pancreatic ductal adenocarcinoma.[25] Furthermore, Yu et al conducted a study on rectal cancer, indicating that patients who underwent radical surgical treatment gained a survival benefit by avoiding perioperative low-dose dexamethasone.[26] The authors supposed that perioperative administration of dexamethasone might augment recurrence and mortality after tumor resection possibly by immunosuppression. On the contrary, a multicentric cohort study investigated the association between intraoperative dexamethasone and postoperative mortality in patients undergoing solid cancer resection and indicated dexamethasone decreased 1-year mortality and cancer recurrence.[27] Another study by Zhang et al reported that perioperative use of low-dose glucocorticoids improved RFS in patients with pancreatic cancer and suggested dexamethasone may have prosurvival effects by its proapoptotic properties and suppress the perioperative stress response, which has detrimental effects on perioperative immune function and augments the risk of cancer recurrence.[28] Nevertheless, in terms of lung cancer, Cata et al considered there was no association between dexamethasone and long-term survival after NSCLC surgery, in accord with our findings.[29] Thus,

the effects of DXM on long-term survival appear to vary by tumor type, but the potential mechanisms remain unclear and need to be further validated in prospective studies.

In the matched cohort, cox proportional hazards regression analysis showed preoperative Hemoglobin >136 g/L and mediastinal lymph node dissection improved RFS and OS. Hemoglobin represents the most widely utilized test parameter in clinical settings. Several studies have reported the prognostic value of hemoglobin level for cancers and demonstrated that higher pretreatment hemoglobin level is related with better long-term outcomes.[30–32] Due to the heterogeneity of the study subjects, the preoperative hemoglobin levels analyzed were also different. Considering few patients with anemia due to adequate preoperative preparation in this study, the mean was chosen as the cutoff value for analyses. Our results are consistent with previous studies to some extent. As for mediastinal lymph node dissection, earlier studies have demonstrated that complete mediastinal lymph node dissection reduces the risk of postoperative recurrence and death,[33,34] which is also reflected in our results.

In addition to the factors mentioned above for improving long-term prognosis, this study also found several adverse factors, including maximal tumor size >3.0cm, postoperative complications, postoperative radiotherapy and radiotherapy. A tumor size of 3cm in diameter has been regarded as the prognostic threshold in the staging of bronchogenic carcinoma since 1974, due to a significant survival difference between tumors ≤3 and >3 cm obtained on large databases by MD Anderson Cancer Center and Lung Cancer Study Group.[35,36] Evidences from retrospective studies suggests tumor size ≤3cm was associated with a more favorable outcome in their patient population.[36,37] In the present study, maximal tumor size >3.0cm was associated with prolonged OS (HR, 1.647; 95% CI, 1.252–2.166; P < 0.001). Recently, studies have shown that postoperative complications, including a severe inflammatory reaction, after various types of cancer surgery are associated with poor cancer-specific survival.[38–40] The findings from Nojiri et al revealed that the presence of postoperative respiratory complications following lung cancer surgery was a significant predictor of cancer recurrence.[38] Yamamichi et al reviewed data from 1129 patients with primary lung cancer and found postoperative complications are independent predictors of the overall and recurrence-free survival in lung cancer patients, especially advanced-stage cancer patients.[39] Our results also showed that postoperative complications had a significant impact on postoperative outcomes and were associated with short RFS (HR, 1.341; 95% CI, 1.022–1.759; P = 0.034) and OS (HR, 1.336; 95% CI, 1.008–1.770; P = 0.044). In the postoperative complications, major infectious complications like pneumonia have been reported to be independent risk predictors of long-term survival in lung cancer patients.[40] Therefore, in this sense, the patients who received DXM in this study had a lower incidence of postoperative pneumonia, indirectly indicating that intraoperative DXM use was beneficial to the long-term prognosis. Of note, in this cohort, postoperative radiotherapy and chemotherapy were associated with worsened outcomes. We considered that the possible reason was that the patients undergoing these therapies were at an advanced stage.

Limitation

There were several limitations in this study. First, it was a single-center, retrospective study, possibly resulting in unobserved confounding factors and selection bias. For example, there were variabilities in practices among surgeons from different institution. Furthermore, although PSM has balanced most measurable baseline variables, there may still be unmeasured confounding factors, such as anesthesiologists' individualized decision-making preferences, tumor biological characteristics, and postoperative treatment regimens. Second, patients recruited in this study have undergone lung resection for more than 18 years. Some important clinical data such as preoperative lung function and intraoperative body temperature, which might have influence on the postoperative complications, have not been preserved, limited to the conditions during the cohort period. Therefore, the results of this cohort need to be interpreted with caution, and we will design prospective studies in the future to verify the findings. However, PSM was employed to balance the potential confounders and ensure the uniformity in perioperative characteristics.

Conclusion

In short, intraoperative use of dexamethasone decreased occurrence of postoperative pneumonia and ICU occupancy, and shortened the postoperative hospital stay in patients with NSCLC after lung resection. Given the frequency of

administration of anti-emetic DXM to surgical patients, further prospective studies are needed to determine whether dexamethasone is associated with both short - and long-term outcomes.

Abbreviations

NSCLC, non-small cell lung cancer; DXM, dexamethasone; ICU, intensive care unit; PHS, postoperative hospital stay; OS, overall survival; RFS, recurrence-free survival; PONV, postoperative nausea and vomiting; PPCs, postoperative pulmonary complications; PSM, propensity score matching; BMI, body mass index; COPD, chronic obstructive pulmonary disease; ASA, American Society of Anesthesiologists; TNM, tumor-node-metastasis stage; WBC, white blood cell; PLT, platelets. CRP, C-reactive protein; POP, postoperative pneumonia.

Data Sharing Statement

The study datasets are available from the corresponding author upon reasonable request.

Ethics Approval and Consent to Participate

This study was approved by the Clinical Research Ethics Committee of the Peking University Cancer Hospital (Approval No.2019YJZ22-GZ02). The requirement for written informed consent was waived because of the study's retrospective design.

Patient Confidentiality Statement

This retrospective study complies with institutional ethics and the Declaration of Helsinki. All patient-identifying information (names, hospital numbers, etc.) has been removed or anonymized in the manuscript and data. Presented data are aggregated to prevent individual identification. The Clinical Research Ethics Committee of the Peking University Cancer Hospital waived the informed consent requirement due to the study's retrospective nature. This manuscript contains no information that compromises patient confidentiality. Authors are responsible for maintaining patient privacy.

Author Contributions

Wenzhi Zhu and Liping Zhu contributed equally and share first authorship. All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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