RESULTS OF SURGICAL TREATMENT OF LUNG CANCER INVOLVING THE DIAPHRAGM

Kohei Yokoi, MD
Ryosuke Tsuchiya, MD
Takashi Mori, MD
Kanji Nagai, MD
Tsugio Furukawa, MD
Shigefumi Fujimura, MD
Ken Nakagawa, MD
Yukito Ichinose, MD

Objectives: Lung cancers with diaphragmatic invasion are categorized as T3 lesions, but the surgical results have not been well known. We retrospectively surveyed patients with resected primary lung cancers involving the diaphragm.

Methods: A total of 16,771 patients underwent surgical resection for lung carcinoma between 1986 and 1995 at 31 institutions of the Lung Cancer Surgical Study Group in Japan. By investigating the database, we identified 63 patients (0.38%) who underwent resection of T3 lung cancer invading the diaphragm. These patients constituted the study population, and their clinical and pathologic records were retrospectively analyzed.

Results: Tumor invasion to the diaphragm was diagnosed before operation only in 17 patients (27.0%). Complete resections of the primary lung tumors with the invaded diaphragm were performed in 55 patients (87.3%), of whom 26 had T3 N0 M0 diseases and 29 had T3 N1-2 M0 diseases. The operative mortality was 1.6% in all patients. The 5-year survival of patients with complete resection was 22.6%, but there was no 4-year survivor in patients with incomplete resection ($P = .024$). The survivals of patients with completely resected T3 N0 M0 and T3 N1-2 M0 tumors were 28.3% and 18.1%, respectively ($P = .013$). In those patients, the depth of diaphragmatic involvement significantly affected the prognosis. The 5-year survival of the patients with shallow invasion (parietal pleura or subpleural tissue involvement) was 33.0%, whereas that of the patients with deep invasion (muscle or peritoneal infiltration) was 14.3% ($P = .036$).

Conclusions: In selected patients with lung carcinoma and diaphragmatic invasion, combined resection of the lung and diaphragm offers the prospect of cure with acceptable mortality. However, primary lung tumors with diaphragmatic invasion, especially invasion of the muscle layer or deeper tissue, are not considered to be T3 lesions, because these cancers are generally technically resectable but oncologically almost incurable. (J Thorac Cardiovasc Surg 2000;120:799-805)

In the treatment of patients with non-small cell lung cancer, surgical resection remains the only reliable curative method, but the surgical candidacy of patients

with tumor extension to the adjacent structures has been considered equivocal. Several studies, however, have shown improved survival of selected patients with extrapulmonary invasion after surgery.¹⁻⁴ In the staging system for lung cancer proposed in 1986, tumors with direct extrapulmonary extension have been subdivided on the basis of the anatomic extent of disease and its potential for surgical treatment.⁵ That is, T3 lesions with limited, circumscribed extrapulmonary extension are considered potentially surgically resectable, whereas T4 tumors with extensive extrapulmonary extension are considered unresectable.

Tumors with direct invasion of the diaphragm have been categorized as T3 lesions in the staging system and

From the Lung Cancer Surgical Study Group of the Japan Clinical Oncology Group, Japan.

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Address for reprints: Kohei Yokoi, MD, Division of Thoracic Surgery, Tochigi Cancer Center, 4-9-13 Yohnan, Utsunomiya, Tochigi 320-0834, Japan (E-mail: kyokoi@tcc.pref.tochigi.jp).

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Table I. The characteristics of the 63 patients in this study

Characteristic	No. of patients
Sex	
Male	53
Female	10
Mean age (y)	67.0 ± 7.6*
Symptoms	
Asymptomatic	26
Symptomatic	37
Clinical stage	
IA	4
IB	19
IIA	1
IIB	17
IIIA	19
IIIB	3

*Values are mean ± standard deviation.

