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PREOPERATIVE PULMONARY FUNCTION AS A PREDICTOR OF RESPIRATORY COMPLICATIONS AND MORTALITY IN PATIENTS UNDERGOING LUNG CANCER RESECTION

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Abstract: *Objective*: We evaluated preoperative pulmonary function as a predictor of respiratory complications and mortality in patients undergoing lung cancer resection to confirm the guideline of the British Thoracic Society: lung cancer surgery in patients with predictive postoperative $FEV_{1.0}$ ($\%FEV_{1.0}ppo$)>40% and predictive postoperative diffusion capacity for carbon monoxide ($\%DL_{CO}ppo$)>40% can be carried out with average risk.

Methods: We retrospectively studied 356 consecutive patients who underwent pulmonary resection at our Department from January 1992 to December 2001. Preoperative pulmonary function tests included vital capacity (VC), %VC, forced expiratory volume in one second ($FEV_{1.0}$), $FEV_{1.0}\%$, diffusion capacity for carbon monoxide (DL_{CO}), predictive postoperative $FEV_{1.0}$ ($FEV_{1.0}ppo$), postoperative respiratory function expressed as a percentage of the predicted normal value ($\%FEV_{1.0}ppo$, $\%DL_{CO}ppo$). Postoperative complications were divided into 2 groups: respiratory complications (pneumonia, atelectasis, etc) and other complications (bronchopleural fistula, prolonged air leak, arrhythmia, etc).

Results: Postoperative deaths occurred in 14 (3.9%) patients. Postoperative respiratory complications developed in 27 (7.6%) patients. Pneumonectomy ($p<0.001$), preoperative chemotherapy ($p<0.01$) and advanced stage ($p<0.05$) were identified as risk factors of postoperative deaths.

Patients undergoing lobectomy with $FEV_{1.0}\geqq 1{,}500$ ml did not die of respiratory complications. Patients undergoing pneumonectomy with $FEV_{1.0}ppo\geqq 800$ ml/m^2 did not die of respiratory complications. Patients undergoing pneumonectomy with $\%FEV_{1.0}ppo<40\%$ and $\%DL_{CO}ppo<40\%$ did not survive. Five of the 7 patients who died of respiratory complications were treated with preoperative chemother-

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apy. The values of their %DL_{CO}ppo were all less than 40%. By multivariate analysis, %$FEV_{1.0}$ppo was significant independent factor associated postoperative death.

Conclusions: We conclude that the guideline is useful for the selection for surgery of lung cancer patients. If preoperative chemotherapy is performed, the measurement of %DL_{CO} is recommended before surgery.

Key words: lung cancer, lung resection, pulmonary function, respiratory complication, mortality

INTRODUCTION

Lung cancer often occurs in elderly people or smokers who are frequently associated with the respiratory diseases such as pulmonary emphysema or fibrosis. Many of the patients are found at the advanced clinical stage, so preoperative chemotherapy or pneumonectomy are sometimes needed. It is important to consider the risk of lung resection for respiratory insufficiency patients.

The British Thoracic Society and the Society of Cardiothoracic Surgeons of Great Britain and Ireland produced the recommendations[1] for the selection for surgery of lung cancer patients. The guideline states that the patients with predictive postoperative $FEV_{1.0}$ (%$FEV_{1.0}$ppo)>40% and predictive postoperative diffusion capacity for carbon monoxide (%DL_{CO}ppo)>40% can be carried out with average risk, but the patients with %$FEV_{1.0}$ppo<40% and %DL_{CO}ppo<40% have a higher risk of postoperative complications.

We studied the postoperative respiratory complications and mortality from the point of preoperative pulmonary function in patients who underwent lung cancer resection and we confirmed the guideline.

MATERIALS AND METHODS

We performed thoracotomy on 372 consecutive patients with primary lung cancer at our Department from January 1992 to December 2001. Sixteen patients who underwent segmentectomy or partial resection of the lung were excluded from the study. Therefore, 356 patients are included in the present study.

