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Effect of simultaneous surgical treatment of severe coronary artery disease and lung cancer

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Abstract

Objective: The co-incidence of lung cancer and coronary artery disease (CAD) is increasing in patients of advanced age. This study was performed to demonstrate the efficiency and safety of simultaneous coronary artery bypass grafting and lung cancer surgery in a selected group of older patients.

Methods: Twenty patients with severe CAD and coexisting lung cancer underwent simultaneous surgical interventions (Group A), and 20 patients with lung cancer underwent an isolated lung cancer operation (Group B). In Group A, the combined operations were carried out through 2 incisions in 3 patients, a single incision in 14 patients, and median sternotomy for heart surgery and thoracoscopic lobectomy for lung cancer in 3 patients. The single-incision approach was used in all patients in Group B.

Results: The operation time was longer and the blood loss volume was larger in Group A than B. No significant between-group differences were found in the 5-year relapse-free survival rate or 5-year survival rate.

Conclusions: The simultaneous performance of lung cancer surgery and cardiac surgery was effective and evidently safe in Group A. This treatment approach enabled earlier lung cancer resection and avoidance of the eventual complications associated with further surgical procedures.

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Introduction

Cancer and cardiovascular disease are the leading causes of death in both men and women worldwide. Lung cancer is the most common malignancy and the leading cause of cancer-induced death in China.[1] Coronary artery disease (CAD) is the second leading cause of death in China, where almost one-third of global cardiovascular disease-induced deaths occur.[2] The coexistence of cancer and CAD is common, and the co-incidence is expected to rise due to aging of the population and improvements of diagnostic facilities. The increasing incidence of lung cancer in China may be accelerated by the epidemic of tobacco smoking,[3] and the major risk factors for lung cancer in nonsmoking women include passive smoking, such as tobacco smog and cooking smog.[4] Smoking is also a major risk factor for CAD. Surgery is still the first-choice treatment for lung cancer, but treatment of resectable lung cancer and coexisting severe CAD has not been considered feasible. From May 2009 to June 2016, the Department of Cardiovascular and Thoracic Surgery of the First Affiliated Hospital of Nanjing Medical University performed simultaneous surgery for severe CAD and lung cancer in patients of advanced age. In the present study, we evaluated the efficiency and long-term safety of this combined treatment.

Methods

Ethics approval

All experiments in this retrospective investigation were performed in accordance with relevant guidelines and regulations. Informed consent to publish relevant information and images was obtained from all participants and/or their legal guardians. This study was approved by the Ethics Committee of Shanghai East Hospital (certificate number: 2017-048) with the clinical trial registration number ChiCTR1800014511.

Patients

From May 2009 to June 2016, simultaneous surgery for lung cancer and CAD was performed in patients assigned to Group A in this study. Few patients presented with symptomatic pulmonary disease, including cough, chest pain, or discomfort after exercise. Most patients were diagnosed with lung cancer by annual physical examination. All patients underwent coronary angiography; additionally, computed tomography, positron emission tomography or positron emission tomography/computed tomography, pulmonary function testing, or bronchoscopy was performed before the operation.

Tumors were classified and staged preoperatively in accordance with the University of California Integrated Staging System Tumor Node Metastasis Classification.[5] Most of the patients had two- or three-vessel disease with New York Heart Association class II cardiac function. Postoperative pathological examination showed that half of the patients had stage III lung cancer.

To compare the long-term safety of the combined procedures, an equal number of patients with lung cancer were retrospectively assigned to Group B. These patients

underwent isolated pulmonary resection during the same time period by the same group of surgeons. Potential confounders between Groups A and B were further balanced using propensity score matching.[6] Propensity scores were calculated from a logistic regression model based on variables that were predictors of the efficiency and safety of combined surgery.[7] Pairs were then matched using a one-to-one nearest-neighbor matching method to improve precision without increasing bias. During the matching, we ensured that the patients' ages, sexes, cardiovascular comorbidities, and especially the histological aspects of the patients' lung tumors in the control group were as similar as possible. Patients from the two groups were matched with respect to tumor type and stage. Patients who underwent neoadjuvant therapy were excluded. All included patients routinely underwent clinical examination, blood serum analysis, and cardiac echocardiography. Their clinical, pathologic, and operative records were collected during the study period. The demographic and clinical data of both groups are presented in Table 1.