Table II. Pathologic findings of the resected tumors

Variable	All patients (n = 63)	Patients with complete resection (n = 55)
Histology		
Squamous cell	38	32
Adenocarcinoma	20	19
Adenosquamous	2	2
Large cell	2	1
Mucoepidermoid	1	1
Tumor size (mm)	60.0 ± 27.1*	56.1 ± 22.5*
Combined resected organs		
Diaphragm only	40	37
Diaphragm and other organs	23	18
Pathologic stage		
T3 N0 M0	29	26
T3 N1 M0	12	10
T3 N2 M0	20	19
T3 NX M0	2	0

*Values are mean ± standard deviation.

are considered to be curable by resection.⁵ However, only a few reports have been published concerning results of surgical treatment of patients with those tumors.⁶⁻⁹ Weksler and colleagues⁶ reported that tumors invading the diaphragm were found in 0.17% of patients with thoracotomy for non-small cell lung cancer, and the surgical results in those 8 patients were unfavorable; this was the first report dealing with this issue.

In 1997, the International Union Against Cancer and the American Joint Committee on Cancer adopted a revised stage grouping.¹⁰ In the new staging system, T3 N0 M0 disease is classified as stage IIB and T3 N1 M0 and T3 N2 M0 diseases as stage IIIA. Prognoses of patients with each stage of the disease were documented

Table III. Depth of tumor invasion to the diaphragm in all patients and in those who underwent complete resection

Invasion of the diaphragm	All patients (n = 46)	Patients with complete resection (n = 40)
Parietal pleura	9	9
Subpleural tissue	19	17
Muscle	15	13
Peritoneum	2	1
Beyond peritoneum	1	

as a 38% 5-year survival for T3 N0 M0, 25% for T3 N1 M0, and 23% for T1-3 N2 M0.¹⁰ Nevertheless, the number of patients in the database with tumors involving the diaphragm was unknown.

To obtain information on tumors with diaphragmatic invasion and the surgical results of patients with these diseases, we retrospectively surveyed patients with resected lung cancer involving the diaphragm in the institutions of the Lung Cancer Surgical Study Group in Japan.

Patients and methods

Between January 1, 1986, and December 31, 1995, a total of 16,771 patients underwent resection for carcinoma of the lung at 31 institutions of the Lung Cancer Surgical Study Group in Japan. By investigating the database, we identified 63 patients (0.38%) who had resection of T3 lung cancer invading the diaphragm. These patients constituted the study population. Their clinical and pathologic records were retrospectively analyzed, and at least a 2-year follow-up was obtained for all living patients.

Disease stages were based on the revised TNM classification for lung cancer.¹⁰ Histologic typing was determined according to the World Health Organization classification.¹¹ A resection was designated as *complete* when all gross disease was excised and the margins of resection were microscopically clear of disease.

Survival was measured from the operation until death or the last date of the follow-up (February 28, 1998), and the data are reported as mean and 95% confidence intervals (CI) for the mean. The survival curves were calculated by the Kaplan-Meier method, and comparisons among the curves were made by means of the log-rank test. All calculations were performed with the use of the StatView (version 5.0; SAS Institute Inc, Cary, NC) software package.

Results

Characteristics of the 63 patients are shown in Table I. Among the 37 symptomatic patients (58.7%), the most common symptoms were cough in 16 patients, hemop-

Fig 1. Survival curves of patients who underwent surgery for lung carcinoma with diaphragmatic invasion according to completeness of resection.

tysis in 9, and fever and chest pain in 7 each. All patients underwent chest computed tomographic scanning for the evaluation of lung tumors, and magnetic resonance imaging of the chest was performed on 6 patients. In consequence, tumor invasion to the diaphragm was suspected before the operation in only 17 (27.0%) of the patients. The clinical stages of the tumors were therefore diversely assessed as shown in Table I. Three patients with clinical stage IIIB disease were believed to have atrial invasion, a satellite nodule within the ipsilateral primary tumor lobe, or N3 disease.

