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Is previous delay to surgery necessarily associated with worse prognosis in operable stage non-small cell lung cancer?

Short Title: Effect of delayed surgery on operable stage NSCLC

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Abstract

Introduction: To assess the impact of delayed surgery on the prognosis of patients with operable stage non-small cell lung cancer (NSCLC).

Methods: A retrospective review of 140 patients with clinical operable stage NSCLC (I, II, IIIA) who underwent curative surgery was conducted. Patients were divided into two groups: those who underwent surgery within 3 months of initial lung tumor detection (non-delayed group, n=82) and those with surgery beyond 3 months (delayed group, n=58). Patient characteristics, reasons for surgical delay, pathology, surgical outcomes, and long-term survival were analyzed.

Results: The median time from lung tumor detection to surgery was 13.7 months (range, 3.1 months-12.1 years) in delayed group, and 0.9 months (range, 3 days-2.8 months) in non-delayed group ($P < 0.001$). The delayed group had a higher proportion of patients at clinical stages I and II, and a lower proportion at clinical stage IIIA as compared with non-delayed group ($P=0.046$). The incidence of lymphovascular invasion was significantly lower in delayed group ($P=0.031$). There was no significant difference between groups in terms of pathological upstaging, positive surgical margins, surgical morbidity and mortality, adjuvant treatment, disease-free survival, and overall survival.

Conclusions: The prognosis for patients with delayed diagnosis or surgery for NSCLC may not necessarily be worse than for those who receive timely surgery. For

these patients, in spite of previous delay, surgical resection remains an important treatment option if lung cancer is assessed as an operable stage disease preoperatively.

Keywords: delay; non-small cell lung cancer; surgery; survival

Introduction

Lung cancer is the most common cause of cancer-related death worldwide [1]. In Taiwan, with the wide use of chest computed tomography (CT) for health examination and for lung cancer screening in high-risk patients, lung cancer has replaced colorectal cancer as the first common malignancy in general population since 2021 [2], and continues to result in the largest number of cancer deaths for more than 4 decades, accounting for one-fifth (19.4%) of all cancer mortality in 2023 [3]. It is clear that lung cancer is a considerable public health problem and an important burden on healthcare systems in terms of morbidity and mortality [4, 5]. However, significant reductions in lung cancer mortality rate can be made by identifying cancer early and avoiding delays in treatment [6].

Non-small cell lung cancer (NSCLC), accounting for more than 80% of all lung cancers [7, 8], is a potentially curable disease by surgical resection. The most important factor for prognosis of NSCLC is related to the stage at the time of operation, which is dependent on when the tumor is identified. Unfortunately, in clinical practice we have observed that a part of lung cancers have been present on the chest radiographs or CT scans for several months or even for many years before

surgery. The reasons for delays in the diagnosis and surgical treatment of lung cancer are contributed to a variety of doctor- or patient-related factors. Ellis and Vandermeer found that patients spent a median of 138 days waiting from the initial symptom to commencement of treatment [9]. Koyi et al. also noted that the mean total time from the first onset of symptoms until treatment was 203 days, and further pointed out that of this total time, the mean patient's delay was 43 days (21.2%), and the rest was doctors' delay (78.8%) [10].

Although the general belief is that the earlier the diagnosis and treatment the better the outcome in all cancer patients, the impact of surgical delay in NSCLC on survival is uncertain. Some studies conclude that delayed surgery for lung cancers worsen the stage of the disease and the patient prognosis [11-14]. Other papers, however, show that the diagnostic and therapeutic delay is not a significant factor to influence survival [15-20]. The aim of this study was to investigate the causes for delayed surgery, and to comprehensively assess the association of delayed surgery with pathologic features, surgical outcomes and survival in patients with an operable stage NSCLC (I, II, and IIIA).