Preoperative pulmonary function tests included vital capacity (VC), forced vital capacity (FVC), $FEV_{1.0}$, DL_{CO}. The percent vital capacity (%VC) was a percentage of the actual VC over calculated standard value using the formula of Baldwin *et al*[2]. $FEV_{1.0}$ percent ($FEV_{1.0}$%) was expressed by $FEV_{1.0}/FVC\times100$. Percent DL_{CO} was a percentage of actual DL_{CO} over calculated standard value using the formula of Nishida[3]. Normal DL_{CO} for men=$(20.6-0.086\times age)\times height/100$, and for women=$(15.9-0.038\times age)\times height/100$. Values of DL_{CO} were obtained in 273 patients

(76.7%).

Contralateral $FEV_{1.0}$ was calculated by the formula: contralateral $FEV_{1.0} = A \times FEV_{1.0} \div$ body surface area (BSA). Predictive postoperative $FEV_{1.0}$ ($FEV_{1.0}$ppo) and $\%DL_{CO}$ ($\%DL_{CO}$ppo) were calculated by the formula[4]: $Fppo = \{A + [1 - (b-n)/(C-n)] \times (1-A)\} \times F$, where F is the value of $FEV_{1.0}$ or $\%DL_{CO}$ before operation, b is the number of subsegments of the resected lung lobe, and n is the number of subsegments obstructed by the tumor, which was assessed by the findings on the chest computed tomography, bronchofiberscopy, or a combination of them. C is the total number of subsegments of the affected lung: 22 branches in right and 20 branches in left. A is the fraction of perfusion obtained by quantitative pulmonary scintigraphy to the unaffected lung.

Postoperative $FEV_{1.0}$ expressed as a percentage of the predicted normal value ($\%FEV_{1.0}$ppo) was calculated by the formula: $\%FEV_{1.0}ppo = FEV_{1.0}ppo/normal\ FEV_{1.0} \times 100$. The formula of Berglund was applied to calculate the normal $FEV_{1.0}$. Normal $FEV_{1.0}$ for men $= 34.4 \times height - 33 \times age - 1{,}000$, and for women $= 26.7 \times height - 27 \times age - 540$.

Postoperative complications were divided into 2 groups: respiratory complications and other complications. Respiratory complications were determined as follows[5]: (1) atelectasis where more than two sessions of sputum aspiration were required using a bronchoscope; (2) respiratory failure requiring artificial ventilation for more than 48 hours; (3) pneumonia with temperatures higher than 38°C, leucocytosis (more than 10,000/mm^3) and pneumonia findings on chest roentgenograms. The other complications were as follows: arrhythmia, prolonged air leak, pyothorax, bronchopleural fistula, chylothorax, myocardial infarction, pulmonary embolism, recurrent laryngeal nerve palsy, bleeding from gastric ulcer, etc. Prolonged air leak, pyothorax and bronchopleural fistula were not included in respiratory complications, because these complications can develop as a result of surgical technique. Prolonged air leak was defined as the air leak prolonged more than 7 days. Postoperative deaths included both patients who died within 30 days after operation and those who died later but during the same hospitalization.

The significance of the differences between those who did and those who did not experience postoperative complications was determined by the χ^2 test or by Fischer's exact test when the expected cell count was less than 5. Uni-and multivariate analysis of the logistic regression model was used for analysis of the contribution of each variable to postoperative death. A probability value <0.05 was accepted as statistically significant. Statistical analysis was performed on a personal computer with Stat View ver. 5.0 software (SAS Institute, Cary, NC, USA).