The extent of pulmonary resection consisted of a pneumonectomy in 6 patients (9.5%), bilobectomy in 11 (17.5%), lobectomy in 43 (68.3%), and segmentectomy or wedge resection in 3 (4.8%). Combined resected organs other than the diaphragm were chest wall in 10 patients, parietal pleura in 8, pericardium in 6, and omentum in 1 patient. The diaphragm was resected en bloc with the tumor in all patients; primary closure of the diaphragm was performed in 60 patients and reconstruction with a patch in 3 patients.

Table II shows pathologic findings of the tumors of all patients and those with complete resection. The most common histologic type was squamous cell carcinoma and the next most common, adenocarcinoma. The excised tumors were comparatively large, and the 6 incompletely resected tumors were more than 70 mm. Two patients were classified as having stage T3 NX M0 disease because they had no lymph nodes sampled peri-

operatively. A complete resection was accomplished in 55 (87.3%) patients. It was performed in 37 (92.5%) of the patients with combined resection of the diaphragm only, but in 18 (78.3%) of the patients with excision of the diaphragm and other neighboring structures.

Information on the depth of tumor invasion to the diaphragm was available in 46 patients (Table III). Regarding the degree of tumor penetration into the diaphragm, 60.9% of all the tumors showed shallow invasion representing parietal pleura or subpleural tissue involvement and the remaining 39.1% showed deep invasion, meaning muscle or peritoneal infiltration. In the completely resected tumors, the rates were 65.0% and 35.0%, respectively.

One patient (1.6%) died within 30 days of the operation. However, afterward, 5 patients died of treatment-related complications. Adjuvant therapy was performed in 22 (34.9%) patients. Induction chemotherapy was carried out in only 1 patients. Postoperative therapy was performed in 21 patients, of whom 14 patients received chemotherapy, 3 chemoradiotherapy, and 4 radiation therapy alone. Recurrences occurred in 29 of the patients with completely resected tumors. The site of first relapse was defined in 19 of the patients with recurrence; locally recurrent diseases in 4 (one at the diaphragm), distant metastases in 13, and both local recurrence and distant metastases in 2.

As of February 28, 1998, the median follow-up time of all patients was 531 days with a range of 28 to 3051

Number at risk

T3 N0 M0	26	18	10	5	2
T3 N1-2 M0	29	12	7	4	0

Fig 2. Survival curves of patients with complete resection according to lymph node involvement.

days. Fifteen patients with complete resection were alive, and 13 of them were without recurrence. The 5-year survival of all the patients was 19.4% (95% CI, 8.2%-30.6%). That of the 55 patients who had complete resection was 22.6% (95% CI, 9.8%-35.3%), whereas there were no 4-year survivors among the patients with incomplete resection ($P = .024$) (Fig 1).

Among patients with complete resection, the 5-year survival of patients with combined resection of the diaphragm only was 27.6% (95% CI, 11.2%-43.9%), but no 5-year survivor was found among patients with excision of the diaphragm and other organs ($P = .073$). A significant difference in survival according to the stage of disease is shown in Fig 2. The 5-year survivals of patients with stage IIB (T3 N0 M0) disease and stage IIIA (T3 N1-2 M0) disease were 28.3% (95% CI, 7.9%-48.6%) and 18.1% (95% CI, 3.1%-33.1%), respectively ($P = .013$). Furthermore, the figure was 20.0% (95% CI, 0%-44.8%) for patients with N1 disease, and there were no 5-year survivors in the group of patients with N2 disease, although no significant difference was found in either group ($P = .683$). To estimate the impact of the depth of diaphragmatic involvement on the prognosis, we compared the survival curves according to the degree of invasion (Fig 3). The 5-year survivals of patients with shallow invasion and deep invasion were 33.0% (95% CI, 11.1%-54.8%) and 14.3% (95% CI, 0%-32.6%), respectively. There was a significant difference ($P = .036$) between the groups.

