

# Surgical Treatment of Lung Cancer Combined with Interstitial Pneumonia: The Effect of Surgical Approach on Postoperative Acute Exacerbation

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**Postoperative acute exacerbation of interstitial pneumonia (IP) is known to be a serious complication in the surgical treatment for primary lung cancer combined with IP. This retrospective study was conducted to investigate the influence of three different approaches to the thorax on postoperative acute exacerbation of IP in lung cancer patients. Forty-seven lung cancer patients who developed it underwent pulmonary resection between 1982 and 2003. Among them, approaches to the thorax consisted of posterolateral thoracotomy (PLT) (n=15), muscle-sparing thoracotomy (MST) (n=15), and video-assisted thoracic surgery (VATS) (n=17). Seven of 47 suffered from acute exacerbation of IP. Single variable analysis suggested that exertion dyspnea (Hugh-Jones classification), serum C-reactive protein, serum lactate dehydrogenase and total lung capacity were considered to be preoperative risk factors of acute exacerbation. As for the VATS patient, there was little frequency of postoperative complication in comparison with the other two approaches. However no significant difference was shown in the incidence of acute exacerbation between the three approaches.**

**Conclusion: The use of VATS did not prevent acute exacerbation of IP. However, the incidence of postoperative complications in VATS seemed to be low, therefore further trials are required. (Ann Thorac Cardiovasc Surg 2004; 10: 340–6)**

**Key words:** lung cancer, acute exacerbation of interstitial pneumonia, video-assisted thoracic surgery, muscle-sparing thoracotomy, posterolateral thoracotomy

## Introduction

Interstitial pneumonia (IP) is known to be combined with primary lung cancer and is associated with an increased risk of postoperative acute exacerbation.<sup>1)</sup> Acute exacerbation of IP is a serious postoperative complication and the consequence is extremely poor. Therefore, a surgeon must aim to prevent acute exacerbation of IP.<sup>2)</sup> Pharmacotherapy, breathing exercise could be important for prevention. Various efforts have been made to establish the

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etiology of postoperative acute exacerbation of IP.<sup>3-5)</sup> To minimize surgical intervention for the chest wall, muscle-sparing thoracotomy (MST)<sup>6)</sup> and video-assisted thoracic surgery (VATS)<sup>7)</sup> have been utilized for the past ten years instead of traditional posterolateral thoracotomy (PLT), as surgical intervention could be a risk factor in acute exacerbation of IP. VATS was reported to be an advantageous approach for aged lung cancer patients when the patient was suitable for an anatomic lobectomy.<sup>8,9)</sup> In the present study, we performed pulmonary resection for 47 patients with lung cancer combined with IP and investigated the clinical outcome concerning different three approaches to the thorax as stated above. Furthermore, we investigated predictive factors of acute exacerbation of IP on 7 patients who showed acute exacerbation of IP within 30 days after an operation.

**Table 1. Characteristics of all patients**

Age	Years old	70 (57-86)
Gender	Male/female	42/5
Hugh-Jones classification	≥II/I	14/33
Performance status	≥2/2>	21/26
Brinkman index	Cigarettes per day × years	1132 (0-2760)
Pathological stage	1A/1B/2A/2B/3A/3B/4	10/12/1/9/9/4/2
Histological type	Sq/Ad/La/Sm	29/15/2/1
Classification of IIP	UIP/NSIP	44/3
Preoperative pulmonary function		
%VC	%	92 (52-1238)
FEV <sub>1.0</sub> (%)	%	74 (40-97)
%FEV <sub>1.0</sub>	%	97 (36-128)
FEV <sub>1.0</sub>	L	2.07 (0.84-3.10)
%TLC	%	95 (48-124)

Sq, squamous cell carcinoma; Ad, adenocarcinoma; La, large cell carcinoma; Sm, small cell carcinoma; UIP, usual interstitial pneumonia; NSIP, nonspecific interstitial pneumonia; VC, vital capacity; FEV<sub>1.0</sub>, forced expiratory volume in one second; TLC, total lung capacity  
n=47