RESULTS

Data regarding patient characteristics as well as surgical procedure and cancer stage are shown in Table 1. Lymph node clean up, pathological TNM staging were

Table 1. Characteristics of 356 patients who underwent lung resection

Characteristic	No. of Patients	%
Age		
Mean±SD	64.8±8.8	
Range	34-87	
Sex		
Male	244	68.5
Female	112	31.5
Preoperative chemotherapy		
Yes	33	9.3
Type of operation		
lobectomy	321	90.2
pneumonectomy	35	9.8
ND		
0	3	0.8
1	81	22.8
2	245	68.8
3	27	7.6
pT		
0, is	8	2.2
1	147	41.3
2	116	32.6
3	30	8.4
4	55	15.4
pN		
0	209	58.7
1	51	14.3
2	79	22.2
3	17	4.8
p-stage		
0	6	1.7
I	164	46.1
II	47	13.2
III	126	35.4
IV	13	3.7

divided according to the general rule for clinical and pathological record of lung cancer[6]. Pneumonectomy was performed in 35 patients, lobectomy in 321 (two lobes were removed in 21 patients).

Postoperative complications developed in 157 (44.1%) patients: respiratory complications in 27 (7.6%) and other complications in 130 (36.5%). The morbidity of postoperative complications in pneumonectomy was significantly higher than that in lobectomy ($p<0.01$). Bronchopleural fistula developed in 14. The morbidity of bronchopleural fistula in pneumonectomy was significantly higher than that in lobectomy ($p<0.0001$) (Table 2). Preoperative chemotherapy ($p<0.001$) and male ($p<0.05$) were identified as risk factors for postoperative respiratory complications

Table 2. Complications occurring in 356 patients after lung resection

	All cases			Lobectomy			Pneumonectomy		
	$n=356$		%	$n=321$		%	$n=35$		%
Any complications	157	(14)	44.1	134	(7)	41.7	23	(7)	65.7
Respiratory	27	(7)	7.6	23	(3)	7.2	4	(4)	11.4
Atelectasis	17		4.8	17		5.3			
Pneumonia	13		3.7	10		3.1	3		8.6
Expectoration disorder	10		2.8	8		2.5	2		5.7
Interstitial pneumonia	3		0.8	2		0.6	1		2.9
Respiratory failure	2		0.6	2		0.6			
Asthma attack	2		0.6	2		0.6			
Others	130	(7)	36.5	111	(4)	34.6	19	(3)	54.3
Arrhythmia	70		19.7	61		19.0	9		25.7
Prolonged air leak	42		11.8	42		13.1			
Pyothorax	19		5.3	17		5.3	2		5.7
Bronchopleural fistula	14		3.9	6		1.9	8		22.9
Chylothorax	9		2.5	9		2.8			
Myocardial infarction	2		0.6	2		0.6			
Pulmonary embolism	2		0.6	1		0.3	1		2.9

Values in parentheses are number of patients of postoperative death.

Table 3. Clinical correlates of respiratory complications and postoperative death

	No. of Patients	Respiratory Complications	(%)	p	Postoperative Death	(%)	p
Age							
≧70	125	14	11.2	0.06	7	5.6	0.23
<70	231	13	5.6		7	3.0	
Sex							
Male	244	24	9.8	<0.05	13	5.3	0.07
Female	112	3	2.7		1	0.9	
Preoperative chemotherapy							
Yes	33	9	27.3	<0.001	5	15.2	<0.01
No	323	18	5.6		9	2.8	
Pneumonectomy							
Yes	35	4	11.4	0.37	7	20.0	<0.001
No	321	23	7.2		7	2.2	
ND							
0, 1	84	8	9.5	0.44	4	4.8	0.75
2, 3	272	19	7.0		10	3.7	
p-stage							
0, I, II	217	12	5.5	0.07	4	1.8	<0.05
III, IV	139	15	10.8		10	7.2	

(Table 3).

Postoperative deaths occurred in 14 (3.9%) patients. Seven patients died of respiratory complications: pneumonia (5), interstitial pneumonia and expectoration disorder (1). Five of the 7 patients who died of respiratory complications had been

received preoperative chemotherapy. Four of the 7 patients who underwent pneumonectomy after preoperative chemotherapy died of respiratory complications.