The study protocol was reviewed and approved by the Institutional Review Board of St. Martin De Porres Hospital on July 14, 2023 (approval number: 23B-015), and was deemed exempt from informed consent due to the deidentified nature of the analysis.

Methods

Selection of patients

Between July 2011 and December 2022, 205 patients with clinical stage I, II and IIIA NSCLC underwent curative surgery at the St. Martin De Porres Hospital. Patients in whom surgical resection was delayed due to neoadjuvant therapy (n=10), and those in which NSCLC presented as ground-glass opacity-predominant lesions on the CT scan (n=55) were excluded from the study. The remaining 140 patients were included for analysis. All available chest X-ray and CT scanning of the included patients were independently reviewed by 3 chest physicians. The time of first detection of lung tumors was decided by consensus of at least 2 of the 3 chest physicians. Delayed surgery was defined as more than 3 months between first detection of lung tumors on chest radiography or CT scanning and surgical resection. Of the 140 patients, 82 underwent surgery within 3 months in time from first detection of lung tumors to surgical resection (non-delayed group). The remaining 58 patients received surgery beyond 3 months after lung tumor was identified (delayed group).

Preoperative evaluation

All patients had chest radiography and CT scan of the lungs, mediastinum, and upper abdomen for initial assessment of lung tumors. The serum levels of carcinoembryonic antigen (CEA) and squamous cell carcinoma antigen were measured. Biopsy of lung tumors was performed under CT guidance depending on physician’s judgment. When tracheobronchial invasion was suspected, bronchoscopy combined with biopsy was carried out. Positron emission tomography-computed tomography (PET-CT) or mediastinoscopy would be followed when a mediastinal lymph node is 10 mm or

greater in diameter. Brain magnetic resonance imaging (MRI) and whole body bone scan were routinely performed to exclude metastasis. Cancer staging was according to the eighth edition AJCC staging system. All patients underwent pulmonary function studies before surgery.

Operative methods

The majority of patients underwent lobectomy for cancer resection. Sublobar resection, including wedge resection and segmentectomy, was performed in patients with significant comorbidity, reduced pulmonary function (forced expiratory volume in one second < 50%), or older age (>80 years old). Dissection of ipsilateral mediastinal lymph node was performed in all patients.

Adjuvant therapy

Patients with postoperative pathologic evidence of hilar or mediastinal lymph node involvement, or positive surgical margin would receive adjuvant chemotherapy, chemoradiation therapy, or target therapy according to the evaluation of hematology and radiation oncologists. In addition, even if there was no evidence of metastasis to regional lymph nodes (pN_0) on pathology, postoperative chemotherapy was suggested for patients with poorly differentiated tumors, tumors greater than 4cm in diameter, the presence of lymphovascular invasion, or visceral pleural involvement in tumors.

Outcome assessment

Clinical data collected from the medical records included patient age, sex, histological type, date of first detection of lung tumors, date and type of surgery,

clinical and pathologic stage, date of death or last follow-up, and the reasons for delayed surgery. The initial outcomes included histological grade, lymphovascular invasion, pathologic upstaging, positive surgical margins, surgical morbidity and mortality, adjuvant therapy. Chest CT was used and the serum level of CEA or squamous cell carcinoma antigen was determined at 4-month interval to identify possible recurrence or metastasis. If cancer relapse was suspected, brain MRI, bone scintigraphy, or PET-CT scan were further carried out.

Statistical analysis

Categorical data were analyzed with the Fisher's exact test. Mann-Whitney U test was used for analysis of continuous variables. $P<0.050$ was considered statistically significant. The Kaplan–Meier method with the log rank test was used to compare postoperative survival. All statistical analyses were performed using the statistical software package SPSS® version 25.0 (IBM Corp., New York, USA).

Results

Patient characteristics

The clinical data are summarized in *Table 1*. For patients undergoing surgery within 3 months, the median time from first detection of lung tumors to surgery was 0.9 months (range, 3 days-2.8 months), while for patients undergoing surgery more than 3 months, the interval was 13.7 months (range, 3.1 months-12.1 years) ($P<0.001$).