## Patients and Methods

Between June 1982 and April 2003, 1103 patients underwent pulmonary resection for primary lung cancer. Among them, 47 patients had IP. The average age was 70 years old (ranging from 57-86), and the sex ratio was 42 to 5. The clinical outcomes of 47 patients were observed at an out patient clinic of the Nippon Medical School hospital. Fifteen of 47 patients underwent a PLT, and 15 patients underwent a MST, the 17 remaining patients underwent VATS (Table 1). These 47 patients were based on clinical criteria using chest X-ray and chest computer tomography scanning (chest CT scan), and diagnosed as IP.<sup>2)</sup> By a postoperative histopathology diagnosis, 44 examples out of 47 examples were diagnosed as usual interstitial pneumonia (UIP) and 3 examples were nonspecific interstitial pneumonia (NSIP). Preoperative exertion dyspnea (Hugh-Jones classification)<sup>10)</sup> and performance status<sup>11)</sup> were evaluated at the same date of pulmonary function test and blood gas analyses. Surgically related factors and perioperative conditions were evaluated. The diagnosis of acute exacerbation of IP was based on the following criteria mentioned by Yoshimura et al.<sup>12)</sup> in 1984; 1) intensified dyspnea, 2) increase in the interstitial shadow on chest X-ray, 3) increase in fine crackling rales on auscultation, 4) elevation of serum lactate dehydrogenase (LDH), 5) decrease in PaO<sub>2</sub> of more than 10 mmHg under similar condition: all of 1), 2), 3), plus at least either

of 4) or 5) are necessary for diagnosis (Table 2). Clinical outcome within 30 days postoperation was compared between 7 patients with acute exacerbation and 40 patients without acute exacerbation.

### Surgical technique

Surgery was performed using one-lung ventilation under general anesthesia in the decubitus position. In order to enter the thorax, a PLT was performed with a 25-cm-long skin incision by separation of muscle layer and rib. A MST was carried out with a 15-cm-long skin incision without separation of muscle layer. VATS was performed with an average of a 7-cm-long skin incision (4-10 cm) without muscle or costal separation. A few trocar ports were used to lead thoracoscopy and endoscopic apparatus (Ethicon Endo-Surgery Inc., Cincinnati, OH, USA,

**Table 2. Diagnosis of acute exacerbation of IP<sup>12)</sup>**

1) intensified dyspnea
2) increase in the interstitial shadow on chest X-ray
3) increase in fine crackling rales on auscultation
4) elevation of serum LDH
5) decrease in PaO <sub>2</sub> of more than 10 mmHg under similar condition
all of 1), 2), 3), plus at least either of 4) or 5) are necessary for diagnosis

LDH, serum lactate dehydrogenase

**Table 3. Surgery and postoperative complications of the patients who underwent PLT, MST or VATS**

Groups Number	47	PLT 15	MST 15	VATS 17	Statistics	p value
Acute exacerbation of IP	None/present	13/2	11/4	16/1	ns	0.25
Surgically related factors						
Age	Years old	69±5	67±6	73±6 <sup>a</sup>	Significant	<0.05
Gender	Male/female	15/0	13/2	14/3	ns	0.24
Side	Right/left	9/6	11/4	12/5	ns	0.6
Procedures	P/L/PR	1/14/0	0/14/1	0/14/3	ns	0.34
Location of cancer	RU/RM/RL/LU/LL	4/1/4/4/2	1/1/8/2/3	3/1/7/2/4	ns	0.71
Tumor size	mm in diameter	38±15	47±20 <sup>b</sup>	28±14 <sup>b</sup>	Significant	<0.05
Lymph node dissection	ND1/ND2a	1/14	0/15	3/14	ns	0.19
Duration of surgery	min	254±92	261±74	321±133	ns	0.13
Blood loss	ml	424±309	501±355	339±297	ns	0.45
Max. serum CPK	IU/L/M2	835±360	807±307	668±386	ns	0.25
Pathological stage	1A/1B/2A/2B/3A/3B/4	4/4/0/3/1/3/0	1/2/1/5/4/1/1	5/6/0/1/4/0/1	ns	0.2
Histology	Sq/Ad/La/Sm	9/5/0/1	12/3/0/0	8/7/2/0	ns	0.22
Postoperative complications						
Respiratory diseases	None/present	7/8	8/7	15/2	Significant	<0.05
Cardiac diseases	None/present	15/0	14/1	16/1	ns	0.41

