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ORIGINAL ARTICLE

Predictors of survival in patients who underwent video-assisted thoracic surgery talc pleurodesis for malignant pleural effusion

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Abstract

Background: Patients with malignant pleural effusion have a limited life expectancy. An increase in pleural and oncological treatment options and more accurate prognostic evaluation may help individualize treatment strategies. The aim of this study was to identify the prognostic indicators of overall survival (OS) after video-assisted thoracic surgery (VATS) talc pleurodesis for malignant pleural effusion.

Methods: We examined the medical records of all consecutive patients with malignant pleural effusion who underwent VATS talc pleurodesis from 2006 to 2008 at the Samsung Medical Center. Univariate and multivariate analyses were used to identify predictors of OS after VATS talc pleurodesis.

Results: During the study period, 91 patients underwent VATS talc pleurodesis to treat malignant pleural effusion. Early (within 30 days) and late (within 90 days) postoperative mortality rates were 9.9% (9 patients), and 25.3% (23), respectively. Median survival time after VATS talc pleurodesis was 10.5 months. The postoperative respiratory complication rate was 11% (10 patients), and included pneumonia (9) and acute respiratory distress syndrome (4). Multivariate analysis revealed that preoperative chemotherapy ($P = 0.012$), preoperative radiotherapy ($P = 0.003$), and Eastern Cooperative Oncology Group (ECOG) performance score 3 or 4 ($P = 0.013$) were independent risk factors of OS after VATS talc pleurodesis.

Conclusions: We identified previous chemotherapy or radiotherapy and poor performance status (ECOG 3 or 4) as significant predictors of OS after VATS talc pleurodesis. These prognostic factors can help surgeons select candidates for VATS pleurodesis for malignant pleural effusion.

Introduction

Currently, lung cancer is the most common metastatic tumor to the pleura in men, while breast cancer is the most common metastatic tumor to the pleura in women.[1] It is estimated that 8–15% of patients with lung cancer have malignant plural effusion (MPE). MPE accounts for 22% of all pleural effusion cases, and >150 000 new cases are diagnosed annually in the United States.[2] Carcinoma of any organ can metastasize to the pleura, and when malignant cells are detected in pleural fluid or tissue, they denote advanced malignancy and poor prognosis. Current guidelines recommend pleurodesis to prevent the recurrence of effusion in patients with symptomatic MPE.[3] Pleurodesis refers to a procedure during which a sclerosing agent is instilled into the pleural cavity to cause chemical irritation, which leads to pleuritis and, ultimately, to pleural fibrosis and obliteration of the pleural space. Among sclerosing agents, talc has been shown to have the highest efficacy. Use of video- assisted thoracoscopy for talc poudrage is recommended by current guidelines. Median survival after

a diagnosis of MPE is only four to six months.[3] Generally, pleurodesis is not indicated in patients who have a life expectancy of less than three months.

However, there is no definitive method to calculate the life expectancy of patients with MPE. A number of factors may help predict the survival of these patients, including tumor characteristics, comorbidities, and the composition of the effusion.[4–7] Prognostic evaluation of survival of patients undergoing video-assisted thoracic surgery (VATS) talc pleurodesis for MPE may help individualize treatment strategies. Furthermore, identification of patients with a poor prognosis may help minimize discomfort and inconvenience at the end of their lives. The aim of this study was to identify the prognostic indicators of overall survival (OS) after VATS talc pleurodesis for MPE.

Methods

Study design

From January 2006 to December 2008, 91 consecutive patients with recurrent symptomatic MPE underwent VATS talc pleurodesis at the Samsung Medical Center. VATS talc pleurodesis was only performed in patients with documentation of MPE, complete lung expansion on chest radiography after drainage, symptoms resulting from the presence of fluid, improvement of symptoms after drainage, and according to suitability of the patient's general condition for pleurodesis. The medical records of patients who underwent VATS talc pleurodesis were reviewed retrospectively.

