

Pneumonectomy in pulmonary metastasis

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Background: The risk of complication following pneumonectomy is high; therefore, the decision to perform pneumonectomy should be carefully evaluated. A retrospective multicenter study of patients with metastatic lung tumors who underwent pneumonectomy was conducted.

Methods: The database from the Metastatic Lung Tumor Study Group of Japan was retrospectively reviewed. Between 1984 and 2013, 4,742 patients underwent pulmonary metastasectomy. Of the 4,742 patients, 55 patients (1.16%) who underwent pneumonectomy were analyzed, and their survival parameters and prognostic factors were evaluated.

Results: Of the 55 patients who underwent pneumonectomy, 34 patients were male and 21 patients were female. The primary tumor sites were colorectal in 28 patients, head and neck in 12 patients, bone in three patients, bladder in three patients, and other regions in nine patients (breast, uterus, liver, soft tissues in two patients, respectively, and pancreas in one patient). The overall 5-year survival rate of patients following pneumonectomy was 28.9%. The rate was significantly lower than that of patients who underwent other metastasectomy which had an overall 5-year survival rate of 53.4% ($P < 0.001$). There were 3 hospital mortalities (3/55, 5.45%). Univariate analysis revealed that patients 55 years old or older ($P = 0.016$) and patients who had lymph node metastasis ($P = 0.032$) were significant predictors of poor prognosis. Multivariate analysis indicated that the age group 55 years old or older was an independent prognostic factor ($P = 0.040$).

Conclusions: The indication of pneumonectomy should be carefully reviewed, especially for patients 55 years old or older, however characteristics of each primary organ should also be considered.

Keywords: Pneumonectomy; pulmonary metastasis; metastasectomy

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Introduction

Pneumonectomy is considered to be a high risk surgery, often accompanied by complications; therefore, a thorough review is required prior to deciding to perform pneumonectomy (1-5). In 1999, the International Registry

of Lung Metastases (IRLM) reported 171 patients (3.2%) received pneumonectomy, among 5,206 patients who underwent metastasectomy, with hospital mortality rate of 5.2% and 5-year survival rate of 20% (5). The IRLM report was the only available large scale multicenter study conducted on metastatic lung tumors. We retrospectively

analyzed data obtained from multiple institutions on patients who underwent the surgery for metastatic lung tumors in recent years and evaluated the pros and cons of pneumonectomy.

Methods

The Metastatic Lung Tumor Study Group of Japan has conducted a registry of metastatic lung tumor cases that are treated with surgical resection (6). To date, 25 institutions have joined the group, and 4,742 patients were registered between 1984 and 2013. This study was approved by the Institutional Ethics Review Board (Teikyo University Review Board 10–108) and other institutions, and waived the need for informed consent from patients, as long as patient data remained anonymous. The following parameters were collected: gender, age, histology of primary tumor, staging of primary tumor, treatment for the primary tumor, date of primary surgery, type of surgery, curability, disease-free interval (DFI), side of pulmonary metastasis, maximum lesion size, number of resected metastasis, elevation of the tumor marker specific to the primary tumor, date of metastasectomy, other treatments, sites of recurrence after pulmonary metastasectomy and survival follow-up. The surgical indications and procedures were determined by each institution. Lymph node resection was not routinely performed and was at the discretion of each institution. Curability is defined as macroscopic and microscopic complete resection. DFI was calculated using the difference between the date of initial treatment for the primary tumor and the date of pulmonary metastasis diagnosis. Hospital mortality was defined as death within any time interval after an operation, if the patient had not been discharged from the hospital. Hospital-to-hospital transfer was not considered a discharge. Transfer to a nursing home or a rehabilitation unit was considered a hospital discharge unless the patient subsequently died of complications from the operation.

We investigated the surgical outcomes and prognostic factors of pneumonectomy. The date of first pulmonary resection was defined as the starting point. Postoperative follow-up was performed at the discretion of each institution.