PLT, posterolateral thoracotomy; MST, muscle sparing thoracotomy; VATS, video-assisted thoracic surgery; Pn, pneumonectomy; Lob, lobectomy; PR, partial resection; RUL, right upper lobe; RM, right middle lobe; RL, right lower lobe; LU, left upper lobe; LL, left lower lobe; ND1, regional lymph node dissection; ND2a, mediastinal lymph node dissection; Sq, squamous cell carcinoma; Ad, adenocarcinoma; La, large cell carcinoma; Sm, small cell carcinoma; Maximal serum CPK, maximal serum creatine phosphokinase

a, VATS vs PLT (p=0.03); VATS vs MST (p=0.005); b, VATS vs MST (p=0.07)

and U.S. Surgical Corp., Philadelphia, PA, USA).

### Statistical analyses

Statistical analyses were performed using the software package of Stat View 5.0 (SAS Inc., Chicago, IL, USA). A chi-square test and Student t-test were used. The multivariate analysis was performed by a logistic regression test. A p value of less than 0.05 was considered significant.

### Results

The preoperative characteristic of all patients was shown by Table 1. A severe smoking index was shown except in one female patient. Elderly and male patients were dominant. Grade 1 or more of performance status and grade II or more of exertion dyspnea (Hugh-Jones classification) were observed in 16 (34%) and 21 (45%), respectively. Histopathologically, squamous cell carcinoma was dominant (62%). Classification of IP consists of UIP, 44 and NSIP, 3. Acute exacerbation of IP was not shown in 3 patients with NSIP. The patients who underwent a right or left lower lobectomy was 28 (60%) of 47 patients.

The significant difference of an incidence of acute exacerbation of IP was not found between three approaches, but there seemed to be a few more incidences of acute exacerbation of IP of VATS than in the two other approaches. Between the three approaches the thorax, no surgically related factors showed any significant differences except for tumor size (Table 3). VATS was employed more for elderly patients than those in the PLT and MST (p<0.05) and in with a smaller size of tumor than that in the MST (p<0.05). Even though the duration of surgery was longer in VATS in comparison with PLT and MST, there was less bleeding and serum creatine phosphokinase (CPK) as parameters of damage to the chest wall in VATS in comparison with PLT and MST. The incidence of postoperative respiratory complications were less in VATS than those in the remaining two approaches (p=0.03). Seven patients suffered from acute exacerbation of IP. In the patients who underwent PLT there were 2 cases, in MST there were 4 and 1 in VATS (Table 4). Acute exacerbation occurred at the 11th postoperative day on average (ranging 3-20 postoperative days). Case 4, a 76-year-old male underwent left lower lobectomy by PLT, but developed progressive difficulty of breathing from the

