



# The Role of Primary Tumor Resection in Patients with Pleural Metastasis Encountered at the Time of Surgery

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**Background:** Evidence is lacking on whether the resection of lung parenchymal cancer improves the survival of patients with unexpected pleural metastasis encountered during surgery. We conducted a single-center retrospective study to determine the role of lung resection in the long-term survival of these patients.

**Methods:** Among 4683 patients who underwent lung surgery between 1995 and 2014, 132 (2.8%) had pleural metastasis. After excluding 2 patients who had incomplete medical records, 130 patients' data were collected. Only a diagnostic pleural and/or lung biopsy was performed in 90 patients, while the lung parenchymal mass was resected in 40 patients.

**Results:** The mean follow-up duration was 29.8 months. The 5-year survival rate of the resection group (34.7%±9.4%) was superior to that of the biopsy group (15.9%±4.3%, p=0.016). Multivariate Cox regression analysis demonstrated that primary tumor resection (p=0.041), systemic treatment (p<0.001), lower clinical N stage (p=0.018), and adenocarcinoma histology (p=0.009) were significant predictors of a favorable outcome. Interestingly, primary tumor resection only played a significant prognostic role in patients who received systemic treatment.

**Conclusion:** When pleural metastasis is unexpectedly encountered during surgical exploration, resection in conjunction with systemic treatment may improve long-term survival, especially in adenocarcinoma patients without lymph node metastasis.

**Keywords:** Lung neoplasms, Non-small-cell lung carcinoma, Pleural metastasis

## Introduction

Approximately 40% of cases of non-small cell lung cancer (NSCLC) are metastatic at the time of diagnosis [1]. Pleural dissemination, which refers to malignant pleural effusion and/or pleural nodules, is identified in 1%–7.5% of NSCLCs and is a component of the M1a descriptor [1,2]. The median survival duration of patients with M1a disease is 8–11.5 months [2,3]. Owing to the poor prognosis of pleural dissemination, with a 2% 5-year survival rate, NSCLC with pleural dissemination was reclassified from T4 to M1a in the seventh edition of the tumor-node-metastasis (TNM) staging system [2].

NSCLC with a solitary metastasis may be treated by resecting both the primary and metastatic lesions, with a fa-

vorable survival rate [4,5]. Consequently, it was proposed for the eighth edition of the TNM staging system that metastasis at a single site or single organ should be distinguished from other distant metastatic lung cancer [3]. A contralateral lung nodule (the other M1a descriptor) may sometimes also be a surgical candidate. In contrast, NSCLC with pleural metastasis is not a candidate for surgical resection according to standard treatment guidelines, as pleural dissemination is not amenable to complete resection [6]; therefore, the M1a category was not revised for the eighth edition of the TNM staging system [3]. However, several studies have reported reasonable survival outcomes after surgical resection of the primary tumor in patients with pleural dissemination [7-11]. Therefore, it remains unclear whether resection of the primary tumor can improve



survival in patients with pleural metastasis encountered at the time of surgery [12].

We aimed to evaluate the role of primary tumor resection in patients with pleural dissemination of NSCLC and to identify other predictors of long-term survival.

## Methods

### Patients

Among 4,683 patients who underwent lung surgery between 1995 and 2014, 132 (2.8%) were identified as having clinical M0 stage disease and found to have unexpected pleural metastasis at the time of surgery. After excluding 2 patients whose medical records were not complete, 130 patients' data were collected. Survival data were confirmed using medical records, telephone surveys, and the national insurance database. Data were analyzed to test the role of lung resection in long-term survival and to identify other predictors of patients' prognosis. The primary tumor was not resected in 90 patients, in whom only a diagnostic pleural biopsy was performed, whereas the primary lung mass was resected in 40 patients. Systemic treatment (cytotoxic chemotherapy and/or tyrosine kinase inhibitors) was administered to 110 patients (84.6%). Several clinical variables were analyzed to identify factors that could have influenced the long-term survival of these 2 groups. This study was reviewed and approved by the Institutional Review Board at Seoul National University Hospital (IRB approval no., H-1602-050-739). The recommendations of the Declaration of Helsinki for biomedical research involving human subjects were followed. Informed consent was waived.