Demographic and clinical data, in addition to biochemical parameters in serum and pleural fluid, were collected from medical records. The following data were collected from all patients: age at surgery date, gender, diagnosis date, preoperative Eastern Cooperative Oncology Group (ECOG) performance status (PS), type of neoplasm, whether treated with preoperative chemotherapy or radiotherapy, serum and pleural fluid biochemical parameters (pH, protein, glucose, albumin), and serum neutrophil to lymphocyte ratio (NLR).

Surgical procedure

Video-assisted thoracic surgery was performed in all patients under general anesthesia. A 5.5 or 10.5 mm camera port and one 5.5 mm instrumentation port were inserted. The pleural effusion was carefully aspirated; fibrinous adhesions were removed, while fibrous adhesions were divided by diathermy coagulation. A thorough assessment of the pleura and lung surface was made, and multiple biopsies were taken from appropriate areas. The degree of lung expansion was ascertained with sustained positive pressure ventilation. Pleurodesis was performed with 2–5 g of sterile purified graded talc powder insufflated through a talc atomizer under direct vision. At the end of the procedure, one (occasionally 2) of the chest tubes was left in situ. The chest tube was removed when the volume of fluid collected remained under 150 mL/day for three to five days after surgery.

Statistical analysis

Continuous data are presented as means ± standard deviations (SD) unless otherwise noted. The primary outcome was OS after VATS talc pleurodesis. Duration of survival was estimated from the time of thoracoscopic surgery to the date of death or the end of the study (December 2014), and estimated using the Kaplan–Meier product method. Univariate and multivariate analyses with Cox proportional hazards models were used to find hazard ratios (HRs) adjusted for demographic and clinical covariates. All statistical tests were two-sided and a P value less than 0.05 was considered significant. Statistical analyses were performed using SPSS version 22 (SPSS Inc., Chicago, IL, USA).

Results

A total of 91 consecutive patients who underwent VATS talc pleurodesis for recurrent symptomatic MPE were enrolled in this study. The mean time between VATS talc pleurodesis and the first diagnosis of MPE was 2.0 months (range 0–55). Clinical data and patient characteristics are summarized in Table 1 according to 90 day postoperative mortality (group I: survivors at postoperative 90 days, group II: non-survivors at postoperative 90 days). Forty patients (44%) were men and the median age at surgery was 60 years (range 14–85). Most patients had lung cancer (63.7%). Other cancers included: colorectal (4), renal cell (2), thymic (2), pharynx (1), angiosarcoma (1), thyroid (1), cervical (1), giant cell (1), malignant melanoma (1), and pleomorphic (1). Thirty-nine patients (42.9%) underwent preoperative chemotherapy, while 18 patients (19.8%) underwent preoperative radiotherapy. At the time of diagnosis of MPE, 61 patients (70.9%) underwent therapeutic thoracentesis, 6 (7.0%) underwent pigtail catheter placement, 5 (5.8%) underwent large-bore chest tube placement, and 14 patients did not receive any treatment before VATS talc pleurodesis.

The biochemical properties of pleural effusion and serology are summarized in Table 2. The results of pleural fluid analysis in both groups were consistent with exudate. There was no significant difference between groups I and II in terms of pleural pH, serum protein, pleural albumin, pleural glucose, or pleural lactate dehydrogenase (LDH).

Table 1 Patient demographics

Demographic variables	Total patients N (%)	Group I N (%)	Group II N (%)	*P* value
Total	91 (100)	68 (100)	23 (100)	
Age, median (range)	60 (14–85)	58 (30–82)	64 (14–85)	0.653
Gender				0.101
Male	40 (44)	26 (38.2)	14 (60.9)	
Female	51 (56)	42 (61.8)	9 (39.1)	
ECOG				<0.001
0	8 (8.8)	7 (10.3)	1 (4.3)	
1	41 (45.1)	36 (52.9)	5 (21.7)	
2	33 (36.3)	23 (33.8)	10 (43.5)	
3	9 (13.2)	2 (2.9)	7 (30.4)	
4	0 (0)	0 (0)	0 (0)	
Cancer				0.461
Lung	56 (61.5)	45 (66.2)	11 (47.8)	
Breast	7 (7.7)	5 (7.4)	2 (8.7)	
Stomach	7 (7.7)	5 (7.4)	2 (8.7)	
Ovarian	5 (5.5)	3 (4.4)	2 (8.7)	
Other	16 (17.6)	10 (14.7)	6 (26.1)	
Dry seeding, *n* (%)	6(6.6)	6(8.7)	0(0)	0.152
Extrathoracic metastasis	36(40.0)	22(31.9)	14(63.6)	0.012
Preoperative chemotherapy	39 (42.9)	23 (33.8)	16 (69.6)	0.001
Preoperative radiotherapy	18 (19.8)	8 (11.8)	10 (43.5)	<0.001