Statistical analysis

Overall survival (OS) was analyzed using the Kaplan-Meier method. The Chi-square and Student's *t* test were used to

compare the percentages and mean values. Univariate and multivariate Cox proportional hazards regression analyses were used to evaluate potential prognostic factors. The data were analyzed using version 22 of the IBM SPSS software (IBM Corporation, Somers, NY, USA). A *P* value <0.05 was considered statistically significant.

Results

Of the 4,742 patients registered in the database, 55 patients (1.16%) were underwent pneumonectomy. Pneumonectomy were performed on 34 male patients (34/2,655, 1.28%) and 21 female patients (21/2,056, 1.02%); thus, there was no significant gender difference (*P*=0.411). The average age of pneumonectomy patients was 55.5±13.1 years old. The frequency of pneumonectomy on patients who were over 70 years (3/1,053, 0.28%) was lower (*P*=0.001). Further, the study showed a high tendency for pneumonectomy in patients who were in their 50 s (*P*=0.068). In the last 15 years, the frequency of pneumonectomy is significantly lower than in the previous 15 years (0.91% vs. 1.77%, *P*=0.012) (Table 1).

Primary tumors were found to be colorectal in 28 patients (28/2,184, 1.28%), head and neck in 12 patients (12/463, 2.59%), bone in three patients (3/273, 1.10%), bladder in three patients (3/55, 5.45%), and other regions in 9 patients (breast, uterus, liver, soft tissues in two patients, respectively, and pancreas in one patient). These results indicated that there was a high frequency of pneumonectomy in head and neck (*P*=0.002), and bladder (*P*=0.003) primary tumor patients. In contrast, no pneumonectomy was performed on kidney patients (0/335, *P*<0.05) (Table 1).

The average follows up period for patients who underwent pneumonectomy was 34.7 months, the number of patients surviving more than 5 and 10 years were 10 and 4, respectively. The 5-year survival rate for patients who underwent pneumonectomy was 28.9%, which was significantly lower (*P*<0.001) than that of the other metastasectomy, which had a rate of 53.4% (Figure 1A). It was shown that in patients 55 year or older, which is the mean age for pneumonectomy, there was a significant difference in 5-year survival rate between patients who underwent pneumonectomy and patients who underwent other metastasectomy (15.2% vs. 54.7%, *P*<0.001) (Figure 1B), whereas, such difference was not observed in patients under 55 years (54.0% vs. 49.0%, *P*=0.623) (Figure 1C). Regarding organ specificity in 5-year survival rate between

Table 1 Patients characteristics

Variable	Metastasectomy		Pneumonectomy		P
	n=4,742	n=55	%		
Sex					
Male	2,655	34	1.28		0.411
Female	2,056	21	1.02		–
N/A	31	–	–		–
Age (years)					
Mean (SD)	58.9 (15.2)	55.5 (13.3)			
–39	432	6	1.34		0.889
40–49	389	6	1.54		0.681
50–59	941	18	1.91		0.068
60–69	1,354	22	1.63		0.225
70–	1,063	3	0.28		0.001
N/A	563	–	–		–
Operation year					
1984–1998	1,418	26	1.77		0.012
1999–2013	3,124	29	0.91		–
N/A	200	–	–		–
Primary site					
Colorectal	2,184	28	1.28		0.468
Head & neck	463	12	2.59		0.002
Breast	307	2	0.65		0.390
Kidney	335	0	0		0.040
Uterus	277	2	0.72		0.483
Bone	273	3	1.10		0.923
Soft tissue	282	2	0.71		0.466
Liver	109	2	1.84		0.505
Bladder	55	3	5.46		0.003
Esophagus	103	0	0		0.266
Stomach	65	0	0		0.379
Testicle	72	0	0		0.354
Other	217	1	0.46		0.325

patients who underwent pneumonectomy and patients who underwent other metastasectomy, there was a significant difference in colorectal patients (28.4% vs. 54.3%, $P=0.004$), but no significant difference in head and neck patients

(28.1% vs. 52.6%, $P=0.100$) (Figure 2A,B).