### Statistical analysis

Categorical variables are presented as numbers and percentages. Continuous variables are presented as means and standard deviations. Statistical analysis was performed using IBM SPSS ver. 22.0 (IBM Corp., Armonk, NY, USA). In the univariate analysis, categorical variables were compared using the chi-square test and the Fisher exact test. Continuous variables were compared using the Student t-test. Survival curves were obtained using the Kaplan-Meier method and compared between the 2 groups using the log-rank test. Prognostic factors for survival were analyzed with a Cox proportional hazard ratio model fit with a backward selection method. The proportional hazards assumption, tested by a log minus log plot, was satisfied. Variables with  $p \leq 0.1$  in the univariate analysis were included

in the multivariate analysis. Interactions between any 2 variables in the multivariate models were tested. A  $p$ -value of  $\leq 0.05$  was considered to indicate statistical significance in both the univariate and multivariate analyses.

## Results

### Clinicopathologic characteristics

Patients' characteristics are described in Table 1. The study population had a male predominance (total, 130; male-to-female ratio, 75:55) and most patients had adenocarcinoma ( $n=109$ , 83.8%). The mean age was 61.5 years. The mean follow-up duration was  $29.8 \pm 23.7$  months. There were no cases of surgery-related mortality. Of the 65 patients tested for epidermal growth factor receptor (*EGFR*) mutation status, 50.5% were positive. Clinical variables including age, sex, tumor size, tumor location, histologic cell type, systemic treatment, clinical T stage, clinical N stage, *EGFR* mutation status, and preoperative pulmonary function were similar between the 2 groups.

### Survival

The overall 5-year survival rate was 20.1% (Fig. 1). The median survival time was estimated at 26.3 months. Patients who received systemic treatment survived longer than those who did not (5-year survival rate, 22.3% versus 6.2%;  $p < 0.001$ ). The 5-year survival rate of the resection group was superior to that of the biopsy group (5-year survival rate, 34.7% versus 15.9%;  $p = 0.016$ ) (Fig. 2). There was no significant difference in survival according to the extent of resection ( $p = 0.719$ ). When patients were stratified according to whether they received systemic treatment, the survival curves of the 2 groups showed different patterns. A protective role of primary tumor resection was only observed in patients who received systemic treatment (Fig. 3A). In the systemic treatment group, patients who underwent primary tumor resection showed better survival outcomes than those who underwent biopsy (5-year survival rate, 40.0% versus 17.2%;  $p = 0.009$ ). However, among patients who did not receive chemotherapy, the median survival time was extremely poor in both groups (resection group versus biopsy group: 11.8 months versus 8.3 months), indicating that resection failed to improve survival ( $p = 0.775$ ) (Fig. 3B).

**Table 1.** Clinicopathological characteristics of the patients

Characteristic	Total (N=130)	Primary tumor resection group (n=40)	Biopsy group (n=90)	p-value
Age (yr)	61.5±11.7	62.7±11.1	61.0±12.0	0.425
Female sex	55 (42.3)	16 (40.0)	39 (43.3)	0.723
Never-smoker	74 (56.9)	21 (52.5)	53 (58.9)	0.566
Forced expiratory volume in 1 second (predicted %)	98.1±21.4	102.6±21.7	95.7±21.0	0.117
Tumor size (cm)	3.2±1.4	3.3±1.7	3.1±1.2	0.428
Tumor location				0.670
Central	35 (26.9)	12 (30.0)	23 (25.6)	
Periphery	95 (73.1)	28 (70.0)	67 (74.4)	
Histology	130	40	90	0.287
Squamous cell carcinoma	12 (9.2)	6 (15.0)	6 (6.7)	
Adenocarcinoma	109 (83.8)	32 (80.0)	77 (85.6)	
Others	9 (6.9)	2 (5.0)	7 (7.8)	
Systemic treatment (yes)	110 (84.6)	35 (87.5)	75 (83.3)	0.543
Cytotoxic chemotherapy (yes)	96 (73.8)	28 (70.0)	68 (75.6)	0.522
Tyrosine kinase inhibitor (yes)	72 (55.4)	21 (52.5)	51 (56.7)	0.705
T stage				0.503
1	38 (29.2)	14 (35.5)	24 (26.7)	
2	61 (46.9)	18 (45.0)	43 (47.8)	
3	22 (16.9)	7 (17.5)	15 (16.7)	
4	9 (6.9)	1 (2.5)	8 (6.2)	
N stage				0.168
0	86 (66.2)	26 (65.0)	60 (66.7)	
1	21 (16.2)	10 (25.0)	11 (12.2)	
2	21 (16.2)	4 (10.0)	17 (18.9)	
3	2 (1.5)	0	2 (2.2)	
Surgery	130	40	90	
Pleural or lung biopsy		-	90 (100.0)	
Primary tumor resection		40 (100.0)	-	
Wedge resection		16 (40.0)		
Lobectomy		21 (52.5)		
Pneumonectomy		3 (7.5)		
Length of hospital stay	8.0±7.9	9.9±11.7	7.1±5.2	0.153
Epidermal growth factor receptor mutation (yes) (n=65)	33/65 (50.5)	16/27 (59.3)	17/38 (44.7)	0.248

Values are presented as mean±standard deviation or number (%).