There was a significantly higher proportion of patients at clinical stage I and II NSCLC and a lower proportion at stage IIIA in delayed group as compared with those

who underwent surgery within 3 months (98.3% *versus* 89% and 1.7% *versus* 11%, respectively, *P*=0.046).

Table 1 Clinical data of 140 patients undergoing curative surgery for clinical operable stage non-small cell lung cancer

Patient characteristics	**Surgery＜3 months (n=82)**	**Surgery＞3 months (n=58)**	***P****
Age (years), median (range)	65 (34-86)	65.5 (45-87)	0.481†
Sex, n (%)			0.063
Male	47 (57.3)	24 (41.4)	
Female	35 (42.7)	34 (58.6)	
Histological type, n (%)			0.195
Adenocarcinoma	62 (75.6)	51 (87.9)	
Squamous cell carcinoma	15 (18.3)	5 (8.6)	
Other	5 (6.1)	2 (3.4)	
First detection on, n (%)			0.921
chest radiography	60 (73.2)	42 (72.4)	
computerized tomography	22 (26.8)	16 (27.6)	
Time from first detection of tumors to surgery (months), median (range)	0.9 (0.1-2.8)	13.7 (3.1-145.4)	<0.001†
Clinical stage, n (%)			0.046
I, II	73 (89)	57 (98.3)	
IIIA	9 (11.0)	1 (1.7)	
Surgery type, n (%)			0.373
Lobectomy	68 (82.9)	43 (74.1)	
Sublobar resection	12 (14.6)	12 (20.7)	
Bilobectomy/pneumonectomy	2 (2.4)	3 (5.2)	

*Fisher's exact test, except for †Mann-Whitney U test.

The causes of delayed surgery included 46 patients (79.3%) due to doctor delay (22 described as a benign lesion, 15 missed diagnosis on chest radiography, and 9 treatment of comorbidity) and 12 (20.7%) due to patient delay **(***Table 2***)**.

Table 2 Reasons for surgical delay in 58 patients

Cause (n=58)	**n (%)**
Doctor delay	46 (79.3)
Described as a benign lesion	22 (37.9)
Missed diagnosis on chest radiography	15 (25.9)
Treatment of comorbidity	9 (15.5)
Patient delay	12 (20.7)

Pathologic findings and surgical complications

The pathological features, including histological grade, pathologic upstaging, and positive surgical margins were not significantly different between the groups (*Table 3*), while the presence of lymphovascular invasion was more frequently found in patients undergoing surgery within 3 months (P=0.031). In the series, two postoperative deaths occurred in non-delayed group. One patient, who had a clinical stage IIIA squamous cell carcinoma and had undergone pneumonectomy, died of respiratory failure 1 day after surgery. The other patient, in whom a lobectomy had been performed for a clinical stage I adenocarcinoma, died from brain stem infarction on postoperative day 3. However, the analysis showed that there was no significant difference between the groups in surgical morbidity and mortality (*Table 3*).

Table 3 Pathologic features, surgical morbidity and mortality in 140 patients undergoing curative surgery for clinical operable stage non-small cell lung cancer

	Surgery＜3 months (n=82)	**Surgery＞3 months (n=58)**	***P****
Histological grade, n (%)			0.369
1, 2	55 (67.1)	43 (74.1)	
3, 4	27 (32.9)	15 (25.9)	
Lymphovascular invasion, n (%)	31 (37.8)	12 (20.7)	0.031
Pathologic upstaging, n (%)	17 (20.7)	8 (13.8)	0.291
Positive surgical margins, n (%)	2 (2.4)	3 (5.2)	0.649
Morbidity, n (%)	4 (4.9)	7 (12.1)	0.200
Empyema	2	2	
Hemothorax	0	2	
Pneumonia	1	2	
Acute respiratory failure	1	1	
Mortality, n (%)	2 (2.4)	0 (0)	0.511

*Fisher's exact test.

