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Research Article

Difficult Prediction of Exacerbation of Interstitial Pneumonia after Lung Cancer Resection

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Abstract

Background: Postoperative acute exacerbation of Idiopathic Interstitial Pneumonia (IIP) is known to be a catastrophic complication in the surgical treatment for primary lung cancer with concomitant IIP. Investigation of clinical factors associated with postoperative acute exacerbation of IIP in primary lung cancer patients was conducted.

Methods: Between 2000 and 2009, 5630 lung cancer patients underwent surgical resection in ten institutes in north Japan (Hokkaido); wherein, 249 patients (4.4%) had concomitant IIP. Univariate logistic regression models were used to determine risk factors for exacerbation of IIP in 36 clinicopathological factors (preoperative demographic data, serum data, pulmonary function, comorbidity, operative data, and pathological data).

Results: Nine of 249 patients (3.6%) developed acute exacerbation of IIP and 7/9 patients died of the exacerbation. The univariate analyses showed no risk factor for postoperative acute exacerbation of IIP.

Conclusion: It is very difficult to predict the occurrence of acute exacerbation of interstitial pneumonia after surgical treatment of patients with lung cancer and interstitial pneumonia. Further factors or parameters should be investigated to predict the occurrence.

ABBREVIATIONS

IIP: Idiopathic Interstitial Pneumonia; IPF: Idiopathic Pulmonary Fibrosis; AEIP: Acute Exacerbation of Interstitial Pneumonia; SPD: Surfactant Protein-D; KL6: Sialylated carbohydrate antigen KL-6

INTRODUCTION

Idiopathic Interstitial Pneumonia (IIP) [1] is known to occur concomitantly with primary lung cancer and is associated with an increased risk of acute exacerbation during the postoperative period [2]. Acute exacerbation of IIP is a serious postoperative complication and the consequence is extremely problematic. Therefore, a surgeon must aim to prevent acute exacerbation of IIP. Pharmacotherapy and breathing exercise could be important for prevention. Various efforts have been made to establish the etiology of postoperative acute exacerbation of IIP [3,4]. We may be able to reduce the occurrence of the exacerbation if there are the risk predictors and we know them. In this study, pulmonary resection was conducted on 249 patients with lung cancer and

concomitant IIP. The risk factors for acute exacerbation of IIP were investigated in 9 patients, who presented with clinical manifestations within 30 postoperative days.

MATERIALS AND METHODS

Patients

Between January 2000 and December 2009, 5625 patients with primary lung cancer underwent pulmonary resection in ten institutes in Hokkaido, Japan. Two hundred sixty nine patients presented with concomitant interstitial pneumonia and 249 of 269 patients had Idiopathic Interstitial Pneumonia (IIP). Twenty patients had interstitial pneumonia caused by some intractable diseases, such as collagen disease, pulmonary silicosis, and the like. These 249 primary lung cancer patients with IIP were included in this study. Preoperative, intraoperative, and postoperative data were collected on all patients from each institutional data base. The retrospective study was approved by the IRB of Sapporo medical university school of medicine and hospital.

Table 1 shows the patients' demographic characteristics. The mean age of the patients was 69±8 years and 226/249 (90.8%) were male. The subtypes of IIP were 84.7% for Idiopathic Pulmonary Fibrosis (IPF), 2.4% for non-specific IP, and 12.9% for undefined IP. Serum levels of KL-6, Surfactant Protein D (SPD), and LDH were slightly elevated. Only the diffusing capacity of the lungs for carbon monoxide was decreased as regards pulmonary function test. Histological data of the primary lung cancer and the stage are shown in Table 2. The most prevalent histological subtype was squamous cell carcinoma (53.8%) and pathological stage 1 accounted for 65.8% of all patients.

Diagnosis of IP

Diagnosis of IP was based on the criteria in American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus by the American Thoracic Society and European Respiratory Society [5]. The diagnosis was mostly confirmed by pathological examination of the resected specimens; however, 12.9% of the patients were diagnosis with IP only by preoperative radiographical examination. Most of the patients had incipient IP and underwent upper lobe lobectomy.

