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Running title: Postoperative Atrial Fibrillation is Less Frequent in Pulmonary Segmentectomy Compared with Lobectomy

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Abstract

Objective: The aim of this study was to elucidate the characteristics and predictors of postoperative atrial fibrillation (POAF) from the standpoint of surgical mode.

Methods: Retrospective analysis was carried out on 607 patients who underwent lobectomy or segmentectomy for clinical stage IA lung cancer. We investigated the clinical factors to determine the predictors of the development of POAF.

Results: Of the 607 patients, 443 underwent lobectomy, and 164 underwent segmentectomy. POAF developed in 37 patients. Of these, 34 (7.7%) were in the lobectomy group, and 3 (1.8%) in the segmentectomy group. In the univariate analysis for predictors of POAF, age ($p<0.01$), history of ischemic heart disease ($p=0.03$), FEV1.0% ($p<0.01$) and surgical mode ($p=0.01$) showed significant differences between the groups. The multivariate analysis revealed that increasing age ($p<0.01$, HR: 1.059, CI: 1.015-1.106), surgical mode ($p= 0.02$, HR: 5.734, CI: 1.350-24.361) and FEV1.0%<70% ($p=0.03$, HR: 2.182, CI: 1.067-4.461) were independent predictors of POAF.

Conclusion: POAF was significantly less following segmentectomy compared with lobectomy.

Introduction

Currently, atrial fibrillation (AF) is recognized as one of the common complications accompanying pulmonary resection. Its incidence after thoracic surgery for lung cancer ranges from 4 to 37% (1-3). Though AF is not considered to be a lethal complication, it could result in a fatal thromboembolitic event, such as cerebral infarction requiring prolonged hospitalization (4, 5). Thus prevention of AF is one of the most important objectives of postoperative patient care. Randomized trials comparing sublobar resection with lobectomy are few, and reports on comparison of postoperative complications in these groups are rare. The aim of this study was to elucidate the characteristics and predictors of postoperative atrial fibrillation (POAF) from the standpoint of surgical mode.

Materials and methods

Study population

A retrospective study was conducted on 778 consecutive patients with clinical stage IA primary lung cancer who underwent resection between February 2008 and March 2013 at our institute. The criteria for exclusion from the analysis were: 1) patient with a history of paroxysmal or chronic atrial fibrillation; 2) patient who underwent preoperative treatments such as chemotherapy and/or radiotherapy; 3) patient who underwent pneumonectomy, bilobectomy, sleeve lobectomy, or wide wedge resection. As a result, 171 patients were excluded, and 607 patients were enrolled in this study. This retrospective study was performed under a waiver of authorization approved by the institutional review board of Juntendo University School of Medicine, Tokyo, Japan.

Mode of surgery

All the patients enrolled were reclassified according to the TNM Classification of Malignant Tumors, 7th edition (6). The indication of surgery was decided according to the TNM staging. Sublobar resection was indicated when there was: 1) a minimally invasive lung cancer; 2) simultaneous multiple primary lung cancers; and 3) a lung cancer arising in a compromised host. The study included clinical stage IA lung cancer only. The decision on the surgical mode, namely, sublobar resection, which is a wide wedge resection, or segmentectomy, was based on the surgical margin of the tumor.

Postoperative care

At our institution, patients who undergo lobectomy or segmentectomy are put on the same protocol for postoperative care. The volume of infusion during the operation is controlled by the anesthesiologist who is requested to balance the infusion by approximately +5 ml/kg/h. Food intake starts from the following day after surgery, and if the patient can ingest more than 50% of the food provided in the hospital, the infusion is stopped. There are however, times when the infusion is continued for the purpose of correcting dehydration caused by a large amount of drainage. ECG monitoring is performed for two days after surgery if there are no complications. If arrhythmia is detected, ECG monitoring is continued. The criteria for drain removal are as follows: 1) no abnormality in the drainage findings, 2) the amount of drainage per day is 300 ml or less, and 3) there is no air leakage. When the postoperative course is uneventful, the patients are discharged in 4 to 7 days after surgery.