Five-year survival rates following pneumonectomy were 15.2% for patients 55 years or older and 54.0% for patients under 55 years ($P=0.004$). Further, analysis of DFI following

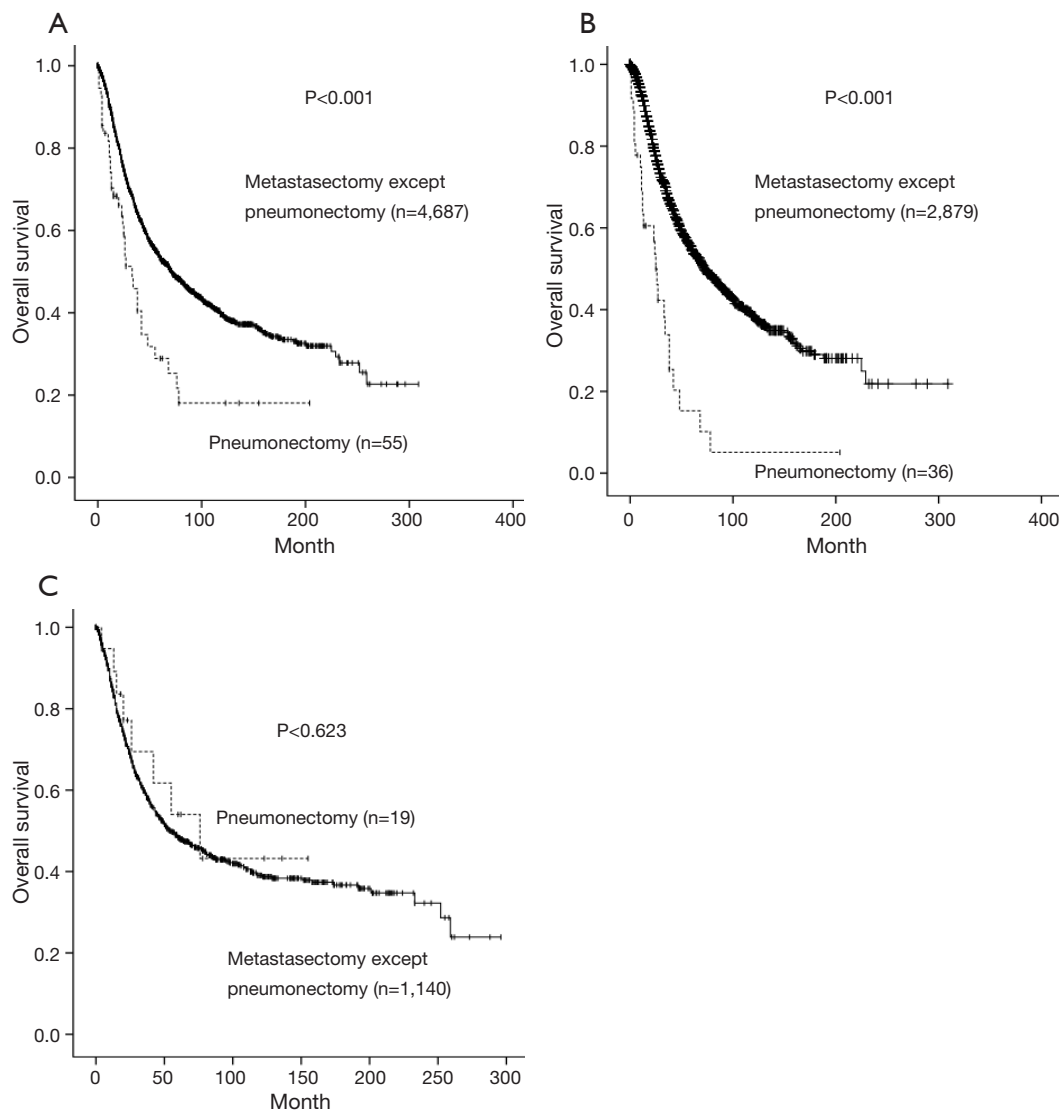


Figure 1 Survival curve according to the pneumonectomy and the metastasectomy except pneumonectomy, all cases (A), age 55 year or older (B), and under 55 years old (C).