Seven patients died of other complications: bronchopleural fistula (5), pulmonary embolism and pyothorax (1) respectively. Four of the 5 patients who died of bronchopleural fistula were above pathological stage three. Deaths due to bronchopleural fistula were patients who underwent pneumonectomy (2) (including wedge pneumonectomy (1)), wedge lobectomy (1) and bilobectomy (1). The patients treated with preoperative chemotherapy were not included among the patients who died of bronchopleural fistula. Pneumonectomy ($p<0.001$), preoperative chemotherapy ($p<0.01$) and advanced lung cancer ($p<0.05$) were identified as risk factors for postoperative deaths (Table 3).

The mortality rate was 31.3% (5/16) in right pneumonectomy and 10.5% (2/19) in left. The mortality rate in pneumonectomy after preoperative chemotherapy was 36.4% (4/11); 50% (3/6) in right and 20% (1/5) in left. But there was no statistical significance.

In patients who underwent lobectomy, three patients died of respiratory complications. All 3 were $FEV_{1.0}<1,500$ ml. No patients with $FEV_{1.0}>1,500$ ml died of respiratory complications. Causes of the postoperative deaths of the patients whose $FEV_{1.0}$ was more than 1,500 ml were bronchopleural fistula (3) and pyothorax (1).

Fig. 1 shows the $\%FEV_{1.0}ppo$ in lobectomy patients who were divided into 4 groups: no complication, survivor with respiratory complications, death with respiratory complications and death without respiratory complications. One of the 8 patients with $\%FEV_{1.0}ppo<40\%$ died of respiratory complications.

Fig. 2 shows the relationship between $\%FEV_{1.0}ppo$ and $\%DL_{CO}ppo$ in lobectomy

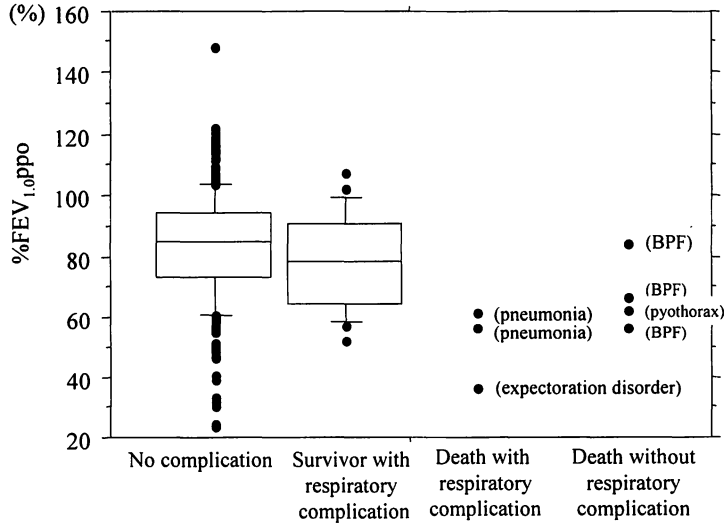

Fig. 1. $\%FEV_{1.0}ppo$ in patients who underwent lobectomy (n=321). Disease in parentheses is cause of postoperative death. BPF, bronchopleural fistula.

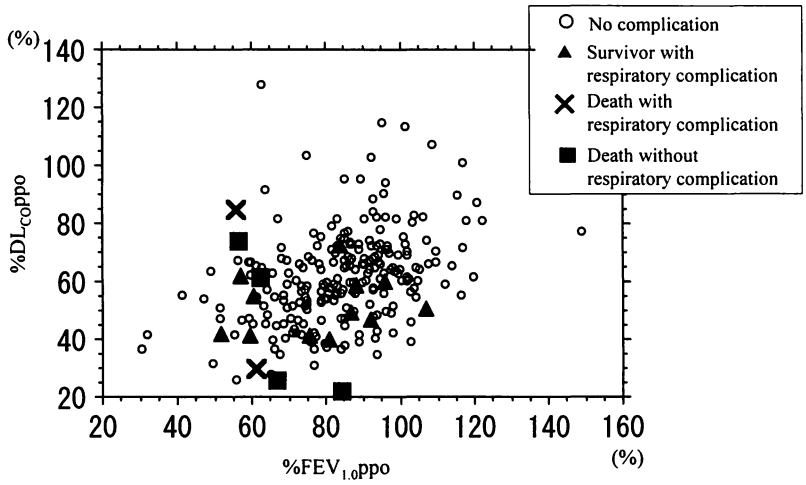

Fig. 2. $\%FEV_{1.0}ppo$ vs. $\%DL_{co}ppo$ in patients who underwent lobectomy (n=250).