Diagnosis of acute exacerbation of IIP

The acute exacerbation of IPF is characterized by diffuse and rapid alveolar damage superimposed on a background of IPF that probably occurs as a result of a massive lung injury due to some unknown etiologic agent. The definition of acute exacerbation of IPF was first described by Yoshimura [6]. The characteristics include (1) intensified dyspnea, (2) increase in the interstitial shadow on chest radiograph, (3) increase in fine crackles on auscultation, (4) elevation of serum lactate dehydrogenase, and (5) decrease in arterial oxygen tension of more than 10 mm Hg under similar condition. After then, some diagnostic criteria have been described [7-12]. In this study, the definition described by Yoshimura or Hyzy was applied (Table 3).

Peri-operative and postoperative management

Chest radiograph was routinely taken at least on the 1st to 3rd Post-Operative Day (POD) and on the day after chest tube removal. Additional chest radiographs were taken, depending upon the patients' clinical state, as opposed to including all symptoms and signs. If infiltrates were revealed on chest radiograph, high-resolution CT (HRCT) scan was performed for the differential diagnosis of these lung diseases.

In all institutes, oxygen inhalation was administered at minimal level to maintain SpO_2 >90 to 92% if patients did not complain of dyspnea or underwent any change in cardio-respiratory conditions due to mild hypoxia.

The steroid pulse therapy with methylprednisolone (1 or

Table 1: Preoperative characteristics of idiopathic interstitial pneumonia patients with lung cancer.

Variables	N=249	%
Age (year)	69±8	
Male sex	226	90.8
BI	1038±674	
Type of IP		
IPF	211	84.7
NSIP	6	2.4
Undefinitive IP	32	12.9
KL-6 (U/ml)	729±467	
SP-D (ng/mL) (n=134)	179±143	
LDH (IU/L)	247±102	
VC (L)	3.32±0.71	
%VC (%)	108.1±59.63	
FEV1 (L)	2.38±0.54	
FEV1.0% (%)	75.0±11.3	
DLCO ml/min/mmHg (n=158)	11.6±3.6	
%DLCO (%) (n=158)	66.3±20.4	
DLCO/VA (n=158)	3.01±0.98	
DLCO/VA% (n=158)	66.6±22.5	

BI = Brinkmannn Index; IP = interstitial pneumonia; IPF = Idiopathic pulmonary fibrosis;
NSIP = Non-specific IP; SPD = Surfactant Protein D; DLCO = Diffusing Capacity of the lung for Carbon monoxide; VA = Alveolar Ventilation

Table 2: Pathological data of idiopathic interstitial pneumonia patients with lung cancer.

Variables		N	%
Histology	Sq	134	53.8
	Ad	76	30.5
	Others	39	15.7
P-stage	1A	87	34.9
	1B	77	30.9
	2A	11	4.4
	2B	28	11.2
	3	35	14.1
	Undefinitive	11	4.4

Sq = Squamous cell carcinoma; Ad = Adenocarcinoma; P-stage = pathological stage by 6th Edition of ISAC

Table 3: Definition of acute exacerbation of IPF described by Hyzy [11].

Previous or concurrent diagnosis of IPF*
Unexplained worsening or development of dyspnea within 30 d
High-resolution CT scan with new bilateral ground-glass
abnormality and/or consolidation superimposed on a
background reticular or honyecomb pattern consistent with a UIP pattern†
Worsening hypoxemia from a known baseline arterial blood gas‡
No evidence of pulmonary infection by endotracheal aspiration or BAL
Exclusion of alternative causes, including
Left heart failure
Pulmonary embolism
Identifiable cause of acute lung injury§

*This criterion can be met by the presence of radiologic and/or histopathologic changes consistent with a UIP pattern if a diagnosis of IPF has not been previously established by American Thoracic Society/ European Respiratory Society criteria.
†Current high-resolution CT scan is acceptable without prior highresolution CT scan for comparison if none is available.
‡Includes evaluation for common bacterial organisms and viral pathogens.
§Causes of lung injury include sepsis, aspiration, trauma, transfusion of blood products, pulmonary contusion, fat embolization, drug toxicity, acute pancreatitis, inhalational injury, and cardiopulmonary bypass.