Discussion

The treatment and prognosis of patients with non-small cell lung cancer are dependent on the stage of the disease. Surgical resection has been shown to offer a significant chance of cure for patients with lung carcinoma confined to the parenchyma. However, the surgical candidacy of patients with tumor extension to the adjacent structures has elicited considerable controversy. T3 lesions such as tumors invading the chest wall, pericardium, or main bronchus are generally considered potentially surgically resectable for cure.¹⁻⁴ Tumors with direct invasion of the diaphragm have also been categorized to the T3 lesions in the staging system and considered to be curable by resection.¹⁰ Nevertheless, because lung cancer involving the diaphragm is a rare disease, only a few reports have been published concerning surgical treatment of patients with those tumors, and those reports contained small numbers of cases.⁶⁻⁹ Consequently, very little information has been presented on the clinical features and proper treatment of tumors with diaphragmatic involvement.

From the present retrospective study, we have obtained clinical data and surgical results on a number of patients with lung cancer involving the diaphragm. The incidence of diaphragmatic invasion encountered at thoracotomy for resection of lung carcinoma was low at 0.38%, and this rate was comparable with those of previous reports (0.17%⁶ to 0.4%⁹). More than half of the patients were symptomatic, but their symptoms were nonspecific. Accurate diagnosis of diaphragmatic

Number at risk					
Shallow invasion	26	17	12	7	2
Deep invasion	14	7	3	2	0

Fig 3. Survival curves of patients with complete resection according to the depth of diaphragmatic invasion.

invasion was very difficult even with chest CT, because there are no accurate criteria for diagnosing the diaphragmatic invasion of lung tumors. Accordingly, the clinical stage of the patients was very diverse.

Surgical treatment consisted of en bloc resection of the primary tumor and the involved diaphragm in all patients. Moreover, in 23 patients (36.5%) with T3 disease, other involved structures (parietal pleura, chest wall, and pericardium) were resected along with the primary lesions. Tumors involving the diaphragm tend to invade the neighboring structures. The repair method of the diaphragm was usually primary closure irrespective of the tumor size. Since complete resection was accomplished in 87.3% of the study population, tumors with diaphragmatic invasion are considered resectable lesions with an acceptable mortality only when they are T3 N0-2 M0 tumors. The histologic types of tumors were squamous cell carcinoma in 60.3% of the patients and adenocarcinoma in 31.7%; these rates are comparable with those of the report by Rocco and associates.⁹ As for the degree of tumor penetration into the diaphragm, deeper invasion of the diaphragm may indicate a more advanced tumor.

Our survival data confirmed that incomplete resection of lung cancer with diaphragmatic involvement offered the patients no curative benefit. In patients with complete resection, combined resection of organs other than the diaphragm had an adverse effect on survival. On the contrary, there is a statistically significant survival advantage for node-negative disease and shallow tumor invasion into the diaphragm. That is, the 5-year

survival of patients with T3 N0 M0 tumors and/or shallow invasion was about 30%, whereas that of patients with T3 N1-2 M0 and/or deep invasion was less than 20%. These survival results are equivalent to those of Rocco's series⁹ and are better than those of other reports in which there were no long-term survivors.⁶⁻⁸

Comparing the surgical results in each TNM stage and specific T3 organs of large series, the data of patients with diaphragmatic invasion are worse in all stage categories (Table IV).^{1-4,7-10,12,13} The T3 N0 M0 subgroup is classified as stage IIB in the revised TNM staging system, and the 5-year survivals were reported as 33% to 52%. That of our patients was 28.3%, which is comparable with that of the group with stage IIIA disease. Furthermore, the survival of 18.1% in the T3 N1-2 M0 subgroup, which is included in stage IIIA, is lower than that (5-year survival, 23%) of the patients with T1-3 N2 M0 tumors in Mountain's series.¹⁰ Our survival data are comparable with those (5-year survival: 18%-25%) of completely resected stage IIB diseases documented by Watanabe,¹⁴ Tsuchiya,¹⁵ and their associates. From this point of view, tumors invading the diaphragm may be indicative of T4 disease as described by Inoue,⁷ Adebajojo,⁸ and their colleagues, or T4₁ disease proposed by Grunewald and Le Chevalier,¹⁶ which is considered to be potentially resectable in selected cases.