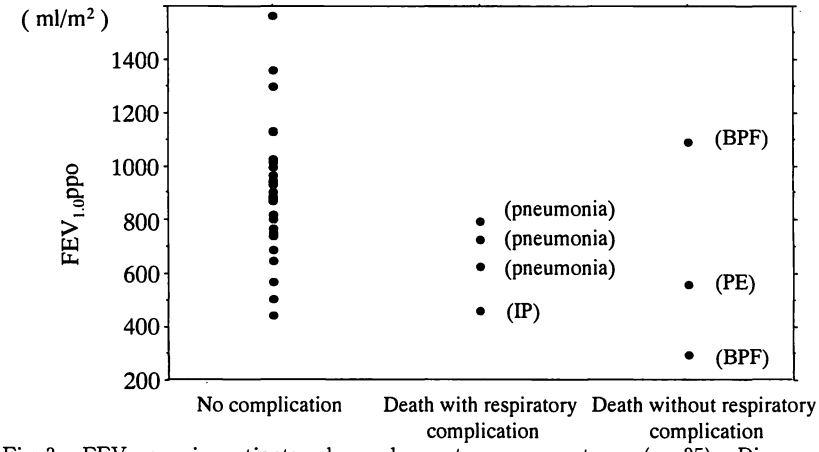

Fig. 3. $FEV_{1.0}ppo$ in patients who underwent pneumonectomy (n=35). Disease in parentheses is cause of postoperative death. BPF, bronchopleural fistula; PE, pulmonary embolism; IP, interstitial pneumonia.

patients. Among the 19 patients with $\%FEV_{1.0}ppo > 40\%$ and $\%DL_{co}ppo < 40\%$, one patient who had preoperative chemotherapy died of pneumonia and two patients died of bronchopleural fistula. One of the 229 patients with $\%FEV_{1.0}ppo > 40\%$ and $\%DL_{co}ppo > 40\%$ died of respiratory complications.

Fig. 3 shows the $FEV_{1.0}ppo$ in pneumonectomy patients who were divided into 3 groups: no complication, death with respiratory complications and death without respiratory complications. One patient with $FEV_{1.0}ppo \geqq 800\ ml/m^2$ died of bronchopleural fistula. But no patients with $FEV_{1.0}ppo \geqq 800\ ml/m^2$ died of respiratory complications.

Fig. 4 shows the relationship between $\%FEV_{1.0}ppo$ and $\%DL_{co}ppo$ in

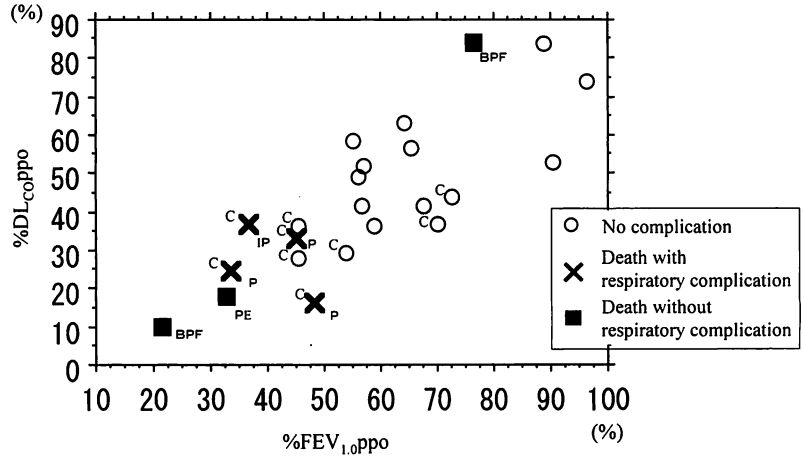

Fig. 4. $\%FEV_{1.0}ppo$ vs. $\%DL_{co}ppo$ in patients who underwent pneumonectomy (n=23). C at upper left of the mark shows patient who was treated with preoperative chemotherapy. Disease at lower right of the mark shows cause of postoperative death. BPF, bronchopleural fistula; PE, pulmonary embolism; P, pneumonia; IP, interstitial pneumonia.