Diagnosis and management of POAF

After surgery, postoperative atrial fibrillation (POAF) was detected by continuous electrocardiography (ECG) monitoring or examination for palpitation when the patients were not wearing the monitor. POAF was defined as an irregular rhythm with absent P-waves confirmed by ECG. Our basic methods for managing POAF are described below. First, we try to control the heart rate using a β-blocker or calcium channel blocker. If the patient is hemodynamically stable, we pursue restoring the sinus rhythm using class IA or IC antiarrhythmic drugs. If the patient is unstable, direct cardioversion is considered. Finally, if AF persists for more than 48 hours, anticoagulation therapy is initiated. In the past, warfarin was prescribed, but recently we use a factor Xa inhibitor and that has led to a reduction in hospitalization period as it does not require dosage adjustment like warfarin.

Definition of chronic obstructive pulmonary disease (COPD)

Before planned surgical treatment of lung cancer, we always evaluate the patient's respiratory system by using pulmonary function test (PFT). Based on the preoperative PFT, we defined COPD as an FEV1.0/FVC ratio (FEV1.0%) <70% in this study.

Details of ischemic heart disease

Our history of ischemic heart disease includes 9 cases of myocardial infarction, 27 angina pectoris, 8 vasospastic angina, and 9 coronary stenosis. Of these patients, 25 received placement of a coronary artery stent, 9 underwent coronary artery bypass grafting, and 43 were on antiplatelet medication.

Statistical analysis

We analyzed preoperative and operative clinical factors, including gender, age, BMI, pack-year of smoking, preoperative respiratory function, history of ischemic heart disease, history of lung cancer surgery, surgical mode, operation time, amount of bleeding, and mediastinal lymph node dissection. In the univariate and multivariate analyses, a logistic regression analysis was used to identify predictors. A probability value of less than 0.05 was set as the cut-off point for the selection of variables for the multivariate analysis. All statistical analyses were performed using R for Windows GUI front-end ver.3.0.2 (R Development Core Team 2013, A Language and Environment for Statistical Computing, R Foundation for Statistical Computing, Vienna, Austria. URL: http://www.r-project.org).

Results

The study comprised 607 consecutive patients who underwent lung resection, we performed lobectomy in 443 patients and segmentectomy in 164. With regard to preoperative factors, men and smoking status were high in the lobectomy group. There was no difference in age, BMI and preoperative respiratory function between the two groups. History of pulmonary resection was greater in the segmentectomy group. With regard to operative factors, operation time was longer in the segmentectomy group than the lobectomy group. Mediastinal lymph node dissection was frequently adapted in the lobectomy group (Table 1).

We investigated the incidence of POAF per surgical site between lobectomy and segmentectomy (Table 2, 3). We performed left upper division segmentectomy in 42 (25.6%) and S6 segmentectomy in 40 (24.4%) patients. These accounted for about half of the segmentectomy group. POAF occurred in total of 37 (6.1%) patients; 34 were in the lobectomy group, and 3 in the segmentectomy group. All patients with POAF in the segmentectomy group underwent left upper division segmentectomy (Table 3).

Table 4 shows the comparison of preoperative and operative risk factors in patients with and without POAF. In the univariate analysis, age ($p<0.01$), a history of ischemic heart disease ($p =0.03$), and FEV1.0% ($p<0.01$) showed a significant difference between the groups. With regard to intraoperative factor, surgical mode showed a significant difference ($p=0.01$). However, there was no significant difference regarding mediastinal lymph node dissection ($p=0.09$). In the multivariate analysis, increasing age ($p<0.01$, HR: 1.059, CI: 1.015-1.106), surgical mode ($p=0.02$, HR: 5.734, CI: 1.350-24.361) and FEV1.0%<70 ($p=0.03$, HR: 2.182, CI: 1.067-4.461) were independent predictors (Table 5).

Discussion

Postoperative atrial fibrillation (POAF) is a common complication after major lung resection and there are various reports on the risk factors of AF (1, 7-9).

Incidence of POAF in our study was 6.1%, which was lower than other reported values. This difference in incidence rate can be explained by the limitation of the clinical stage, absence of a uniform definition of POAF, and oversight of its sometimes transient nature. In this study, the definition of POAF was based on electrocardiographic evidence.

Previous reports showed that the risk factors for POAF include increasing age, increasing extent of pulmonary resection, male sex, clinical stage, history of ischemic heart disease or congestive heart failure, and mediastinal lymph node dissection (1-3, 8-11). Many authors have expressed contrasting opinions on these factors. The risk factors identified most frequently in these studies are increasing age and extent of pulmonary resection.