## Prognostic factors for long-term survival

In the univariate analysis, clinical N stage and adenocarcinoma histology were additional significant factors associated with favorable survival outcomes, whereas age, sex, and clinical T stage were not significant (Table 2). In the multivariate Cox regression analysis, primary tumor resection, systemic treatment, clinical N0 stage, and adenocarcinoma histology remained significant factors associated with favorable outcomes (Table 3).

## Interaction analysis

A significant interaction was found between primary tu-

mor resection and systemic treatment ( $p=0.017$ ). This demonstrated a differential effect of systemic treatment on the impact of primary tumor resection. After adjusting for interaction between primary tumor resection and systemic treatment, clinical N0 stage (hazard ratio [HR], 1.811; 95% confidence interval [CI], 1.158–2.832;  $p=0.009$ ) and adenocarcinoma histology (HR, 0.344; 95% CI, 0.172–0.689;  $p=0.003$ ) remained significant predictors of favorable survival. We then estimated the HRs for mortality according to whether primary tumor resection was performed. The HR of systemic treatment decreased from 0.296 (95% CI, 0.158–0.555;  $p<0.001$ ) to 0.069 (95% CI, 0.024–0.200;  $p<0.001$ ), suggesting that resection of the primary tumor may significantly strengthen the effect of systemic treat-

ment (Table 3).

### Discussion

Although the mainstay of treatment in patients with advanced-stage cancer is systemic chemotherapy [13], our study showed that surgery can yield an additional survival benefit in carefully selected patients. Metastasis to a single organ, such as the adrenal gland or brain, can be treated with resection of the primary tumor and local management of the metastatic lesion, either with surgery or with a gamma knife. Therefore, the recent eighth edition of the TNM staging system for lung cancer proposed a subclassification of the M description based on the number of metastatic lesions and sites [3]. Oligometastasis in the brain,

liver, bone, adrenal gland, skin, and distant lymph nodes, which can be managed with aggressive local treatment, has a survival rate similar to that of M1a disease and better than that of cases with multiple metastases to a single organ [3,14]. These outcomes contributed to the subclassification of the M stage, which was divided into M1a and M1b, corresponding to a distinction between stage IV and stage IVa, in the eighth edition [3].

Pleural dissemination, which accounts for 13%–14% of all cases of metastatic lung cancer, remained in the M1a category [2,3], and the role of primary tumor resection in cases of pleural dissemination has not been established. Unlike brain or adrenal metastases, complete resection is not possible in pleural dissemination, with the exception of

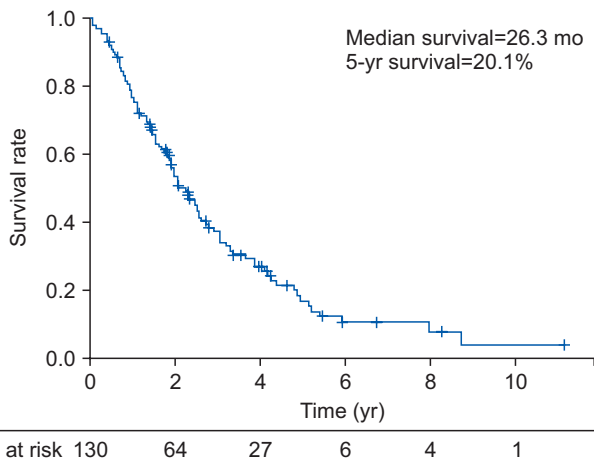


Fig. 1. Kaplan-Meier plot of the overall survival rate of non-small cell lung cancer patients with pleural metastasis.