2 g /day for 3 or 4 days as one course) was used as the first line treatment for postoperative AEIP. In this series, neither immunosuppressive agent nor nitric oxide inhalation therapy was used.

Definition of Terms

In this study, each term was defined as follows: 1) Smokers were people smoking cigarettes or a pipe by themselves currently or previously. 2) Heart disease as a preoperative comorbidity was defined as a condition requiring medical treatment or surgical treatment for a structural or functional abnormality of the heart, or of the blood vessels supplying the heart, that impairs its normal functioning. 3) Chronic obstructive pulmonary disease was a condition defined by a fixed FEV_1/FVC <0.70. 4) Diabetes mellitus was a condition in which glucose intolerance is not treated with changes in diet and an exercise regimen.

Statistical analysis

Statistical evaluation was performed by using standard computer software (IBM SPSS 16.0, SPSS Inc, Chicago, IL). All continuous data are presented as mean +/- standard deviation. Differences in continuous and categorical values were tested by unpaired Student's t test and chi-square test (or Fisher's exact test), respectively. To account for the risk factor of morbidity or mortality after pulmonary resection for lung cancer, the Logistic regression analysis was used. Clinicopathological related factors were quantified by univariate analysis and then all factors with p<0.10 in a univariate analysis were included in a multivariate logistic regression analysis together.

RESULTS AND DISCUSSION

Results

Of 249 pulmonary lung cancer patients with IIP, postoperative complications occurred in 42 patients (16.9%); wherein, AEIP occurred in 9 patients (3.6%). Furthermore, 8 patients (3.2%) died a month after pulmonary resection and the cause of death was postoperative AEIP in 7 patients. These data are shown in Table 4.

Details of the patients with AEIP within 30 days after surgery are shown in Table 5. AEIP developed in 9 patients on a mean of 9 days after surgery (2-27 days). The site of first appearance of consolidation on chest radiograph was on the contralateral side of the primary lung cancer in 5 patients and the upper lobe in 3 patients. Seven of nine patients died of respiratory failure due to deterioration of IIP despite intensive care with steroid pulse therapy. Two patients recovered but the tumor recurred and one died 41 months after surgery.

Preoperative conditions and data of the patients with and without AEIP within 30 days after surgery are shown in Table 6. All data, but the level of SPD, are similar between the two groups. The serum level of SPD was higher in patients with AEIP than in patients without (380 ng/ml vs 180 ng/ml, p=0,001). However, the rate of patients with high serum SPD level (SPD > 200 ng/mL) was similar between the two groups.

Surgically related factors are shown in Table 7. These factors did not differ between the two groups either. Univariate logistic regression analysis for each variable revealed that even the serum level of SPD ≥200 ng/ml was not a risk factor for the acute exacerbation of IP within 30 days after surgery (Odds ratio = 8.92, 95% Confidence interval 0.97-83.3, p-value = 0.054). Multivariate analysis further revealed no predictive factor for postoperative AEIP.

Discussion

Postoperative AEIP is known to be one of the catastrophic complications in the surgical treatment for primary lung cancer with concomitant IIP. According to the annual report by the Japanese association of thoracic surgery [13], 1036 of 27881 patients (3.7%) who underwent pulmonary resection for primary lung cancer during the year 2008 had interstitial pneumonia as a preoperative comorbidity. Although the whole hospital mortality

Table 4: Postoperative complications.

Variables	Number	%
AEIP	9	3.6
Pneumonia	11	4.4
Air leak> 7days	12	4.8
Requiring surgical repair	2	0.8
BPF	3	1.2
Empyema	4	1.6
Aterectasis	2	0.8
Bleeding	2	0.8
Chylothorax	1	0.4
Af	5	2.0
Wound trouble	3	1.2
Delirium	1	0.4

AEIP = Acute Exacerbation of Interstitial Pneumonia; BPF = Bronchopleural Fistula; Af = Atrial Fibrillation

Table 5: Details of patients with AEIP after surgery.