the removal of primary tumor, showed that 5-year survival rates following pneumonectomy were 0% for DFI of 0 to 12 months and 38.8% for DFI over 12 months ($P=0.035$) (Table 2).

Univariate analysis of OS indicated that the age 55 year or older ($P=0.016$) and positive lymph node metastasis ($P=0.032$) were indicators of poor prognosis. Mediastinal or hilar lymph node dissection was performed on 48 patients, and mediastinal metastasis was found in 15 patients while hilar metastasis was found in 12 patients. However, gender, increased level of tumor markers, tumor size, numbers

of metastasis, curability, and surgery site did not result in survival benefit (Table 2).

Multivariate analysis using age 55 or older, DFI of 0 to 12 months and lymph node metastasis, which are risk factors identified by survival rate and univariate analysis, indicated that age over 55 ($P=0.040$) was an independent risk factor (Table 3).

Among 55 patients who underwent pneumonectomy, there were 3 hospital mortalities (5.45%). These patients were all male in their 50s and had positive lymph node metastasis. One of the patients suffered cancer death

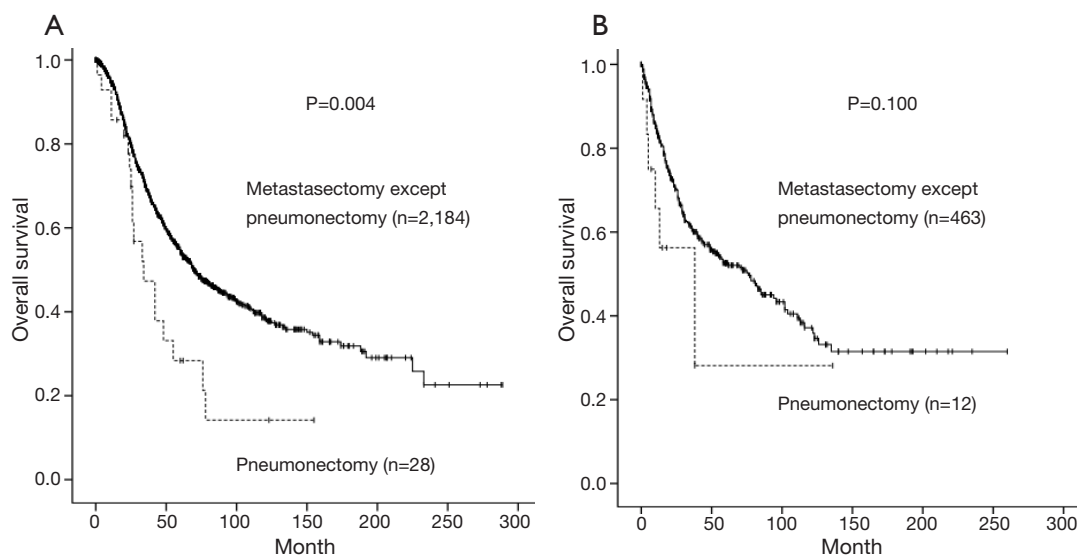


Figure 2 Survival curve according to the pneumonectomy and the metastasectomy except pneumonectomy, colorectal cases (A), and head and neck cases (B).

42 days after pneumonectomy, following the appearance of metastatic lesions in various regions of the body after an incomplete resection. The remaining two patients were an operative death on 23 days after surgery, and a sudden death due to unknown reason 35 days after surgery (*Table 4*).