Group I, survivors at postoperative 90 days; Group II, non-survivors at postoperative 90 days. ECOG, Eastern Cooperative Oncology Group.

Table 2 Biochemical properties of pleural effusion and serology

Variables, mean ± SD	Total patients	Group I	Group II	*P* value
Pleural pH	7.34 ± 0.15	7.35 ± 0.16	7.33 ± 0.12	0.530
Serum protein (g/dL)	6.04 ± 1.13	6.07 ± 1.06	5.95 ± 1.32	0.704
Pleural albumin (g/dL)	2.59 ± 0.50	2.64 ± 0.52	2.43 ± 0.43	0.092
Serum albumin (g/dL)	3.71 ± 1.10	3.86 ± 1.20	3.27 ± 0.58	**0.014**
Pleural glucose (mg/dL)	101.0 ± 40.0	102.35 ± 42.91	97.05 ± 30.70	0.389
Pleural LDH (IU/L)	945.1 ± 1040.6	772.07 ± 735.81	1438.10 ± 1545.88	0.016
Neutrophil to lymphocyte ratio	4.42 ± 3.32	3.96 ± 3.36	5.78 ± 2.88	**0.010**

Bold text denotes significance at <0.05. Group I, survivors at postoperative 90 days; Group II, non-survivors at postoperative 90 days. LDH, lactate dehydrogenase.

The NLR was higher in group II (5.78 ± 2.88) than in group I (3.96 ± 3.36).

At the time of surgery, 62 patients (68.1%) underwent pleural biopsy, as well as talc pleurodesis. Incidence of postoperative respiratory complications, including pneumonia (9 patients), acute respiratory distress syndrome (4), or a combination (3), was 11% (10).

Among patients who underwent VATS talc pleurodesis, early (within 30 days) and late (within 90 days) postoperative mortality was 9.9% (9 patients) and 25.3% (23), respectively. Median survival time was 10.5 months (range 0.2–60.3). The OS curve after VATS talc pleurodesis showed a one-year survival rate of 44.2%, three-year survival rate of 10.2%, and five-year survival rate of 2.2% (Fig 1).

Factors adversely affecting mortality in univariate analysis included ECOG PS 3 or 4 (HR 2.35, 95% confidence

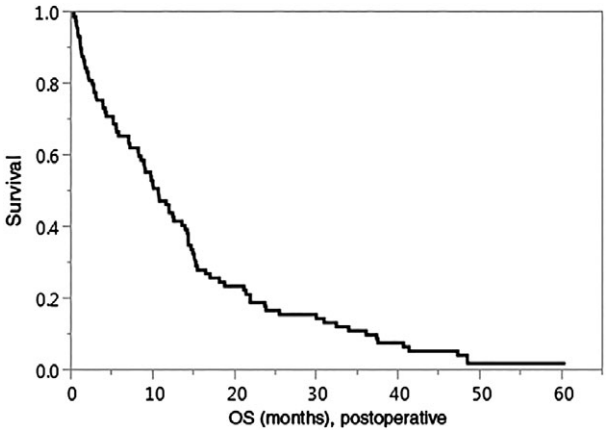

Figure 1 Overall survival (OS) curve after video-assisted thoracic surgery talc pleurodesis (1-year survival rate 44.2%; 3-year survival rate 10.2%; 5-year survival rate 2.2%).