	Sex	Age	IIP type	Tumor location	VATS	Pro-cedure	Complication but AEIP	First appearance site of consolidation on CXP	AEIP onset PO day (day)	PO status (day)		Cause of death
1	M	56	IPF	RLL	N	Lob		CL-LL	2	442	Alive	-
2	M	78	IPF	LLL	Y	WR	Air leak	CL-UL	27	69	Dead	RF
3	M	66	IPF	RUL	Y	Seg	BPF, Empyema	IL-LL	6	1216	Dead	Recurrence
4	M	78	IPF	LUL	N	Lob	Air leak	IL-LL	6	559	Dead	RF
5	M	72	IPF	LLL	Y	Lob		CL-LL	7	9	Dead	RF
6	M	72	IPF	RUL	N	Lob		CL-UL	2	17	Dead	RF
7	M	68	IPF	LLL	Y	Lob		CL-LL	7	42	Dead	RF
8	F	58	IPF	LUL	Y	Lob	Pneumonia	IL-LL	3	57	Dead	RF
9	M	75	IPF	LLL	Y	Lob		IL-UL	19	26	Dead	RF

IPF = Usual interstitial pneumonia; VATS = Video Assisted Thoracoscopic Surgery; AEIP = Acute Exacerbation of Interstitial Pneumonia; Lob -= Lobectomy; WR = Wedge Resection; Seg = Segmentectomy; BPF = Bronchopleural Fistula; CL = Contralateral; IL = Ipsilateral; LL = Lower Lobe; UL = Upper Lobe; RF = Respiratory Failure

Table 6: Preoperative conditions and data of the patients with acute exacerbation of IP within 30 days after surgery and patients without.

Variables		AEIP (+)	(n=9)	AEIP (-)	(n=240)	P-value
Age (year)		69±8		69±8		0.939
Male sex		8		218		0.588
Brinkman Index		779±499		1048±679		0.242
	>800	2		34		0.627
Smoker		8		216		0.56
Preop CTX		0		4		0.862
Preop RTX		0		4		0.862
KL-6 (U/ml)		855±404		722±470		0.434
SP-D (ng/mL)		318±238	(n=8)	170±132	(n=126)	0.004
SP-D>200 (ng/mL)		5		39		0.114
LDH (IU/L)		268±68		246±103		0.539
Pulmonary function						
PaO2 (torr)		78±13		83±11		0.286
VC (L)		2.95±0.61		3.33±0.72		0.14
%VC (%)		92.9±16.4		104.9±201.4		0.082
FEV1 (L)		2.19±0.40		2.39±0.54		0.305
FEV1.0% (%)		80.5±7.7		74.7±11.4		0.132
DLCOml/min/mmHg		10.2±4.7	(n=3)	11.6±3.6	(n=155)	0.588
%DLCO (%)		56.8±6.4	(n=3)	66.4±20.5	(n=155)	0.51
Histology =S q		3		107		0.735
Stage I		5		157		0.467
Upper lobe location of the tumor		4		87		0.728
Preoperative Comorbidity						
	Heart	4		53		0.217
	COPD	2		73		0.728
	DM	3		60		0.729
	Concomitant cancer	2		38		0.64

CTX = Chemotherapy; RTX = Radiotherapy; KL-6 = sialylated carbohydrate antigen KL-6; SP-D = Surfactant Protein D; LDH = Lactate Dehydrogenase; DLCO = Carbon Monoxide Diffusing Capacity; Sq = Squamous cell carcinoma; COPD = Chronic Obstructive Pulmonary Disease; DM = Diabetes Mellitus

rate was about 0.9% (248 patients died after the operation), 63 of 248 patients (25.4%) died of interstitial pneumonia, including AEIP. Additionally, 157 patients suffered from AEIP during hospitalization.