Discussion

Metastatic lung tumors are caused by cancer cells that develop in other organs and travel through blood circulation to the lungs (7,8). Chemotherapy, a systemic therapy to treat advanced stage cancers, should be the choice for treating metastatic lung tumors; however, it is almost impossible to treat the tumor completely by chemotherapy alone, therefore, resection, a local therapy, is required (8,9). Metastatic lung tumors are often treated using a local therapy alone, but the therapeutic methods vary. Whether to perform surgery or chemotherapy first depends on the primary organ (9,10). At present, no standard therapeutic method to treat metastatic lung tumors has been established.

In 1997, the IRLMA published a report involving 5,206 patients and was the only large scale study conducted on metastatic lung tumors (7). In 1999, Koong published a report on pneumonectomy by subanalyzing the IRLMA report (5). Since then, other reports have been published that have analyzed between 200 and 1,200 patients at

a single institution (1-4). This study was conducted by analyzing the data from 4,742 patients that had been collected over 30 years since 1984 at 25 institutions.

Historical details of the pneumonectomy for metastatic lung tumors were described by Koong in 1999 (5). Pneumonectomy was widely performed in the 1960s but became less popular after the 1970s. By the 1980s, pneumonectomy was performed in only 1% to 3% of metastatic lung tumor patients. According to this study, the frequency of performing pneumonectomy was low, having been performed in only 1.16% of all metastasectomy. In the last 15 years, the frequency of pneumonectomy is significantly lower than in the previous 15 years. We believe that due to technological advances of PET-CT and CT resolution, early phase cases increased. And, recently, there is a tendency to avoid pneumonectomy.

Compared with other surgery, such as lobectomy, pneumonectomy is frequently accompanied by complications; therefore, it is important to thoroughly evaluate the pros and cons of performing pneumonectomy. According to an annual summary published in 2010 by the Japanese Association for Thoracic Surgery, hospital mortality of patients who underwent pneumonectomy due to lung cancer was 3.0%, which was significantly higher compared with those who underwent lobectomy, which was 0.9% (11). Thomford reported that hospital mortality following pneumonectomy on patients with metastatic lung

Table 2 Prognostic factors-univariate analysis and 5-year survival

Variable	n	Overall survival: univariate analysis			5-year survival (%)	P
		Risk ratio	95% CI	P		
Sex						0.525
Female	21	1.128	0.365–3.483	0.834	30.1	
male	34	–	–	–	28.0	
Age						0.004
<55	19	4.125	1.264–13.459	0.016	54.0	
≥55	36	–	–	–	15.2	
Disease free interval						0.035
≤12 mo	11	0.321	0.062–1.664	0.161	0.0	
>12 mo	44	–	–	–	36.2	
Tumor marker						0.866
Low	33	1.000	0.326–3.069	1.000	30.3	
High	22	–	–	–	25.9	
Tumor size						0.347
<3 cm	17	0.639	0.187–2.185	0.473	8.8	
≥3 cm	38	–	–	–	38.7	
Number of tumors						0.949
Single	27	1.059	0.353–3.178	0.919	31.5	
Multiple	28	–	–	–	34.9	
Curability						0.320
Complete	51	1.781	0.173–18.368	0.624	28.6	
Incomplete	4	–	–	–	25.0	
Lymph node metastasis						0.111
Negative	28	3.500	1.085–11.292	0.032	35.3	
Positive	27	–	–	–	22.9	
Order						0.365
Primary	41	0.691	0.200–2.389	0.559	27.8	
Completion	14	–	–	–	27.8	
Side						0.555
Left	36	2.000	0.592–6.756	0.260	30.3	
Right	19	–	–	–	26.8	

tumors was 0% (1); however, a different study reported that it was 5% to 10% (2-5), which was approximately the same proportion obtained in this study, which was 5.45% (Table 5).