Table 3 Univariate analysis of factors associated with overall survival in MPE patients who underwent VATS talc pleurodesis

Variables	Hazard ratio	95% confidence interval	*P* value
Age (years)			
<70	1.00		
≥70	1.30	0.76–2.23	0.342
Gender			
Female	1.00		
Male	1.30	0.74–1.73	0.564
Disease duration			
<12 months	1.00		
≥ 12 months	1.98	1.24–3.15	0.004
Pleural fluid pH			
<7.3	1.00		
≥ 7.3	1.16	0.72–1.86	0.556
Pleural fluid LDH (IU/l)			
<1500	1.00		
≥ 1500	1.63	0.86–3.09	0.139
Neutrophil to lymphocyte ratio			
<9	1.00		
≥9	1.67	0.86–3.09	0.132
Extra-thoracic metastasis			
Absent	1.00		
Present	1.97	1.27–3.07	0.003
Preoperative chemotherapy			
No	1.00		
Yes	3.44	2.13–5.54	<0.001
Preoperative radiotherapy			
No	1.00		
Yes	4.19	2.35–7.49	<0.001
ECOG PS			
0–2	1.00		
3–4	2.35	1.52–3.65	<0.001

ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; MPE, malignant plural effusion; PS, performance score; VATS, video-assisted thoracic surgery.

interval [CI] 1.52–3.65; $P < 0.001$), preoperative chemotherapy (HR 3.44, 95% CI 2.13–5.54; $P < 0.001$), preoperative radiotherapy (HR 4.19, 95% CI 2.35–7.49; $P < 0.001$), extra-thoracic metastasis (HR 1.97, 95% CI 1.27–3.07; $P = 0.003$), and disease duration over 12 months (HR 1.98, 95% CI 1.24–3.15; $P = 0.004$; Table 3). Biochemical factors, age, and gender did not significantly influence OS after VATS talc pleurodesis. Factors adversely affecting mortality in multivariate analysis included ECOG PS 3 or 4 (HR 1.85, 95% CI 1.14–3.01; $P = 0.013$), preoperative chemotherapy (HR 2.19, 95% CI 1.19–4.03; $P = 0.012$), and preoperative radiotherapy (HR 2.68, 95% CI 1.39–5.18; $P = 0.003$; Table 4).

Table 4 Multivariate analysis of factors associated with overall survival in MPE patients who underwent VATS talc pleurodesis

Variables	Hazard ratio	95% confidence interval	*P* value
Disease duration			
<12 months	1.00		
≥12 months	1.00	0.58–1.72	0.994
Extra-thoracic metastasis			
Absent	1.00		
Present	1.36	0.83–2.23	0.228
Preoperative chemotherapy			
No	1.00		
Yes	2.19	1.19–4.03	**0.012**
Preoperative radiotherapy			
No	1.00		
Yes	2.68	1.39–5.18	**0.003**
ECOG PS			
0–2	1.00		
3–4	1.85	1.14–3.01	**0.013**

Bold text denotes significance at <0.05. ECOG, Eastern Cooperative Oncology Group; MPE, malignant plural effusion; PS, performance score; VATS, video-assisted thoracic surgery.

Discussion

Malignant pleural effusion signifies a reduced life expectancy and continues to be a leading cause of poor quality of life in patients with malignancies. Median survival following diagnosis ranges from 3 to 15 months and is dependent on the stage and type of the underlying malignancy.[8,9] To increase the quality of remaining life, symptomatic MPE should be controlled. In current guidelines for MPE, pleurodesis using graded talc is recommended for symptomatic MPE, and VATS talc poudrage is recommended for pleurodesis in patients with good performance status.[3] Recent reports also support VATS talc pleurodesis in the aspects of efficacy, safety, and improvement of quality of life.[10,11]

Several studies have reported different prognostic factors affecting survival in patients with MPE. Our findings that pleural biochemical profiles are not prognostic risk factors for OS after VATS pleurodesis differ from those reported in previous studies. However, Sahn and Good reported that low pleural fluid glucose concentration and pH were associated with a decreased survival rate.[12] Furthermore, Bielsa *et al.* showed that pleural fluid LDH level was associated with survival.[5] Burrows *et al.* showed that only PS was associated with mortality.[7] Clive *et al.* found that the LENT prognostic score, which is based on pleural fluid LDH, ECOG PS, NLR, and tumor type, predicted survival in patients with MPE.[13] Another study showed that prognosis of patients after talc pleurodesis was independent of age, gender, type of malignancy, and amount of pleural effusion.[14] To our knowledge, there are no universally accepted prognostic factors for VATS pleurodesis of MPE.

