Original Article

Video-Assisted Thoracic Surgery for Patients with Lung Cancer and Interstitial Pneumonia

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Purpose: A serious complication following primary lung cancer surgery on patients with interstitial pneumonia (IP) is the postoperative acute exacerbation of IP. Because few studies have examined the feasibility of using video-assisted thoracic surgery (VATS) on these patients, we reviewed our experience with this technique.
Methods: We examined 78 patients; 11 had IP (IP group) and 67 did not (non-IP group).
Results: Patients in the IP group were older than those in the non-IP group (p = 0.097), and they had a significantly higher incidence of squamous cell carcinoma than patients in the non-IP group (p = 0.002). Dominating the IP group, though not statistically significant, were males, the intention to undergo VATS, and limited surgery. VATS was performed on 10 lesions in the IP group and on 45 in the non-IP group. No surgery-related exacerbation of preoperative IP or development of postoperative IP was found in either group.
Conclusion: VATS is the preferred surgical choice for lung cancer patients with IP. (Ann Thorac Cardiovasc Surg 2010; 16: 236–241)

Key words: interstitial pneumonia, lung cancer, video-assisted thoracic surgery, KL-6

Introduction

Pulmonary fibrosis (PF) is associated with an increased risk of lung cancer and has a relative risk of 7.3 to 14.1 compared to the general population.[1,2] Furthermore, lung cancer is the cause of death in up to 10% of patients with PF.[1]

Postoperative acute exacerbation of interstitial pneumonia (IP) is a serious complication following surgical treatment for primary lung cancer with IP. Postoperative morbidity and mortality rates in patients with lung cancer have decreased with advances in perioperative management, and the overall morbidity and mortality rates after surgical treatment for lung cancer have been reported to range from 17% to 47% and 0.9% to 7.7%, respectively.[3] However, patients with idiopathic pulmonary fibrosis (IPF) have a high risk of complications and death. The overall morbidity and mortality rates after lung biopsy for interstitial lung disease have been reported to range from 15% to 19.1% and 3% to 8.5%, respectively.[4–6] Video-assisted thoracic surgery (VATS) is the preferred technique for lung biopsy in patients with PF because it is associated with less morbidity, shortened duration of chest tube drainage, and reduced length of hospital stay, compared with patients who undergo open lung biopsies.[7]

During the past 15 years, VATS has been used for the treatment of lung cancer, instead of traditional posterolateral thoracotomy, to minimize the extent of surgical intervention involving the chest wall. The application of VATS for the treatment of lung carcinoma is now spreading to many countries.[8,9]

VATS is now the first choice for treatment of patients

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Table 1. Characteristics of patients with IP or without IP**

Gender	IP (N = 11)	Non-IP (N = 67)	*p* -value
Male : Female	10 : 1	40 : 27	$p = 0.097$
Age			
Mean ± SD (years)	70.3 ± 12.6	65.0 ± 10.5	$p = 0.045$
Range (years)	36 – 83	33 – 82	
Histological type	(N = 12*)	(N = 68*)	
Sq / Ad + La[3*]	7* / 1 + 2*	9 / 35* + 7	$p = 0.002$
Metastasis	2	17	$p = 0.891$
Pathological stage (NSCLC)	(N = 10*)	(N = 51*)	
I + II / III + IV	6* + 3 / 1	33* + 10 / 7 + 0	$p = 0.865$
Operative method	(N = 12*)	(N = 68*)	
Pneu + Lob / Seg + Part[4*]	0 + 8* / 0 + 4*	1 + 46* / 6 + 14	$p = 0.521$
VATS (converted) / Thoracotomy	12* (2) / 0	48* (3) / 20	$p = 0.080$
Limited operation / standard	2 / 10	2 / 66	$p = 0.196$
Amount of operative bleeding (ml)	225 ±197	196 ± 248	$p = 0.547$
Duration of operation (min.)	264 ± 116	238 ± 88	$p = 0.421$
Postoperative hospitalization (days)	9.1 ± 2.1	8.4 ± 2.9	$p = 0.300$
Postoperative complications / no PC	0 / 11	6 / 61	$p = 0.584$

* double-cancer-treated simultaneous operation

** interstitial pneumonia

3* Ad: Adenocarcinoma; Sq: Squamous cell carcinoma; La: Largecell carcinoma

4* Pneu: pneumonectomy; Lob: lobectomy; Seg: Segmentectomy; Part: partial resection

with lung cancer in our hospital and has been adopted also for use with patients having both lung cancer and IP. Few studies, however, have documented the feasibility of VATS for such patients. Here we have compiled and reviewed our experience with VATS used in patients with both lung cancer and IP.