Surgical procedures

All patients underwent double-lumen endotracheal tube intubation under general anesthesia. In Group A, the cardiac and lung surgeries were carried out simultaneously. Coronary revascularization was performed on the beating heart via off-pump coronary artery bypass grafting (CABG) followed by pulmonary resection. Arterial or venous grafts were harvested and then implanted. In Group A, a single left internal mammary artery graft was used in 1 patient, a single saphenous vein graft was used in 10 patients, their combination was applied in 8 patients, and a saphenous vein + radial artery graft was adopted in 1 patient. Median sternotomy for CABG and left thoracotomy for lung resection were

Table 1. Demographic and clinical characteristics of patients

Characteristics of patients	Group A (n = 20)	Group B (n = 20)	P
Female	4 (20%)	4 (20%)	1.000
Age, years	70.60 ± 7.62	68.40 ± 5.35	0.297
NYHA Class			0.000
I	1	17	
II	17	3	
III	2	0	
CAD classification			0.000
Stable angina	16 (80%)	2 (10%)	
Unstable angina	4 (20%)	0 (0%)	
Number of diseased vessels	2.55 ± 0.69		
Tumor pathological type			1.000
Adenocarcinoma	13 (65%)	13 (65%)	
Squamous cell carcinoma	6 (30%)	6 (30%)	
Small cell carcinoma	1 (5%)	1 (5%)	
Hypertension	14 (70%)	3 (15%)	0.001
Diabetes mellitus	7 (35%)	2 (10%)	0.127
Cerebrovascular disease	11 (55%)	1 (5%)	0.001
Smoking	11 (55%)	10 (50%)	1.000

Data are presented as n (%), n, or mean ± standard deviation
NYHA, New York Heart Association; CAD, coronary artery disease

used in two patients. Median sternotomy for CABG and right thoracotomy for lung resection were used in one patient. Median sternotomy for both the lung and cardiac operations was employed in six patients. Left lateral thoracotomy was employed in eight patients. Median sternotomy for CABG and thoracoscopic lobectomy for lung cancer were employed in three patients. Thoracoscopic lobectomy was performed by a standardized three-port anterior approach.[5] Patients in Group B underwent isolated lung resection. According to our standard protocol, complete lymphadenectomy was performed in both groups.

At the end of the procedures, patients in Group A underwent insertion of separate pleural and mediastinal tubes, whereas only pleural cavity drainage was performed in Group B. All patients in Group A were given low-molecular-weight heparin 6 hours after the surgical procedures. Antiaggregation therapy with 100 mg of acetylsalicylic acid and 75 mg of clopidogrel was commenced in Group A.

Follow-up

All patients were followed up by clinic visits at 1 and 3 months postoperatively and then at 6-month intervals. They all underwent a standard clinical examination, echocardiography, electrocardiography, and lateral chest X-ray examination during each visit after the initial 6 months and then every 6 months during the study period.

Statistical analysis

Perioperative and follow-up outcomes were compared between the two groups. Continuous values are presented as mean ± standard deviation. Demographic and clinical data were compared between the two groups using Fisher's exact test or the chi-square test. All statistical analyses were performed using IBM SPSS Statistics for Windows, version 19.0 (IBM Corp., Armonk, NY, USA). Survival curves of all patients were created using the Kaplan–Meier method.

Results

Patient characteristics

The patients' demographic and clinical characteristics are summarized in Table 1. Groups A and B both comprised 4 women and 16 men with a mean age of 70.60 ± 7.62 and 68.40 ± 5.35 years, respectively. No significant differences in comorbidities were found between the two groups, including hypertension, diabetes mellitus, and smoking as the main risk factors for CAD. With respect to cardiac function, no remarkable differences were found in the left ventricular ejection fraction between the two groups. In Group B, the pairing method succeeded in ranking patients with similar pathological tumor types. In Group A, the mean number of diseased vessels was 2.55 ± 0.69.

Surgical outcomes

No perioperative death or recurrent myocardial ischemia occurred in either group. The mean operation time and postoperative hospital stay were longer and the blood loss and postoperative total drainage volumes were larger in Group A than B as a result of two operations having been performed within one session. Postoperative mechanical ventilation was used in Group A. In Group A, 3 patients underwent operations by two incisions for CABG and tumor resection separately, 14 patients underwent a single-incision operation, and 3 patients underwent median sternotomy for heart surgery and thoracoscopic lobectomy for lung cancer. All patients in Group B underwent a single-incision operation for standard lung cancer resection. The operation time and blood loss volume were

significantly greater in Group A than B because of the greater trauma induced by the combined surgeries (P = 0.000 and 0.000, respectively).