**Table 4. Details of the patients with acute exacerbation of IP within 30 days postoperation**

	Age	Gender	Pathology and stage	Approach	Surgery	Date of onset	Eligibility criteria*	Term	Prognosis
Case 1	66	Male	Sq, 3B	PLT	RML	20 POD	1, 2, 3, 4, 5	78 days	Dead
Case 2	58	Male	Sq, 2B	MST	RLL	8 POD	1, 2, 3, 4	764 days	Dead
Case 3	74	Male	La, 3A	VATS	RLL	14 POD	1, 2, 3, 4, 5	325 days	Dead
Case 4	76	Male	Sq, 1A	PLT	LLL	3 POD	1, 2, 3, 4, 5	41 days	Dead
Case 5	77	Male	Sq, 3A	MST	RBS	4 POD	1, 2, 3, 4, 5	496 days	Alive
Case 6	63	Male	Sq, 2B	MST	LLL	14 POD	1, 2, 3, 5	134 days	Dead
Case 7	73	Male	Ad, 3A	MST	RLL	7 POD	1, 2, 3, 4	28 days	Dead

\*, Eligibility criteria of acute exacerbation of IP by Yoshimura et al.

IP, interstitial pneumonia; Sq, squamous cell carcinoma; Ad, adenocarcinoma; La, large cell carcinoma; Sm, small cell carcinoma; PLT, posterolateral thoracotomy; MST, muscle sparing thoracotomy; VATS, video-assisted thoracic surgery; RML, right middle lobectomy; RLL, right lower lobectomy; LLL, left lower lobectomy; RBS, right basal segmentectomy; POD, postoperative day

**Table 5. Preoperative conditions and examinations of the patients with or without acute exacerbation of IP within 30 days postoperation**

Groups Number	With acute exacerbation		Without acute exacerbation		Statistics	p value
	7		40			
Age	Years old	69±7	70±6	ns	0.81	
Gender	Male/female	7/0	35/5	ns	0.32	
Performance status	≥2/2>	6/1	15/25	ns	0.29	
Hugh-Jones classification	≥II/I	0/7	14/26	Significant	<0.01	
Brinkman index	Cigarettes per day × years	868±312	1173±648	ns	0.26	
Blood examinations						
WBC	10 <sup>2</sup> /μl	8283±5773	6902±1572	ns	0.22	
Serum CRP	mg/dl	7.2±6.2	0.6±0.1	Significant	<0.01	
Serum LDH	IU/l	6/1	12/28	Significant	0.01	
KL-6	U/ml	457±174	508±210	ns	0.63	
SP-D	ng/ml	121±68	131±86	ns	0.82	
Pulmonary function test						
% VC	%	80±15	94±15	Significant	0.04	
%FEV <sub>1.0</sub>	%	87±12	96±28	ns	0.5	
%TLC	%	77±18	99±15	Significant	0.01	
Arterial blood gas analyses						
PaO <sub>2</sub>	mmHg	87±8	86±14	ns	0.82	
PaCO <sub>2</sub>	mmHg	38±2	38±3	ns	0.72	

IP, interstitial pneumonia; WBC, white blood cell; CRP, C-reactive protein; LDH, lactate dehydrogenase; SP-D, surfactant protein D; % VC, percent vital capacity; %FEV<sub>1.0</sub>, percent forced expiratory volume in one second; %TLC, percent total lung capacity

3rd postoperative day. Case 7, a 73-year-old male underwent right lower lobectomy by MST, but developed a decrease of PaO<sub>2</sub> and reticulonodular shadow in chest X-ray from the 7th postoperative day. These two patients died of respiratory insufficiency during postoperative hospital stays.

There were significant differences in the preoperative conditions in the presence of acute exacerbation of IP (Table 5), i.e., exertion dyspnea (Hugh-Jones classification) (p<0.01), serum CRP (p<0.01), serum LDH (p=0.01). Even though significant differences were not

found, white blood cell count, serum KL-6, and serum surfactant protein D (SP-D) markedly increased in patients with acute exacerbation of IP postoperatively. Arterial blood gas analysis (PaO<sub>2</sub>) showed no significant difference in the patients regardless of the presence of acute exacerbation of IP in a range of postoperative day 30. The pulmonary function test showed a decrease in both percentage total lung capacity (%TLC) (p=0.01) and percent vital capacity (%VC) (p=0.04).