The association between age and POAF was closely examined by Amar et al. In their analysis of 527 patients undergoing lobectomy, pneumonectomy, or esophagectomy, they found that increasing age was the strongest predictor of onset of POAF (12). Results of our analysis confirmed that increasing age was an independent predictor.

Asamura et al examined 267 patients and reported increasing onset of AF with increasing volume of lung resection(13). Other investigators reported that pneumonectomy was the highest risk factor of POAF (2, 11, 14). Moreover, reports on the incidence of POAF in segmentectomy are very few. In addition, Vaporciyan A. et al reported that hilar manipulation (mainly pulmonary vein dissection) is important not only for extent of pulmonary resection but also the incidence of POAF (1). Their analysis showed similar incidence of POAF between the single-wedge and multiple-wedge resections. Another investigator suggested a hypothesis for the cause of POAF as an atrial or pulmonary vein inflammation (15). Thus, we had to consider whether or not to include hilar manipulation in the operation. Moreover, we could investigate the extent of impact due to pulmonary resection only as our study excluded wide wedge resections.

Previous reports suggest that segmentectomy and lobectomy are equivalent regarding surgical stress, such as operation time and the amount of bleeding (16-18). Though both operations need hilar manipulation, the findings from our study showed that POAF is less frequent in segmentectomy than lobectomy. In addition, all three cases with POAF in the segmentectomy group underwent left upper division segmentectomy, which involved the removal of a large volume of the lung. The results of this study showed that extent of pulmonary resection is a great predictor of POAF. Thus, segmentectomy is less likely to affect hemodynamics compared with lobectomy.

Xin reported a higher incidence of POAF in patients who underwent a left lobectomy than those who underwent a right lobectomy (19). In our lobectomy group, POAF occurred most frequently in the right upper lobe, however, there was no significant difference in incidence of POAF between the resected sites.

COPD (FEV1.0%<70) was an independent risk factor in our data. Previously Kearney et al found predicted postoperative FEV1.0 to be an independent risk factor for operative death (20). There are few reports on the association between preoperative pulmonary function and POAF. Sekine et al reported that COPD (FEV1.0≤70% predicted and FEV1.0/FVC ratio≤70%) was a significant risk factor for the development of supraventricular arrhythmias following lung resection in COPD patients (21). Their analysis did not demonstrate that postoperative predicted FEV1.0 was a risk factor for arrhythmias.

History of ischemic heart disease was a significant predictor in our univariate analysis, and is supported by previous studies (2, 11). Dyszkiewicz et al reported a history of ischemic heart disease, and preoperative symptoms of congestive heart failure (NYHA III) posed a significant risk of POAF (2). In our multivariate analysis, however, a history of ischemic heart disease did not prove to be a significant predictor of POAF.

There are several limitations to our study. First, it was a single institution retrospective clinical study with only 37 AF events, making the sample size too small to evaluate. Second, we could not detect all the AF events as this arrhythmias is very transient. Some patients might have had episodes of AF that were not documented by ECG. In addition, echocardiographic examinations were not performed for all patients discovered to have AF. As such, the specific reasons for the incidence of POAF remain unexplained. Finally, there are other factors not accounted for in this analysis, such as thyroid function and plasma concentrations of potassium and magnesium, and this may have affected the probability of POAF.

In Japan, registrations for the JCOG0802 / WJOG4507L clinical trial have been completed and observation of prognosis is underway. This trial is a prospective, randomized, multi-institutional study, designed to compare the prognosis and postoperative pulmonary function of patients with non-small lung cancer, 2 cm or less in diameter, undergoing either lobectomy or segmentectomy. The secondary endpoint of this study includes the incidence of postoperative complications such as arrhythmia, the results of which will be disclosed later.

Conclusion

In our retrospective study, POAF was significantly less frequent in segmentectomy than lobectomy. Segmentectomy is less likely to affect hemodynamics compared with lobectomy. Thus, segmentectomy should be indicated for high risk patients.

Conflict of interest: none declared.