Long-term outcome

The median follow-up after surgery was 3.2 years (range, 1.5 months to 11.6 years);

long-term results are shown in *Table 4*.

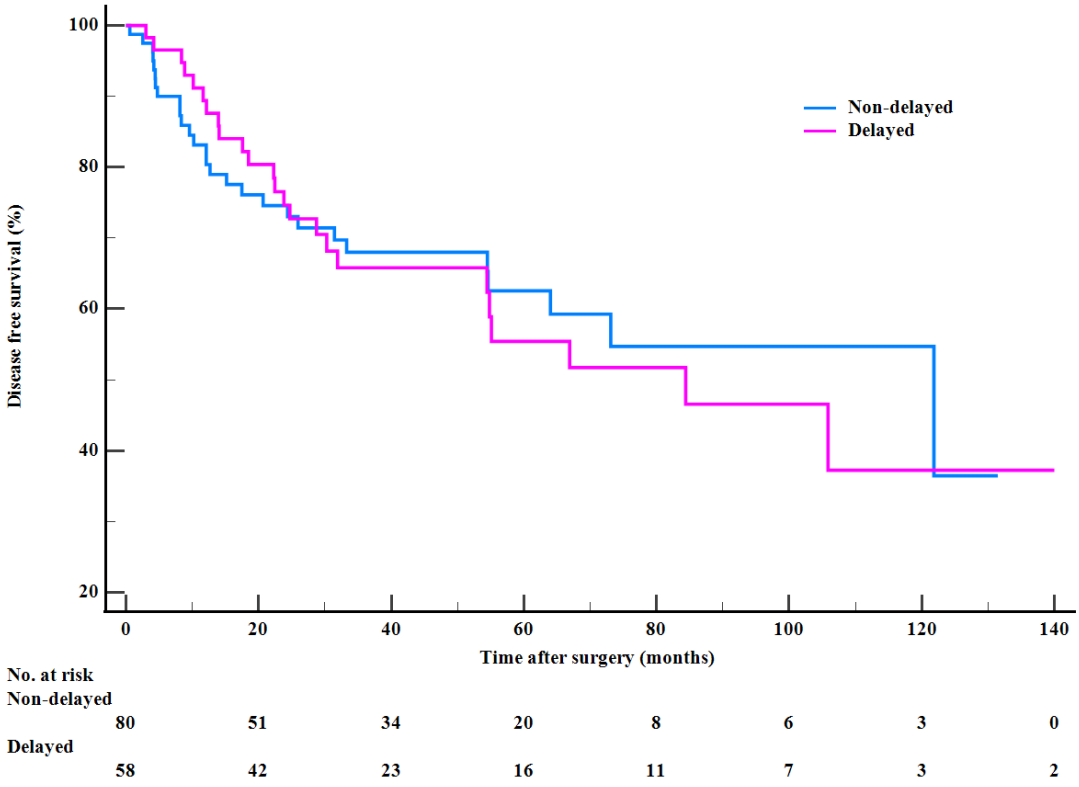
Table 4 Outcome for 138 patients undergoing curative surgery for clinical operable stage non-small cell lung cancer