Conclusion

In selected patients with lung carcinoma and diaphragmatic invasion, combined resection of the lung and diaphragm offers the prospect of cure with an acceptable

Table IV. Survival of patients with completely resected T3 N0-2 M0 lung cancer

T3 organs	First author	Year	No. of patients	Five-year survival (%) by node status		
				N0	N1	N2
All T3 organs	Naruke ¹²	1988	191	33	39	
	Watanabe ¹³	1991	88	52	47	10
	Mountain ¹⁰	1997	142	38	25	
	Inoue ⁷	1998	122	34	38	11
	Adebonojo ⁸	1999	72	47	33	15
Chest wall	Shah ¹	1995	55	45	38	0
	Pitz ²	1996	83	36	23	14
	Downey ³	1999	175	49	27	15
Mediastinum + main bronchus	Pitz ⁴	1996	64	45	37	0
Diaphragm	Rocco ⁹	1999	15	27	0	0
	Yokoi (present study)	2000	55	28	20	0

mortality when a complete resection is accomplished. Nevertheless, primary lung tumors with diaphragmatic invasion, especially invasion of the muscle layer or deeper tissue, are considered to be unsuitable for T3 lesions, because these cancers are generally technically resectable but oncologically almost incurable diseases.

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Appendix

This study was carried out as a work in the Lung Cancer Surgical Study Group (Chairman: Harubumi Kato, MD) of the Japan Clinical Oncology Group. Principal investigators of institutions participating in this study include Yoshio Hosokawa, MD (Kinikyo Central Hospital, Hokkaido), Mitsuo Kawamura, MD (Nakadohri General Hospital, Akita), Sigefumi Fujimura, MD (Tohoku University, Miyagi), Toru Sato, MD (Yamagata Prefectural Central Hospital, Yamagata), Simao Fukai, MD (National Seiranso Hospital, Ibaraki), Ryuta Amemiya, MD (Ibaraki Prefectural Central Hospital & Cancer Center, Ibaraki), Kohei Yokoi, MD (Tochigi Cancer Center, Tochigi), Yuichi Ozeki, MD (National Defense Medical College, Saitama), Kanji Nagai, MD (National Cancer Center East, Chiba), Ryosuke Tsuchiya, MD (National Cancer Center, Tokyo), Koichi Kobayashi, MD (Keio University, Tokyo), Ken Nakagawa, MD (Cancer Institute Hospital, Tokyo), Masumi Kurashige, MD (Toho University Ohashi Hospital, Tokyo), Shiro Yamazaki, MD (Toho University Omori Hospital, Tokyo), Hiroaki Nomori, MD (Saiseikai Central Hospital, Tokyo), Kiyoshi Koizumi, MD (Nippon Medical School, Tokyo), Masahiro Kase, MD

(Yokohama Municipal Citizen's Hospital, Kanagawa), Hirokuni Yoshimura, MD (Kitasato University, Kanagawa), Teruaki Koike, MD (Niigata Cancer Center Hospital, Niigata), Yoh Watanabe, MD (Kanazawa University, Ishikawa), Nobuhiro Nishizawa, MD (Saku General Hospital, Nagano), Tetsuya Mitsudomi, MD (Aichi Cancer Center, Aichi), Tsutomu Yasumitsu, MD (Osaka Prefectural Habikino Hospital, Osaka), Takashi Mori, MD (National Kinki Central

Hospital, Osaka), Hirohito Tada, MD (Osaka City General Hospital, Osaka), Hajime Maeda, MD (Toneyama National Hospital, Osaka), Hiroshige Nakamura, MD (Tottori University, Tottori), Hideyuki Saeki, MD (National Shikoku Cancer Center, Ehime), Yukito Ichinose, MD (National Kyusyu Cancer Center, Fukuoka), Tsugio Furukawa, MD (Saga Prefectural Koseikan Hospital, Saga), and Keiichiro Genka, MD (National Okinawa Hospital, Okinawa).