pneumonectomy patients. All 4 with $\%FEV_{1.0}ppo<40\%$ and $\%DL_{co}ppo<40\%$ died of postoperative complications. The causes of death of the 4 patients were pneumonia after preoperative chemotherapy, interstitial pneumonia after preoperative chemotherapy, bronchopleural fistula and pulmonary embolism. Two of the 7 patients who underwent pneumonectomy with $\%FEV_{1.0}ppo>40\%$ and $\%DL_{co}ppo<40\%$ died of pneumonia after preoperative chemotherapy. One of the 12 patients who underwent pneumonectomy with $\%FEV_{1.0}ppo>40\%$ and $\%DL_{co}ppo>40\%$ died of bronchopleural fistula.

Univariate analysis indicated that the factors related significantly to postoperative death following lung resection were preoperative chemotherapy, operation procedure (lobectomy vs. pneumonectomy), *p*-stage (I, II vs. III, IV), %VC, $FEV_{1.0}$, $\%DL_{co}$, contralateral $FEV_{1.0}$, $\%FEV_{1.0}ppo$ and $\%DL_{co}ppo$ (Table 4). Age, sex, extent of lymph node resection, VC and $FEV_{1.0}\%$ were unrelated to postoperative death.

In multivariate analysis, $\%FEV_{1.0}ppo$ ($p=0.0131$; relative risk, 0.938; 95% confidence interval, 0.892-0.987) was significant independent factor associated postoperative death, whereas preoperative chemotherapy ($p=0.8648$), operation procedure ($p=0.2886$), *p*-stage ($p=0.1133$), %VC ($p=0.2359$) and $\%DL_{co}ppo$ ($p=0.4912$) were not significant independent factors.

Pulmonary function tests before and after preoperative chemotherapy were studied in 26 of 33 patients who had preoperative chemotherapy. Most of the patients were treated with 2 courses of preoperative chemotherapy. Eight patients were treated with a combination chemotherapy consisting of cisplatin and vindesine. Seven patients were treated with cisplatin, vindesine and mitomycin C. Four

Table 4. Univariate analysis of perioperative variables contributing occurrence of postoperative death following lung resection

Variable	p	Relative Risk	95% CI
preoperative chemotherapy (− vs +)	0.002	6.230	1.954～19.867
lobectomy vs pneumonectomy	<0.0001	11.214	3.671～34.260
p-stage (I, II vs III, IV)	0.0185	4.128	1.268～13.435
%VC	0.0015	0.946	0.914～0.979
$FEV_{1.0}$	0.0494	0.999	0.998～1.000
$\%DL_{CO}$	0.0017	0.949	0.918～0.980
contralateral $FEV_{1.0}$	0.0489	0.997	0.995～1.000
$\%FEV_{1.0}ppo$	<0.0001	0.925	0.897～0.955
$\%DL_{CO}ppo$	<0.0001	0.920	0.883～0.959

CI: confidence interval

patients were treated with cisplatin and etoposide. Seven patients were treated with other drugs. Preoperative chemotherapy had adverse effect on $\%DL_{CO}$. The average value of $\%DL_{CO}$ was 71±11% before chemotherapy and 60±10% after chemotherapy. The decrease was significant ($p<0.01$). One patient with $\%DL_{CO}<40\%$ before right lower lobectomy and two patients with $\%DL_{CO}<45\%$ before pneumonectomy died of respiratory complications.

DISCUSSION

Lobectomy and pneumonectomy are consistently described with mortality rates of 2-4% and 6-8%, respectively. Mortality rates following resection should not be in excess of 4% for lobectomy or 8% for pneumonectomy[1]. In the present study, the mortality rate was 3.9%.