All patients had a histological diagnosis of lung cancer. Squamous cell carcinoma, adenocarcinoma, and small cell carcinoma were identified in 6, 13, and 1 patient in Group A, respectively. The stages of lung cancer were comparable between the two groups. The surgical outcomes are summarized in Table 2. The postoperative complications, mainly respiratory complications, were minor and curable in both groups (data not shown).

Follow-up

No patient was lost to follow-up. The patients in Group A were followed up from 3 to 79 months. Six patients died of tumor metastasis or recurrence, one died of renal failure, and one died of intolerance of chemotherapy, but no patient died of cardiovascular events. The remaining 12 patients survived from 14 to 79 months during the follow-up. The patients in Group B were followed up from 6 to 75 months. Eight patients died of tumor metastasis or recurrence and one died of uremia at 74 months after surgery, but no patient died of cardiovascular events during the follow-up. The remaining 11 patients survived from 19 to 75 months during the follow-up.

The 3-year survival rates in Groups A and B were not significantly different (43.1% vs. 66.7%, respectively). The survival rates are summarized in Figure 1.

Discussion

We evaluated the efficacy and long-term safety of combined surgery in patients with severe CAD and resectable lung cancer. An extensive literature review suggests that this is currently the largest single-center report in this field in China. Our experience indicates that simultaneous off-pump CABG and lung cancer surgery can be implemented safely. Despite some differences in clinical indicators between combined surgery and single lung cancer resection (e.g., operation time, blood loss, and hospital stay), the safety of the

Table 2. Comparison of surgical outcomes

Variables	Group A (n = 20)	Group B (n = 20)	P
Operation time, minutes	346.35 ± 78.55	171.55 ± 62.57	0.000
Intraoperative blood loss, mL	635.00 ± 373.15	105.00 ± 68.63	0.000
Intraoperative plasma transfusion, mL	275.00 ± 339.74	75.00 ± 140.96	0.020
Intraoperative RBC transfusion, U	1.65 ± 2.98		
Mechanical ventilation time, minutes	989.75 ± 265.02		
ICU stay, minutes	2489.50 ± 2016.17		
Postoperative hospital stay, days	19.65 ± 12.97	14.05 ± 4.98	0.079
24-h drainage after operation, mL	394.00 ± 312.38	230.50 ± 75.64	0.029
Postoperative total drainage, mL	2902.95 ± 1956.01	1224.50 ± 1111.79	0.002
Stage of lung cancer			0.425
I	6 (30%)	9 (45%)	
II	4 (20%)	5 (25%)	
III	10 (50%)	6 (30%)	
Tumor size, cm	3.37 ± 1.48	3.17 ± 1.45	0.676

Data are presented as mean ± standard deviation or n (%)
RBC, red blood cell; ICU, intensive care unit

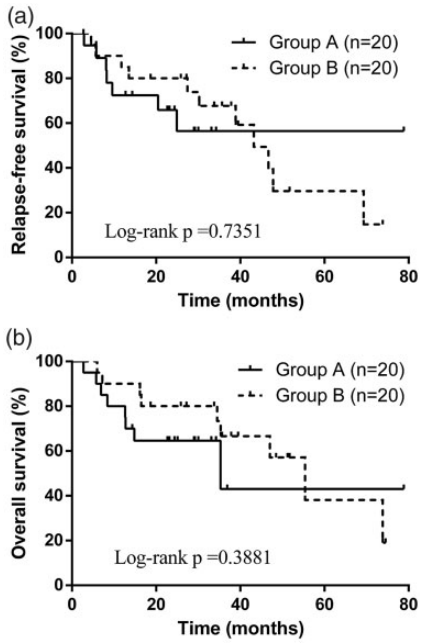

Figure 1. Kaplan–Meier survival curves for (a) relapse-free survival and (b) overall survival according to matched patients in our study

combined surgery was evident. The long-term outcomes, such as the 3-year survival rate, were similar between the two groups. Furthermore, the combined procedure enabled earlier lung cancer resection and avoided the eventual complications associated with further surgical procedures.