The purpose of our study was to evaluate the potential clinical and biochemical factors that were predictive of survival in patients who underwent VATS talc pleurodesis to enable the selection of appropriate candidates for VATS talc pleurodesis. We found that preoperative

chemotherapy, radiotherapy, and ECOG PS 3–4 were poor prognostic factors for OS after VATS talc pleurodesis in multivariate analysis.

Although there is controversy over the direct effect of chemotherapy on postoperative complications, Kuzniar *et al.* showed that recent chemotherapy was an independent predictor of respiratory complications after VATS talc pleurodesis.[15] We believe that the higher incidence of postoperative respiratory complications and poor general condition of patients who have previously received chemotherapy could affect survival in patients who undergo VATS talc pleurodesis. Moreover, preoperative radiotherapy was also identified as highly predictive of survival. However, among 18 patients who underwent radiotherapy, only three patients had radiotherapy to the lung field, while the other 15 patients had radiotherapy to another organ aside from the lung. Previous local radiotherapy is thought to have a systematic effect and influences the immune system.[16] Recent reports have revealed that local radiotherapy recruits biological effectors outside the treatment field and has systemic effects.[17,18] In other words, radiotherapy to a localized target may inevitably expose all tissues to some dose of radiation, mediated by cellular and microenvironmental signaling.[19] Other reports showed that bystander effects in cells that were not directly irradiated, including induction of genomic instability, gene mutations, and cell death, had effects outside the field of radiation.[20,21] The immune system can also be activated by ionizing radiation to produce proinflammatory mediators of genomic instability.[22,23]

We found that ECOG PS was predictive of survival. This finding is consistent with other studies.[7,24,25] Many reports have shown that the Karnofsky Performance Scale (KPS) score at the time of thoracoscopic pleurodesis is predictive of survival in patients with recurrent symptomatic MPE.[7] Steger *et al.* showed that survival rate was negatively influenced by a preoperative KPS index of less than 60%.[24] The American Thoracic Society demonstrated that ECOG PS 2–3 was associated with in-hospital mortality and three-month mortality.[2] A previous study also reported a strong correlation between ECOG PS and survival in patients with lung cancer and other malignancies.[26]

Over the past decade, VATS has dramatically evolved into a sophisticated technique involving some of the most complex thoracic procedures. Recently, uniportal thoracoscopic surgery has been defined as a less invasive method than the standard three portal VATS. Alar and Ozcelik reported that uniportal VATS should be preferred to conventional three-port VATS to minimize the spread of infection and tumor cells to the chest wall in infectious and malignant diseases.[27] We think that uniportal VATS pleurodesis is feasible and may yield results similar to those obtained with conventional VATS pleurodesis, but do not have sufficient evidence to prove this as yet.

Recently, awake VATS has been used to avoid the perceived increased risk in selected patients of various diseases. Awake thoracic surgery using regional anesthesia has been recommended to reduce anesthesia-related risk in high-risk patients.[28] Patients with MPE could be good candidates. We consider awake VATS pleurodesis as a feasible option, but it needs to be proven as safe and effective in VATS talc pleurodesis.

Our study had several limitations. First, our sample size was relatively small. A larger sample size would increase the robustness of our conclusions. Second, our retrospective study design could have introduced systemic bias, including patients who were unavailable for complete follow-up.

In conclusion, we found that preoperative chemotherapy, preoperative radiotherapy, and preoperative ECOG PS were predictors of early death in patients who underwent VATS talc pleurodesis. We suggest that a history of preoperative chemotherapy or radiotherapy in addition to preoperative ECOG PS should be considered when predicting life expectancy and determining indications for VATS talc pleurodesis.

Disclosure

No authors report any conflict of interest.

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