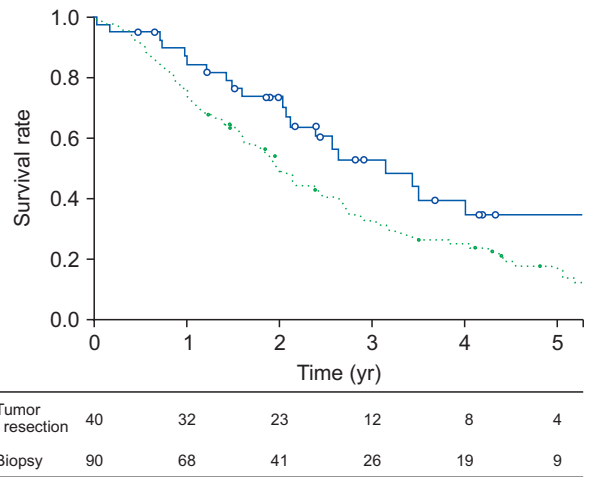


Fig. 2. Kaplan-Meier plots of survival rates according to primary tumor resection (solid line: primary tumor resection group; dotted line: biopsy group).

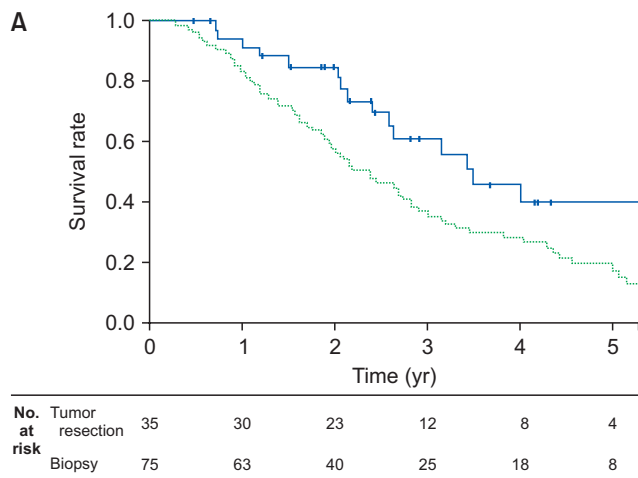


Fig. 3. Kaplan-Meier plots of survival rates according to systemic treatment (solid line: primary tumor resection group; dotted line: biopsy group). (A) Patients who received systemic treatment. (B) Patients who did not receive systemic treatment.

**Table 2.** Univariate analysis of prognostic factors for long-term survival in non-small cell lung cancer

Variable	Hazard ratio (95% confidence interval)	p-value
Age (vs. ≥65 yr)		
<65 yr	1.225 (0.815–1.840)	0.328
Sex (vs. male)		
Female	0.990 (0.660–1.484)	0.961
Smoking (vs. ever-smoker)		
Never-smoker	0.700 (0.468–1.045)	0.081
Epidermal growth factor receptor mutation (vs. wild-type)		
Yes	0.621 (0.327–1.180)	0.146
Tumor size (vs. ≥3 cm)		
<3 cm	0.951 (0.626–1.445)	0.815
Tumor location (vs. central)		
Periphery	0.795 (0.511–1.236)	0.308
Clinical T stage (vs. ≥T2)		
T1	0.883 (0.568–1.374)	0.581
Clinical N stage (vs. ≥N1)		
N0	0.644 (0.419–0.990)	0.045
Systemic treatment (vs. no)		
Yes	0.254 (0.149–0.431)	<0.001
Resection (vs. biopsy only)		
Primary tumor resection	0.557 (0.343–0.903)	0.018
Extent of resection (vs. wedge resection) (n=40)		
≥ Lobectomy	0.842 (0.330–2.146)	0.719
Histology (vs. squamous cell carcinoma)		0.039
Adenocarcinoma	0.512 (0.263–0.997)	0.049
Others	0.981 (0.396–2.429)	0.966

extra-pleural pneumonectomy. Yokoi et al. [15] reported a 5-year survival rate as high as 54.5% after extra-pleural pneumonectomy in carefully selected patients. More recent studies have reported that surgical resection of the primary tumor in NSCLC with pleural dissemination was beneficial in selected patients, particularly in those with N0 status, T1-2 disease, and adenocarcinoma histology [7-10,16,17]. Resection of the primary lesion may provide effective local control because chemoradiation therapy often fails, with a locoregional failure rate of 31%–100% [18,19]. In addition, as minimally invasive surgery has been adopted and experience with lung cancer surgery has been accumulated, surgery-related morbidity and mortality have decreased [20,21], and hence, surgical resection of a parenchymal lung lesion can be safely performed without adding significant operative complications. In our study, it was evident that primary tumor resection was performed in patients with good physical status, clinical N0 stage, and minimal pleural seeding. However, Li et al. [17] reported that there