Materials and Methods

We conducted a retrospective cohort study of consecutive patients who underwent pulmonary resection for lung cancer at Jikei University Kashiwa Hospital from July 1, 2005, to May 31, 2008. The patients were categorized into 2 groups, those with preoperative IP (IP group) and those without preoperative IP (the non-IP group). These classifications were based on analyses of preoperative chest radiographs and computed tomography scans. In the IP group, there are nine primary lung cancers, one lung metastasis from breast cancer, and one lung metastasis from an extragonadal germ cell tumor.

Although there is no evidence relating IP exacerbation to a high concentration of oxygen administration, to prevent IP exacerbation we avoided administering high concentrations of oxygen by limiting the oxygen pressure to less than 100 mmHg during the perioperative period, and by ensuring early extubation of the tracheal and chest tubes and early ambulation postoperatively.[10] The IP patients were recommended a longer hospital stay to allow rapid detection of IP exacerbation. All patients except those with advanced lung cancer underwent VATS,[9] and for these procedures, a minithoracotomy incision of approximately 2 cm was made as an access port in the 4th intercostal space of the anterior axillary line. Four other stab wounds of approximately 2 cm each were made. The major vascular structures, the lober bronchus were divided by using endostaplers. The operative specimens were removed carefully from each wound after the wounds were extended to 4–5 cm without a rib retractor.[11,12] The thoracotomy incision was extended when necessary, either for palpation or retraction of the specimen. Conversion to thoracotomy was performed when an incision needed to be extended and a rib divided. Open procedures were done through posterolateral or lateral thoracotomy. Limited resection was defined as a segmental resection of a partial resection for patients with lung cancer equal to or exceeding 2 cm in size because of the high risk of the operation.

The data are reported as mean ± standard deviation. Statistical analyses of categorical data were performed using a Student's t-test. The differences were considered statistically significant when $p < 0.05$.

Table 2. Details of patients with IP and lung cancer who underwent surgery

No.	Age & gender	Disease	Preop.* KL-6	Postop.2* KL-6	Operative			Discharge (POD3*)	Prognosis	Other factors
					Procedure	Time (min.)	bleeding (ml)			
1	62, m5*	Sq- IB	–	–	Converted- lobectomy	375	510	8	Alive 11M	LN recurrence
2	75, m	Ad- IA	376	277	VATS4*-lobectomy	275	200	12	Alive 18M	
3	73, m	Sq- IIB	–	453	VATS-lobectomy	305	150	13	Alive 17M	
4	75, m	Sq- IIA	555	–	VATS-lobectomy	355	500	9	Dead 6M	Bone meatastasis
5	78, m	Sq- IB	690	433, 679	VATS-partial resection	185	0	6	Alive 13M	
6	72, m	La- IIA	432	279	Converted-bilobectomy	460	470	12	Alive 8M	Asbestos
7	36, m	Meta	381	–	VATS-partial resection	75	0	5	Alive 5M	Germ cell tumor
8	83, m	(1)Sq- IB (2)Sq- IA	896	542	VATS-lobectomy(1) VATS-partial resection(2)	265	100	9	Alive 2M	Double cancer
9	76, f6*	Meta	1650	732	VATS-lobectomy	206	150	9	Alive 1M	Breast cancer
10	81, m	Sq- IA	500	465	VATS-partial resection	70	0	8	Alive 1M	Lung colon, cancer
11	62, m	Sq- IIIA	308	206	VATS-lobectomy	335	400	9	Alive 1M	Rheumatoid arthritis

: preoperative; 2: postoperative; 3*: postoperative date; 4*: video-assisted thoracic surgery; 5*: male; 6*: female

Results

The preoperative characteristics of two groups of patients are shown in Table 1. Seven patients developed IPF for unspecified reasons (Table 2). Four patients developed IPF for specified reasons: 1 had a past history of asbestos exposure, another had rheumatoid arthritis, and the remaining 2 patients who were diagnosed with metastatic lung cancer developed IPF as a result of chemotherapy. Further, patients showed IP on preoperative computed tomography scans, and 2 showed it during chemotherapy. Patients in the IP group were older than those in the non-IP group ($p = 0.097$), and the incidence of squamous cell carcinoma was significantly higher in the former ($p = 0.002$). Males, the intention to undergo VATS, and limited surgery respectively dominated the IP group ($p = 0.097$, $p = 0.080$, $p = 0.196$), but the numbers were statistically insignificant. (Table 1).