Surgically related factors showed no significant differences between the two groups (Table 6). There was no

**Table 6. Surgically related factors of the patients with or without acute exacerbation of IP within 30 days postoperation**

Groups Number		With acute exacerbation 7	Without acute exacerbation 40	Statistics	p value
Surgically related factors					
Side	Right/left	4/3	28/12	ns	0.74
Approach	PLT/MST/VATS	2/4/1	13/11/16	ns	0.25
Procedures	Pn Lob/PR	0/6/1	1/36/3	ns	0.47
Combined resection	Partial resection of ribs	1	6	ns	0.06
Lymph node dissection	ND1/ND2a	1/6	3/37	ns	0.55
Duration of surgery	min	282±74	280±112	ns	0.97
Blood loss	ml	556±320	393±319	ns	0.22
Max. serum CPK	IU/L/M2	727±252	767±372	ns	0.8
Oxygen inhalation and blood gas analyses					
FIO <sub>2</sub>		0.56±0.26	0.73±0.29	ns	0.23
PaO <sub>2</sub>	mmHg	209±75	208±115	ns	0.98
Pathological stage	1A/1B/2A/2B/3A/3B/4	2/0/0/1/3/1/0	8/12/1/8/6/3/2	ns	0.46
Histology	Sq/Ad/La/Sm	5/1/1/0	24/14/1/1	ns	0.38
Postoperative complications					
Respiratory diseases	None/present	6/1	12/28	Significant	<0.01
Air leak	7 days or more	2	9		
Atelectasis	IPPB and cleaning by BFS	0	2		
Pneumonia	Necessity of ICU	4	0		
Chylothorax	Necessity of management	0	1		
Cardiac diseases	None/present	6/1	39/1	ns	0.05
Arrhythmia	Necessity of medication	1	1	ns	

IP, interstitial pneumonia; PLT, posterolateral thoracotomy; MST, muscle sparing thoracotomy; VATS, video-assisted thoracic surgery; Pn, pneumonectomy; Lob, lobectomy; PR, partial resection; ND1, regional lymph node dissection; ND2a, mediastinal lymph node dissection; IPPB, intermittent positive pressure breathing; BFS, bronchofiberscope; ICU, intensive care unit

**Table 7. Single variable analysis of risk factors on the acute exacerbation of IP within 30 days postoperation**

Factors		With acute exacerbation	Without acute exacerbation	Statistics	p value
Hugh-Jones classification	≥II/I	7/0	14/26	Significant	<0.01
Serum CRP (mg/dl)	≥2/2>	5/2	5/35	Significant	0.01
Serum LDH (IU/l)	≥400/400>	6/1	12/28	Significant	0.01
%TLC (%)	≤95/95<	7/0	18/22	Significant	0.01

IP, interstitial pneumonia; CRP, C-reactive protein; LDH, lactate dehydrogenase; %TLC, percent total lung capacity

significant difference in FIO<sub>2</sub> under anesthetic between the two groups. A higher incidence of severe postoperative respiratory complications occurred in patients with acute exacerbation of IP compared to those in patients without acute exacerbation ( $p < 0.01$ ). Arrhythmia needing intensive care was shown in one of 7 patients with acute exacerbation of IP and one of 40 patients without acute exacerbation.

Single variable analysis suggested the preoperative risk factors on acute exacerbation of IP as follows: exertion dyspnea (Hugh-Jones classification)  $\geq$  grade II ( $p < 0.01$ ), serum CRP  $\geq 2.0$  mg/dl ( $p = 0.01$ ), serum LDH  $\geq 400$  IU/l ( $p = 0.01$ ), %TLC  $\leq 95\%$  ( $p = 0.01$ ) (Table 7). There was

no significant difference between the three approaches to the thorax. Multivariate logistic regression test on preoperative factors regarding development of acute exacerbation of IP showed that %TLC was the most significant risk factor (odds ratio, 1.094; 95% confidence intervals, 1.001-1.196;  $p = 0.04$ ).