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Table 1: Clinicopathological features of the Lobectomy/ Segmentectomy groups

Variable		Lobectomy(n=443)		Segmentectomy(n=164)		p-value[a]
Gender	Male	226	(51.0%)	68	(41.5%)	0.04
Age	Years (median)	67	(35-86)	67	(27-84)	0.17
BMI	less than 18.5	33	(7.5%)	9	(5.5%)	0.40
	More than 25	107	(24.2%)	36	(22.0%)	0.57
Smoking status (pack-year)	40 or more	290	(23.9%)	26	(15.9%)	0.03
Preoperative pulmonary function						
FEV1.0%	less than 70%	106	(23.9%)	30	(18.3%)	0.17
%VC	less than 80%	44	(10.0%)	17	(10.6%)	0.83
History of ischemic heart disease		42	(9.5%)	11	(6.7%)	0.28
History of lung cancer resection		12	(2.7%)	24	(14.6%)	<0.01
Operation time	Minutes (median)	144	(35-352)	156	(61-315)	<0.01
Blood loss	ml (median)	20	(0-605)	15	(0-410)	0.09
Mediastinal LN dissection		313	(70.7%)	48	(29.3%)	0.01
POAF		34	(7.7%)	3	(1.8%)	0.01

[a] logistic regression analysis

BMI: body mass index; FEV1.0%: forced expiratory volume % in one second; %VC: % volume capacity; LN: lymph node; POAF: postoperative atrial fibrillation

Table 2. Incidence of AF per site of surgery in the lobectomy group

Resected site		Lobectomy (n=443)		with POAF (n=34)	
Right	Upper	158	(35.7%)	16	(47.1%)
	Middle	44	(9.9%)	3	(8.8%)
	Lower	76	(17.2%)	6	(17.6%)
Left	Upper	106	(23.9%)	5	(14.7%)
	Lower	59	(13.3%)	4	(11.8%)

POAF: postoperative atrial fibrillation

Table 3. Incidence of AF per site of surgery in the segmentectomy group

Right Lung		n	POAF (n=0)	Left Lung	n	POAF (n=3)
Upper	S1	12	0	Upper division	42	3
	S2	13	0	S1+2	3	0
	S3	9	0	Lingular	10	0
	S1+2	3	0			
	S1+3	1	0			
	S2+3	2	0			
	S2+6	1	0			
Lower	S6	19	0	S6	21	0
	S6+8	2	0			
	S8	10	0	S8	1	0
	S7+8	1	0			
				S9	2	0
	S8+9	1	0	S8+9	1	0
	S10	2	0			
	S9+10	1	0	S9+10	2	0
	Basal	1	0	Basal	2	0

POAF: postoperative atrial fibrillation

Table 4: Predictors of POAF in c-stage IA revealed by the univariate analysis

Variable		With POAF (n=37)		Without POAF (n=570)		p-value[a]
Gender	Male	22	(59.5%)	272	(47.7%)	0.17
Age	Years (median)	73	(48-86)	67	(27-86)	<0.01
BMI	less than 18.5	1	(2.7%)	41	(7.2%)	0.32
	More than 25	8	(21.6%)	135	(23.7%)	0.77
Smoking status (pack-year)	40 or more	12	(32.4%)	120	(21.1%)	0.11
Preoperative pulmonary function						
FEV1.0%	less than 70%	16	(43.2%)	120	(21.1%)	<0.01
%VC	less than 80%	5	(13.5%)	56	(9.8%)	0.44
History of ischemic heart disease		7	(18.9%)	46	(8.1%)	0.03
History of lung cancer resection		2	(5.4%)	34	(6.0%)	0.89
Surgical mode	Lobectomy	34	(91.9%)	409	(71.8%)	0.01
	Segmentectomy	3	(8.1%)	161	(28.2%)	
Operation time	Minutes (median)	153	(90-225)	146	(35-315)	0.47
Blood loss	ml (median)	20	(0-185)	20	(0-605)	0.45
Mediastinal LN dissection		27	(73.0%)	334	(58.6%)	0.09

[a] logistic regression analysis.

BMI: body mass index; FEV1.0%: forced expiratory volume % in one second; %VC: % volume capacity; LN: lymph node; POAF: postoperative atrial fibrillation

Table 5: Predictors of POAF in c-stage IA revealed by the multivariate analysis

Variables	odds ratio	95%CI	p-value[a]
Age	1.059	1.015-1.106	<0.01
Surgical mode	5.734	1.350-24.361	0.02
(Lobectomy vs. Segmentectomy)			
FEV1.0%<70	2.182	1.067-4.461	0.03
History of ischemic heart disease	1.801	0.711-4.565	0.21

[a] logistic regression analysis.

CI: confidence interval; FEV1.0%: forced expiratory volume % in one second