Shintani [14] reported that six of 40 patients (15.0%) with IIP had AEIP after the operation and 5/6 died of respiratory failure at POD 47 on average (range 17–95 days)., six of 40 patients (15.0 %) with IIP had AEIP after the operation and 5/6 died of respiratory failure at POD 47 on average (range 17–95 days). We reported that 4 of the 56 patients (7.1%) developed postoperative AEIP, and all of them died of respiratory failure within 42 days after the operation despite immunosuppression with pulse doses of methylprednisolone [15]. Previous reports [16-18] demonstrated that the incidence of postoperative AEIP ranged from 0% to 20.8%, mortality after pulmonary resection from 8.3% to 22.9%, and mortality after occurrence of AEIP from 33.3% to 100%.

RISKS OF AEIP

Our previous single institutional study demonstrated no observed predictive risks of postoperative AEIP after lung resection for primary lung cancer with IPF [15]. The risks, which have been reported in the literatures, are shown in Table 8 [19]. However, these reports, including our previous report, are single institutional studies with small number of patients with IIP ranging from 24 to 54. Generally, the incidence of postoperative complications associated with video-assisted thoracoscopic surgery (VATS) seems low, although the use of VATS could not prevent AE of usual interstitial pneumonia (UIP) [20]. Takahashi [21] reported that both SP-A and SP-D concentrations were significantly correlated with the extent of alveolitis (a reversible change), but not with the progression of fibrosis (an irreversible change). The SP-D concentration, unlike that of SP-A, was also related to the extent of parenchymal collapse and the rate of deterioration per year in pulmonary function. The level of SP-D might be able to show accurate information on the presence of alveolitis, as one of the pathological risks for AEIP, than KL-6 or SP-A. In this study, SP-D was initially considered a risk predictor of AEIP; however, even the high serum level did not correlate with the occurrence of AEIP. Recent report shows that the increase in a-defensins [22] in the peripheral blood and lung or circulating fibrocytes [23] may suggest their use as biomarkers for AEIP because the changes in level are observed before the occurrence of AEIP. Future research on a-defensins or circulating fibrocytes as potential risk factor for the occurrence of postoperative AEIP might be useful.

Methods to decrease incidence of postoperative AEIP

Surgical approaches, such as conventional thoracotomy, muscle sparing thoracotomy, and Video assisted thoracoscopic surgery have no effect on the occurrence of postoperative AEIP [2]. Some unknown or potential etiologic agents of AEIP might be induced by pulmonary resection or some factors related to pulmonary resection, such as selective lung ventilation and manipulation of the ipsilateral lung. If radical oxygen toxicity can be further proven to be associated with the occurrence of AEIP, Misthos [24] recently reported this interesting theory. The authors revealed the following results: (1) Lung re-expansion after One-Lung Ventilation (OLV) provoked severe oxidative stress. (2) The degree of generated oxygen-derived free radicals was associated with the duration of OLV. (3) Patients with lung cancer had a higher production of oxygen-derived free radicals

Table 7: Surgically related data.

Variables	AEIP (+)	(n=9)	AEIP (-)	(n=240)	P-value
OPT (min)	228±36		222±103		0.857
Blood loss (ml)	335±335		245±446		0.551
Blood transfusion	0		10		>0.999
VATS	6		196		0.37
WR	2		43		0.667
SLR	3		59		0.694
UMND	6		142		0.742

OPT = Operation Time; VATS = Video-Assisted Thoracoscopic Surgery; WR = Wedge Resection; SLR = Sublobar Resection; UMND = Upper Mediastinal Node Dissection; AEIP = Acute Exacerbation of Interstitial Pneumonia

Table 8: The risk predictors of the postoperative AEIP.