Heart disease and cancer are the leading causes of death in China. Of these diseases, lung cancer and CAD share several etiological causes. CAD significantly impacts the surgical morbidity of patients with lung cancer and is an independent predictor of operative death.[8] Moreover, the risk of cardiotoxicity in association with chemotherapy and radiotherapy in patients with lung cancer have been extensively studied.[9] For patients with coexisting lung cancer and CAD, a prompt therapeutic regimen for ischemic heart disease is needed to minimize the risk of the lung cancer operation. Moreover, stent placement or bypass grafting is required before the lung cancer resection. However, the most appropriate timing of lung surgery in these patients remains unclear.

Thoracic surgeons have been challenged to choose simultaneous surgery or a two-stage approach.[10] Percutaneous coronary intervention (PCI) and CABG are two common cardiac revascularization treatments. The early complications of surgical treatment involving PCI are associated with a significant risk of major intraoperative cardiac ischemia at 6 weeks to 3 months after the stenting.[11,12] Although the incidence is not high, the outcome is often fatal. Delay is unacceptable once lung cancer has been diagnosed. A propensity-matched study demonstrated that although PCI is associated with lower rates of periprocedural bleeding, CABG offers more freedom from both early and late recurrent ischemia.[13] If CABG is performed first, the postoperative recovery postpones the lung cancer resection. In the present study, we performed simultaneous surgery to treat coexisting diseases and recommend performing off-pump CABG first from the viewpoint of asepsis. The performance of cardiac surgery first can also ensure the coronary artery supply, helping to avoid intraoperative myocardial ischemia and cardiac dysfunction. Off-pump CABG has been commonly used as an advancement in CAD treatment during the past two decades.[14,15] Off-pump CABG can reduce the intraoperative heparin dose and bleeding volume during tumor resection. The extracorporeal circulation increases the concentrations of free oxygen radicals, which may cause cell damage,[16] inhibit the immune system, and enhance tumor growth and dissemination.[17] If extracorporeal circulation is used in CABG, intraoperative tumor metastasis can be avoided by performing lung cancer resection before revascularization.[18]

The tumor size and localization determine the incision location. Median

sternotomy, which may fully expose the cardiovascular system, is commonly used for off-pump CABG. However, lung resection through a median sternotomy is not feasible for some procedures used to treat malignant lung lesions, such as left lower lobectomy. Furthermore, the use of a two-incision surgical approach to open both pleural cavities would cause more pain and increase the incidence of early postoperative complications. With the accumulation of clinical experience, we aimed to perform the combined surgeries through a single incision. In Group A, 3 patients underwent median sternotomy and lateral thoracotomy with two surgical incisions, 14 patients underwent a single surgical incision, and the remaining 3 patients underwent median sternotomy for CABG and thoracoscopy-assisted dissection for right lobectomy. Thoracoscopic equipment was used to minimize the incision size and surgical trauma. All patients in Group B underwent a single-incision operation, and the location of the incision was determined according to the tumor size and location.

The grafting strategy in Group A was selected according to the coronary artery conditions. The left internal mammary artery is most commonly used in the treatment of left anterior descending artery diseases, while the mixed application of arteries and saphenous veins is applied in the treatment of multivessel diseases. In the present study, no myocardial ischemia or myocardial infarction occurred perioperatively in either group. The operation time was longer and the intraoperative blood loss and postoperative drainage volumes were larger in Group A than B because two operations were combined into one session. No perioperative death occurred in either group. The 3-year survival rates were similar between the two groups. All patients underwent their operations by the same team of surgeons. Our department has performed almost 10,000 lung cancer surgeries and 3000 off-pump CABG procedures in recent decades. We are satisfied with our thoracic operations, and few of our patients have shown signs of complications after tumor resection. As previously reported, higher hospital and surgeon volumes are significantly associated with prolonged overall survival.[19] Higher-volume surgeons may have better outcomes because of their superior operative techniques, such as efficient lymph node harvesting and optimal cancer resections. Vigilant follow-up, surveillance of recurrent disease, and timely and appropriate use of chemotherapy also contribute to improved surgical outcomes. Higher-volume hospitals may have better approaches to detect and treat comorbid diseases. Effective perioperative management and performance of operations at tertiary care centers also improve the surgical outcomes.

Nevertheless, this study has several limitations. First, this retrospective study involved a relatively small number of patients. Second, adequate statistical power could not be easily achieved when comparing the clinical outcomes of the two groups. Third, we compared outcomes between the two different surgical techniques and matched the patients' clinical characteristics (including tumor type and stage) using propensity score matching, and the selection process separated the two groups so that no overlap between the groups was possible; however, the similarity between the groups should be explained to a certain degree according to the selection methods. Finally, the positive effect of ongoing technical modifications may have been partially influenced by the surgeons' high level of experience.