**Table 3.** Multivariate Cox regression analysis of prognostic factors for long-term survival in non-small cell lung cancer

Variable	Hazard ratio (95% confidence interval)	p-value
Clinical N stage (vs. ≥N1)		
N0	0.566 (0.362–0.884)	0.012
Histology (vs. squamous cell carcinoma)		0.009
Adenocarcinoma	0.372 (0.186–0.742)	0.005
Others	0.637 (0.248–1.632)	0.347
Systemic treatment & resection		0.017
Primary tumor resection (vs. biopsy only)		
Systemic treatment (yes)	0.464 (0.264–0.815)	0.008
Systemic treatment (no)	1.994 (0.693–5.736)	0.201
Systemic treatment (vs. no)		
Primary tumor resection (yes)	0.069 (0.024–0.200)	<0.001
Primary tumor resection (no)	0.296 (0.158–0.555)	<0.001

were no differences in survival according to performance status, clinical stage, the presence of malignant pleural effusion, or the extent of pleural nodules in cases of adenocarcinoma. Notwithstanding, it is undeniable that when resection of the primary tumor can be safely performed, surgeons might decide to proceed to curative resection.

In several other reports, in which 57%–72% of patients received systemic treatment, chemotherapy was not found to improve survival [7,8,11]. Those conclusions are contradictory to ours. Most patients (85%) received systemic treatment in our series and demonstrated significantly better survival than those who did not, which may have resulted from selection bias. However, the fact that surgical resection of the lung lesion was only beneficial if the patient underwent systemic treatment was interesting. A possible explanation for our observations is that surgery decreased the tumor burden, while chemotherapy treated microscopic disease. In fact, we found that the best long-term survival was achieved when both the tumor size and nodal stage were low. Although our data do not provide direct evidence regarding this possibility, our observations suggest that primary tumor resection may play a more impactful role for tumors with actionable mutations that can be treated with molecular target agents. We analyzed the presence of an *EGFR* mutation as a factor that might affect patients' outcome. Unfortunately, however, we did not routinely examine *EGFR* mutation status and we failed to prove that *EGFR* mutation status had a statistically significant relationship with survival, as was shown in a previous study [17]. Currently, we routinely evaluate *EGFR* mutation status and *ALK* gene rearrangement in all patients, and we

hope to clarify the role of surgical resection of the primary tumor in patients who harbor a targetable mutation in the near future.

It has been suggested that tumor stage, sex, weight loss, and performance status are predictive factors of the success of systemic treatment. Performance status is an extremely powerful prognostic factor for survival and has been considered as the most important factor in selecting patients eligible for chemotherapy [22,23]. However, we did not include performance status in this study, because surgery was planned for all patients, meaning that their performance status was good.

We were not able to extract information regarding the number of pleural nodules. Dry pleural dissemination has been reported to have a better prognosis than wet pleural dissemination [8,9,16,24]. As all the patients were in the cM0 stage, the majority of our patients had dry pleural metastases. However, a multicenter survey reported that there was no significant difference in prognosis according to M1a descriptors (pleural effusion, pleural nodules, contralateral lung nodules) [3].

There are several limitations of this study. Surgical resection is not recommended for cases of extremely advanced lung cancer with overt pleural effusion or pleural nodules; hence, there was obvious selection bias in our study. Importantly, our conclusions should only be applied to patients in whom pleural seeding was unexpectedly diagnosed at the time of surgery. *EGFR* mutation data was available for only half of the patients. In addition, we did not analyze patients' response to chemotherapy or disease progression. As a consequence, we were not able to perform an interaction analysis to eliminate the effect of tumor biology. However, our results suggest that resection of the primary tumor can lead to improved survival if patients can undergo systemic treatment for NSCLC with pleural dissemination that was unexpectedly encountered during surgery, especially in cases of adenocarcinoma without lymph node metastasis. Furthermore, in the era of precision medicine, surgical resection of the primary tumor may serve as an effective local treatment in conjunction with appropriate targeted therapy.

In conclusion, when pleural metastasis is encountered during surgical exploration, primary tumor resection can improve long-term survival in conjunction with systemic treatment, especially in selected patients with adenocarcinoma histology without lymph node metastasis.

## Conflict of interest

No potential conflict of interest relevant to this article was reported.

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