On the other hand, 5-year survival rate for metastatic lung

tumor patients following pneumonectomy is approximately 30%, indicating that there were patients who could be cured by complete resection, and, therefore, the pneumonectomy should not be completely disregarded. In this study, it was

shown that the group consisting of patients under 55 years old with pneumonectomy showed approximately the same prognosis as patients who underwent other metastasectomy; therefore, it may be appropriate to consider the benefits of pneumonectomy in this younger age group. However, performing pneumonectomy should be carefully evaluated for patients who are elderly or DFI of 0 to 12 months. Further, patients with lymph node metastasis showed a poor

prognosis.

One of the significant predictors of survival for treatment of pulmonary metastasis was the number of metastases (7,8). In pneumonectomy, the survival difference between single and multiple metastases did not reach statistical significance, due to the limited number of patient (5). Left side pneumonectomy had a better prognosis compared to right side pneumonectomy for lung cancer surgery (12), though there was no survival difference between left side and right side in this study, due to the limited number of patient.

This study was conducted using data from a registry of patients with metastatic lung tumor that was collected over 30 years at 25 institutions; therefore, there were several limitations to this study. Common reasons for deciding to perform pneumonectomy include the development of tumors at the hilar region, enlarged lymph nodes, or multiple nodules in one lung; however, the reasons for performing pneumonectomy in this study were unknown. The prognosis of 3 hospital mortalities was known, but the detailed prognosis of other patients who underwent pneumonectomy was difficult to obtain.

The IRLM reported pneumonectomy for metastatic lung tumors between 1962 and 1994, while this study reported those performed between 1984 and 2014, when the number of pneumonectomy is decreasing. It is believed

Table 3 Prognostic factors-multivariate analysis with Cox proportional hazards model

Variable	Overall survival: multivariate analysis		
	Risk ratio	95% CI	P
Age			
<55	0.269	0.077–0.942	0.040
≥55	–	–	
Disease free interval			
≤12 mo	3.925	0.628–24.530	0.144
>12 mo	–	–	
Lymph node metastasis			
Negative	0.281	0.079–1.003	0.051
Positive	–	–	

Table 4 Clinical characteristics of patients for hospital mortality

No.	Age	Sex	Organ	Curability	LN	DFI	Side	Postoperative survival	Reason
1	57	M	Head & neck	Incomplete	Positive	25	Right	42 days	Cancer death
2	59	M	Colon	Complete	Positive	32	Right	23 days	Operative death
3	57	M	Spleen	Complete	Positive	71	Left	35 days	Sudden death

DFI, disease free interval.

Table 5 Selected series for pneumonectomy in pulmonary metastases

Author	Period	Institution	Metastasectomy		Pneumonectomy		5-year survival %	Hospital mortality %
			n		n	%		
THOMFORD <i>et al.</i> (1)	1941–1962 (22)	Single	205		31	15.1	N/A	0.0
McCormack and Martini (2)	1960–1975 (18)	Single	448		18	4.0	13.3	5.6
Mountain <i>et al.</i> (3)	1961–1980 (20)	Single	556		52	9.4	N/A	9.6
Putnam <i>et al.</i> (4)	1981–1992 (12)	Single	1,200		19	1.6	31.8	10.5
IRLM (5)	1962–1994 (33)	Multi (18)	5,206		171	3.2	20.0	5.2
This study	1984–2013 (30)	Multi (25)	4,742		55	1.2	28.9	5.5

that the number of pneumonectomy will further decrease as both radiation therapy and chemotherapy continue to progress. Given the lack of alternative therapy, selected patients with sufficient pulmonary reserve may be offered pneumonectomy.

Conclusions

Prior to making the decision to perform pneumonectomy, more careful consideration must be given to the patients 55 year or older and to patients with DFI of 0 to 12 months. Hospital mortality following pneumonectomy for metastatic lung tumor was an acceptable number.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: This study was approved by the Institutional Ethics Review Board (Teikyo University Review Board 10-108) and other institutions, and waived the need for informed consent from patients, as long as patient data remained anonymous.

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