Authors	Published year	No. of IIP patients	Risks of postoperative AEIP
Kumar [2]	2003	24	Lo DLco, Low Kco, High CPI
Koizumi [20]	2004	47	PS>2, CRP>2 mg/dl, LDH>400 IU/L,,%TLC<95%
Okamoto [18]	2004	20	Restrictive change of PFT, LowDLco
Kushibe [19]	2007	33	VC < 80%
Watanabe [15]	2008	54	None
Shintani [14]	2010	40	%VC (<80.6%) and LDH (≥241 IU/L)

K_{co} = Levels of carbon monoxide diffusion capacity corrected for alveolar volume
CPI = Composite Physiological Index; PS = Performance Status; TLC = Total Lung Capacity;
DLCO = Diffusing capacity of the lung for Carbon monoxide

than the normal population. (4) Tumor resection removed a large oxidative burden from the organism. (5) Mechanical ventilation and surgical trauma were weak free radical generators. (6) Manipulated lung tissue was also a source of oxygen-derived free radicals, not only intraoperatively, but also for several hours later. These results indicate that shortening the duration of OLV and avoiding manipulation of lung tissue may inhibit the occurrence of AEIP resulting from oxygen-derived free radicals. Some free radical scavengers capable of inhibiting oxidative injury can be potentially produced as drugs for the treatment of AEIP due to intraoperative oxidative lung injury.

No drug that can decrease the incidence of postoperative AEIP has been established. A few studies reported that steroid, pirfenidone [25], and anticoagulants [26] reduce the occurrence of AEIP in patients with IPF. However, regarding postoperative AEIP, so far, no researchers have reported on a drug that can prevent or decrease the occurrence. Thus, thoracic surgeons use some drugs reported to reduce the incidence of AEIP or slow the deterioration of IPF, such as macrolides [27,28] N-acetylcysteine [29,30], proteinase inhibitor [31,32], and pirfenidone [33,34]. The effect of these drugs in decreasing the incidence of postoperative AEIP remains unclear; therefore, multi-institutional randomized controlled study should be planned in order to determine the effect of these drugs.

Treatment of postoperative AEIP

Although most patients with non-postoperative AEIP have been treated with regimens that include high-dose corticosteroids [35], the vast majority shows only partial and temporary improvement. In postoperative AEIP, most of the patients were treated with similar regimens. The effect remains controversial and unclear. Some investigators have even suggested that mechanical ventilation does not benefit idiopathic pulmonary fibrosis patients presenting with acute respiratory failure [36]. Yokoyama and associates [37] suggest that non-invasive ventilation can be a possible option for the management of acute respiratory failure in patients with AEIP.

Some studies reported that immunosuppressive agents, such as Cyclosporine A [38] and cyclophosphamide [39], improve the prognosis of AEIP. However, Okamoto [18] reported that patients with AEIP under methylprednisolone pulse therapy in combination with cyclophosphamide or cyclosporine A did not significantly improve the outcome of AEIP. In conclusion, there is little evidence that currently accepted treatments are effective in AEIP. Further studies are needed to clarify the pathogenesis and establish preventive measures for AEIP. On the other hand, there are some reports on the effect of hemoperfusion on AEIP. The study by Seo [40] showed that six patients with AEIP underwent polymyxin B-immobilized fiber column (PMX) hemoperfusion treatment. In four of six patients, the alveolar-arterial difference of oxygen, serum KL-6, and lactate dehydrogenase level improved after PMX treatment. These four patients were successfully weaned from mechanical ventilation and survived more than 30 days after the initial PMX treatment. However, this study involved a small number of patients and/or the absence of randomization. A randomized controlled study will be more factual.

Limitation

The retrospective non-randomized study and the small number of patients, who developed postoperative AEIP (N=9), are the study limitations. Data on DLCO and SP-D are obtained from not all patients. Furthermore, multi-institutional study entails differences in surgical procedure, peri-operative management, and treatment regimen of AEIP among institutions. These factors may provide some biases.

CONCLUSION

This study did not reveal any clinical risk factors for the occurrence of postoperative AEIP. Postoperative AEIP induces high mortality in patients with lung cancer and concomitant IIP. Multi-institutional randomized prospective study is required in order to reveal the risks, preventive methods, and treatments of postoperative AEIP.

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