In the IP group, all 12 lesions were scheduled for VATS, but the procedure was completed in 10 (6 lobectomies and 4 partial resections). An 83-year-old patient with two lung cancers underwent partial resection and a lobectomy because a bilobectomy was abandoned as a result of poor pulmonary function. A 78-year-old patient underwent limited resection for a nonsmall cell lung cancer (NSCLC) for the same reason. Two other lesions were resected after the conversion to lateral thoracotomy because of adhesions or lymph node metastasis. Preoperative and postoperative KL-6 were measured in 7 patients and found to be decreased after the operation (Table 2). The postoperative courses of IP patients were uneventful. In the non-IP group, 48 among 68 lesions were scheduled for VATS; 45 were treated as planned.

The degree of operative bleeding, duration of operation, and postoperative hospitalization of IP and non-IP groups were not significant between the two groups (225 ± 197 ml vs. 196 ± 248 ml, $p = 0.547$; 264 ± 116 min. vs. 238 ± 88 min., $p = 0.421$; 9.1 ± 2.1 days vs. 8.4 ± 2.9 days, $p = 0.300$) (Table 1). There was no surgery-related exacerbation of preoperative IP or development of postoperative IP.

Comments

There have been reports on patients having lung cancer with coexistent IP who underwent surgery for lung cancer. There also exist some controversies regarding the operative indications for such patients. Table 3 is a compilation of the reported data on postoperative mortality and morbidity in patients with and without IP. For patients with IP, the pulmonary complication rate, incidence of IP exacerbation, and mortality rate were 10%–41%, 0%–21%, and 0%–17%, respectively.[3,10,13–16] Kumar et al. reported 22 cases (24 operations) of patients with PF and NSCLC. They found that the incidence of operative mortality and postoperative lung injury was higher in patients with pulmonary fibrosis than in control patients (17% vs. 3.1%, $p<0.01$; 21% vs. 3.7%, $p < 0.01$).[13] Kawasaki et al. reported 53 cases of patients with IPF and lung cancer who underwent lobec-

Table 3. Postoperative mortality and morbidity in patients with IP* or without IP

Author		IP				Non-IP			
		total	Pulmonary complication	Pulmonary exacerbation	Mortality	total	Pulmonary complication	Pulmonary exacerbation	Mortality
2008 Akiba		8	0 %	0 %	0 %	61	9.8 % (6)	0 %	0 %
2005 Tanaka[10]		8	13% (1)	13% (1)	13% (1)				
2004 Okamoto[11]		20		20% (4)	15% (3)	81		3.7% (3)	2.5% (2)
2004 Koizumi[12]	total	47	41% (17)	15% (7)	4% (2)				
	PLT[2*]	15	53% (8)	13% (2)	7% (1)				
	MST[3*]	15	47% (7)	27% (4)	7% (1)				
	VATS[4*]	17	12% (2)	6% (1)	0%				
2003 Kumar[13]	total	24		21% (5)	17% (4)#	964		3.7% (36)	3.1% (30)
	Pneumonectomy	6		33% (2)	33% (2)#	215		6.0% (13)	5.1% (11)
	Lobecttomy	17		17% (3)	12% (2)#	695		3.1% (22)	2.6% (18)
	Partial resection	1		0%	0%	54		1.8% (1)	2.0% (1)
2003 Fujimoto[14]		21	10% (2)	0%	0%				
2002 Kawasaki[3]		53	26% (14)#	4% (2)	8% (4)#	658	9.1% (60)		0.8% (5)

#: significant than non-IP case; *: interstitial pneumonia; 2*: posteolateral thoracotomy; 3*: muscle-sparing thoracotomy;
4*: video-assisted thoracic surgery;
**: interstitial pneumonia.

tomies or partial or segmental resections of the lung, comparing them to patients without IPF who underwent pulmonary resections. The patients with IPF had greater postoperative pulmonary morbidity and mortality than those without it (26% vs. 9.1%, p <0.01; 8% vs. 0.8%, p < 0.01).[3] In our report, cases with IP experienced no subsequent complications or mortality. Our positive postprocedural results might be a direct reflection of the meticulous perioperative management, especially avoidance of the administration of high concentrations of oxygen.