Conclusions

The simultaneous surgery described in this report enabled earlier tumor resection, eliminated perioperative cardiac risk and pain, and decreased medical costs by combining two

operations into one session. Experienced surgeons may contribute to improved clinical outcomes in one-stage surgery.

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Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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References

1. Chen W, Zheng R, Zeng H, et al. The incidence and mortality of major cancers in China, 2012. *Chin J Cancer* 2016; 35: 73.
2. WHO. Cardiovascular Diseases (CVDs). June 19, 2015.
3. Yang GH, Li Q, Wang CX, et al. Findings from 2010 global adult tobacco survey: implementation of MPOWER policy in China. *Biomed Environ Sci* 2010; 23: 422–429.
4. Yu YW, Wang CP, Han YF, et al. [Meta-analysis on related risk factors regarding lung cancer in non-smoking Chinese women]. *Zhonghua Liu Xing Bing Xue Za Zhi* 2016; 37: 268–272 [in Chinese, English Abstract].
5. Hansen HJ, Petersen RH and Christensen M. Video-assisted thoracoscopic surgery (VATS) lobectomy using a standardized anterior approach. *Surg Endosc* 2011; 25: 1263–1269.
6. Rosenbaum PR and Rubin DB. The central role of the propensity score in observational studies for causal effects. *Biometrika* 1983; 70: 41–55.
7. Brookhart MA, Schneeweiss S, Rothman KJ, et al. Variable selection for propensity score models. *Am J Epidemiol* 2006; 163: 1149–1156.
8. Ciriaco P, Carretta A, Calori G, et al. Lung resection for cancer in patients with coronary arterial disease: analysis of short-term results. *Eur J Cardiothorac Surg* 2002; 22: 35–40.
9. Hardy D, Liu CC, Cormier JN, et al. Cardiac toxicity in association with chemotherapy and radiation therapy in a large cohort of older patients with non-small-cell lung cancer. *Ann Oncol* 2010; 21: 1825–1833.
10. Yang Y, Xiao F, Wang J, et al. Simultaneous surgery in patients with both cardiac and noncardiac diseases. *Patient Prefer Adherence*. 2016; 18: 1251–1258.
11. Kaluza GL, Joseph J, Lee JR, et al. Catastrophic outcomes of noncardiac surgery soon after coronary stenting. *J Am Coll Cardiol* 2000; 35: 1288–1294.
12. Chassot PG, Delabays A and Spahn DR. Preoperative evaluation of patients with, or at risk of, coronary artery disease undergoing non-cardiac surgery. *Br J Anaesth* 2002; 89: 747–759.
13. Ben-Gal Y, Moses JW, Mehran R, et al. Surgical versus percutaneous revascularization for multivessel disease in patients with acute coronary syndromes: analysis from the ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy) trial. *JACC Cardiovasc Interv* 2010; 3(10): 1059–1067.
14. Takahashi T, Ohtake S, Ueno T, et al. Off-pump coronary bypass using interposed radial artery graft. *Ann Thorac Surg* 1998; 66: 2096–2098.
15. Nishi H, Sakaguchi T, Miyagawa S, et al. Optimal coronary artery bypass grafting strategy for acute coronary syndrome. *Gen Thorac Cardiovasc Surg* 2014; 62: 357–363.
16. Utoh J, Yamamoto T and Miyauchi Y. Is an increase in neutrophil leukotriene-generating capacity a specific phenomenon for cardiopulmonary bypass? *J Thorac Cardiovasc Surg* 1995; 110: 276–277.
17. Byrne JG, Leacche M, Agnihotri AK, et al. The use of cardiopulmonary bypass during

resection of locally advanced thoracic malignancies: a 10-year two-center experience. *Chest* 2004; 125: 1581–1586.
18. Frantisek S, Toporcer T, Kolesar A, et al. Surgical management of a patient with combined heart pathologies and lung cancer. A simultaneous coronary artery bypass surgery, aortic valve replacement, tricuspid valve repair and pulmonary resection. *Cor Vasa* 2014; 56: E75–E79.
19. Kulkarni GS, Urbach DR, Austin PC, et al. Higher surgeon and hospital volume improves long-term survival after radical cystectomy. *Cancer* 2013; 119: 3546–3554.