Even though the number of patients studied was small, the 1-, 3-, and 5-year survival rate of all patients were 76%, 39%, and 39%, respectively. The 1-, 3-, and 5-year survival rate of the patients without acute exacerbation of IP were 85%, 53%, and 46%. Two year survival rate of the patients with acute exacerbation was 29%. At stage I patients ( $n = 20$ ) without acute exacerbation, the 1-, 3-, and

5-year survival rate were 95%, 55%, and 55%, better than those in the patients with acute exacerbation ( $p=0.006$ ).

## Discussion

Etiology of IP is still unknown. However primary lung cancer is known to be often related with IP. Furthermore, for thoracic surgeons, it is a serious problem to encounter the acute exacerbation of IP causing life threatening postoperative complications.<sup>1-5</sup> Even though lung biopsy has been recommended to diagnose IP,<sup>2,13</sup> the high risk of mortality resulting from acute exacerbation of IP could not be ignored.<sup>3</sup> Therefore, it is very important to evaluate the preoperative risk factors in surgical treatment for lung cancer patients with IP.<sup>14</sup> Due to the significant difference in survival rate in the presence of acute exacerbation of IP. We experienced 47 lung cancer patients combined with IP. In order to reduce surgical intervention, we employed minimally invasive approach to the thorax according to the refinement of surgery and perioperative management.<sup>6-9</sup> Even though there was still dispute about whether MST or VATS were less invasive than PLT, we adopted VATS as the first option and MST as the second option for patients with impaired physical conditions.<sup>15</sup> In the presented patients, VATS was tended to be utilized for elderly patients rather than PLT or MST ( $p<0.05$ ). Postoperative respiratory complication, in VATS was less than in MST or PLT ( $p<0.05$ ). Furthermore, even though there was no significant difference, the incidence of acute exacerbation of IP was less in VATS than that in PLT or MST. When surgical management influences the start of acute exacerbation of IP with various conditions, there is no difference, however, further investigation must be undertaken to clarify the advantage of VATS. As for analyses on the preoperative risk factors of acute exacerbation of IP, the results of the present study were as same results as those in prior reports. The presence of inflammation might contribute to cause lung tissue damage. Progressing dyspnea on exertion after operation tended to be found in patients with reduced total lung capacity before operation. High serum concentration of surfactant protein A, D (SP-A, SP-D) and serum KL-6 are considered to be useful markers of UIP and NSIP.<sup>16,17</sup> There was no significant difference in preoperative serum KL-6 and serum SP-D between the patients with and without postoperative acute exacerbation of IP. However, serum SP-D and serum KL-6 increased after surgery with the postoperative acute exacerbation of IP. Regarding medication, the effect of methylprednisolone (mPSL) was not yet

settled, but, at induction of anesthesia, 500 mg of mPSL was given to 19 of 47 patients. Arterial blood oxygen ( $\text{PaO}_2$ ) was maintained around 100 mmHg with minimal  $\text{FIO}_2$  during surgery. When acute exacerbation was diagnosed, 1000 mg of mPSL was given for two days followed by 1 mg/kg of prednisolone. Intensive cardiopulmonary care was carried out.<sup>18</sup> All patients were administered bronchodilators. Digitalis, catecholamine and vasodilators were administered to avoid an increase of right ventricular after load. The patients with NSIP have been observed carefully at the Department of Respiratory Disease of the Nippon Medical School Hospital, which is because medical treatment with steroids is considered to be effective when exacerbation of IP occurs.

## Conclusion

Several reported risk factors were confirmed in this study again. There was no current evidence that VATS was particularly effective in acute prevention of IP. However, the incidence of acute exacerbation of IP seemed to be minimal in VATS compared to that in PLT or MST, hence further investigation is required.

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