Data from more than 2,000 patients in the 1970s have shown that a mortality rate of under 5% should be expected if the preoperative $FEV_{1.0}$ is >1.5 liters for a lobectomy and >2 liters for a pneumonectomy[7]. There is substantial evidence that the perioperative risks of resection are related to the absolute predicted postoperative $FEV_{1.0}$ and the postoperative $FEV_{1.0}$ expressed as % predicted[8].

The DL_{CO} reflects the capillary surface area available for gas diffusion across the alveolus and thus indicates the lung's ability to oxygenate blood. A reduction in DL_{CO} is a predictor of respiratory complications after pulmonary resection. The DL_{CO} may act as an independent variable with respect to other pulmonary function tests[9]. A low preoperative DL_{CO} predicts not only respiratory complications but also poor postoperative quality-of-life[10].

In the present study, postoperative respiratory complications were related to $\%FEV_{1.0}ppo$ or $\%DL_{CO}ppo$. This relation was remarkable in patients who underwent pneumonectomy. The postoperative complications other than respiratory complications were also related to $\%FEV_{1.0}ppo$ or $\%DL_{CO}ppo$. For example, bronchopleural fistula was not involved in respiratory complications in the present

study, but the most significant risk factor for bronchopleural fistula is respiratory complications necessitating ventilation[11]. Our study showed that 2 of the 5 patients who died of bronchopleural fistula had experienced ventilation.

Pneumonectomy with $FEV_{1.0}ppo \geqq 800\ ml/m^2$ can be carried out with average risk. If a patient with $FEV_{1.0}ppo \leqq 800\ ml/m^2$ is candidate for pneumonectomy, the unilateral pulmonary artery occlusion (UPAO) test is recommended, for cardiopulmonary failures sometimes occur after pneumonectomy. Calculation of the total pulmonary vascular resistance index (TPVRI) is as follows: TPVRI=(average pulmonary artery pressure/cardiac output/BSA)$\times$80 dyne$\cdot$sec$\cdot$cm^{-5}. If the TPVRI is <500 dyne $\cdot$ sec $\cdot$ cm^{-5}, pneumonectomy can be carried out with average risk. But if the TPVRI is <700 dyne $\cdot$ sec $\cdot$ cm^{-5}, there is a higher risk of postoperative complications after pneumonectomy. But we must be aware that preoperative evaluations of TPVRI from the UPAO tests sometimes overestimate the right ventricular afterload[12].

But patients should not be excluded from pneumonectomy on the basis of any single criterion. Rather, the use of preoperative studies including predicted postoperative pulmonary function might assist the surgeon in better selecting patients who will potentially benefit from pneumonectomy[13]. Surgery need not be denied on the basis of a low $FEV_{1.0}ppo$. Cutoff values indicate the need for further examination (exercise testing) rather than inoperability[14].

In the present study, 5 of the 7 patients who died of respiratory complications after pulmonary resection had preoperative chemotherapy. The values of the $\%DL_{CO}ppo$ of the 5 patients who died were less than 40%. Some of the anti-cancer agents cause alveolitis, interstitial pneumonitis and fibrosis. The mechanism of injury may relate to vascular or endothelial injury, mediated at least in part by free radical oxygen formed during intracellular reductive activation of the compound under aerobic conditions[15]. As a result of that, the values of $\%DL_{CO}$ decrease. Patients whose $\%DL_{CO}$ before final therapy was reduced $>10\%$ from their individual baseline values, often develop toxicity after the final therapy[16]. If preoperative chemotherapy is performed, the measurement of $\%DL_{CO}$ is recommended after the chemotherapy.

For pulmonary insufficient patients, the cessation of smoking, pulmonary rehabilitation, the inhalation of bronchodilator and cleaning an airway are recommended before operation. Pulmonary rehabilitation that improves the peak expiratory flow and the maximal voluntary ventilation is useful for patients with obstructive pulmonary diseases. During operation, aspiration of airway products is needed. After operation, care not to overhydrate, pain control using epidural anesthesia and getting out of bed early are important for the prevention of respiratory complications.

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