Koizumi et al. compared three thoracic approaches in patients with IP and lung cancer: posterolateral thoracotomy, muscle-sparing thoracotomy, and VATS.[14] Although the incidence of postoperative respiratory complications in the VATS group was lower compared with the other two approaches, no significant difference was evident in the incidence of acute IP exacerbation in any of the three approaches.[14] Nevertheless, it was concluded that further trials are required for conclusive results.[14] And we experienced no instances of exacerbated IP following VATS. We suggest that VATS may in fact help prevent the exacerbation of IP as well as other pulmonary complications. The incidence of squamous cell carcinoma in patients with IPF (46%) was reported to be significantly higher than in patients without IPF (22%)[3]. The incidence of multiple lung cancers in patients with IPF (17%) was also significantly higher.[3] Moreover, the incidence of squamous cell carcinoma was also significantly higher in the IP group in the present report. One case underwent simultaneous tumor resection by VATS. When following the clinical course of patients with IP, we should not overlook the possibility of findingultiple cancers and second primary lung cancer. Fujimoto et al. reported 7 patients who were in clinical stage N2 or N3 with no evidence of metastasis in the upper mediastinum during mediastinoscopy. This discrepancy between clinical and pathological stages may have been due to swelling of the lymph nodes stemming from IPF-related persistent inflammation in the lung parenchyma.[16] One of our cases also with multiple cancers showed mediastinal lymph node swelling without lymph node metastasis. We suggest not abandoning surgery based solely on results from computed tomography, but instead confirming the lymph node status by mediastinoscopy or VATS.

With mortality rates ranging from 59% to 70% and a mean survival of 5 to 6 years, patients with IPF undoubtedly have a poor prognosis.[16] Exacerbation of IPF and an increased incidence of lung cancer account for leading causes of death in patients with IPF.[16]

Two-, three-, and five-year Kaplan–Meier survival rates of patients with IP and NSCLC after resection were reported to be 52%, 54%, and 43%, respectively (Table 4).[3,15,16] Kumar et al. reported that pulmonary resection for lung cancer in patients with PF is justified if the cases are selected appropriately.[15] Kawasaki et al. reported that the overall survival of patients with IPF was significantly lower than in those without it, and that death unrelated to lung cancer after surgery was significantly more frequent in

Table 4. Survival rate of patients with lung cancer who underwent surgery with IP* or without IP

Author		Number of cases	Survival rate	Total deaths	Cause of death	
					Cancer	Non-cancer
2002 Kawasaki[3]	IP -surgery	53	5 -years, 43%	23	65% (15)	35% (8)
	non IP -surgery	658	5 -years, 64%	199	82% (164)	18% (35)
2003 Kumar[13]	IP -surgery	22**	3 -years, 54%	7	29% (2)	71% (5)
2003 Fujimoto[14]	IP- surgery	21	2 -years, 52%	16	44% (7)	56% (9)
	non IP -surgery	43	2 -years, 17%	35	49% (17)	51% (18)

*: interstitial pneumonia; **: 24 operations

patients with IP than in those without it; however, disease-free survival was similar in both groups.[3] They concluded that the survival rate of patients with IPF was lower because of pulmonary complications; therefore careful preoperative evaluation and postoperative management are crucial for achieving optimal surgical outcome in patients with lung cancer and IPF.[3]

Reports opposing chest wall resection and pneumonectomy are based on small sample sizes. They find the incidence of pulmonary exacerbation for pneumonectomy and lobectomy to be 33% and 17%, respectively.[15] These reports emphasize that surgeons should consider not only whether to operate, but also whether surgical resection will improve the long-term prognosis and quality of life for these patients.[15,16]

According to research on the postoperative exacerbation of IP, male smokers with poorly differentiated squamous carcinoma, serum C-reactive protein, high white blood cell count, serum lactate dehydrogenase, exertion dyspnea (Hugh–Jones classification), and total lung capacity are all strong preoperative risk factors.[13,14] Levels of serum KL-6, a mucinlike high-molecular-weight glycoprotein, have been shown to increase during the active stage of IP[17]; thus it was used as an indicator for this disease. KL-6 is mainly produced in the distal airway epithelium, specifically in the alveolar type II or bronchiolar epithelial cells.[17] Serum KL-6 levels were reported to decrease by 36% a week after lobectomy, but returned to preoperative levels 2 months postoperatively.[17] Our data also showed a decrease in KL-6 levels after lung cancer resection, but in contrast to previous reports, KL-6 was not restored to its preoperative levels. We believe that further investigation is required to elucidate the changes in serum KL-6 measurements.

According to our experiences, VATS for patients with lung cancer with or without IP caused few complications and no operative deaths. These results are better than the reports of thoracotomy cases. We cannot conclude that VATS is better than thoracotomy for patients with lung cancer and IP. That's because our experienced patients were not as many, and no statistical comparison was done in these reports between VATS and thoracotomy. Further studies are required to prove the effectiveness of VATS.

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