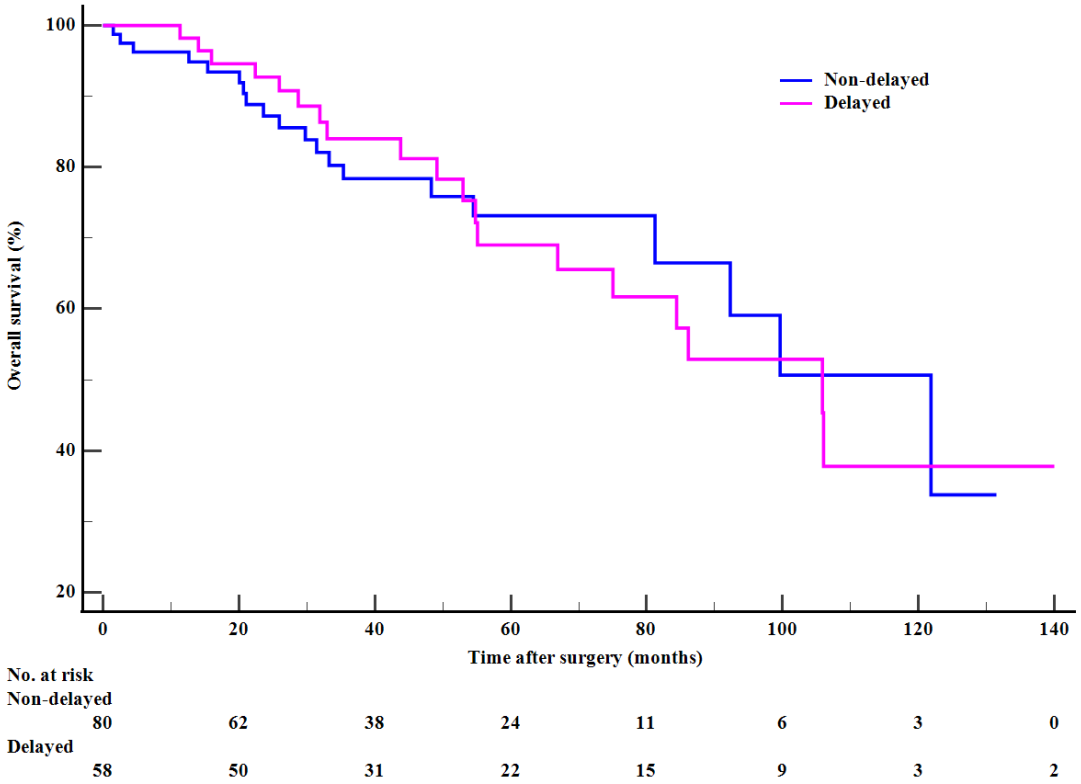
	Surgery＜3 months (n=80)*	Surgery＞3 months (n=58)	*P*†
Adjuvant therapy, n (%)	36 (45.0)	25 (43.1)	0.825
Chemotherapy	16	10	
Chemoradiation therapy	4	5	
Target therapy	8	3	
Refusal therapy	8	7	
Cancer recurrence, n (%)	21 (26.3)	16 (27.6)	0.959
Mortality during follow-up	20 (25.0)	20 (34.5)	0.326
Died from lung cancer, n (%)	13 (16.2)	10 (17.2)	0.877
Died from other cause, n (%)	7 (8.8)	10 (17.2)	0.134

*Two surgical deaths have been excluded. †Fisher's exact test.

There was no statistical difference between non-delayed and delayed groups in terms of adjuvant treatment. During follow-up, twenty one (26.3%) cancer recurrences occurred in non-delayed group. In delayed group, sixteen patients (27.6%) developed cancer recurrence (*P*=0.959). Thirteen (16.2%) patients died from lung cancer in non-delayed group and ten (17.2%) in delayed group (*P*=0.877). The respective 5-year survival rates were 74.6 and 69.0% (*P*=0.934). Kaplan-Meier analysis showed that there was no significant difference between the groups in disease-free survival and overall survival (*P*=0.874 and 0.941, respectively) (*Fig. 1A* and *1B*).

Fig. 1. Comparison of disease-free survival (**A**) and overall survival (**B**) in patients undergoing curative surgery within (non-delayed group) and beyond (delayed group) 3 months for clinical operable stage lung cancer. *P*=0.874 and *P*=0.941, respectively (log rank test).





Discussion

In our institution, clinical staging, including CT scan of the lungs, mediastinum, and upper abdomen, cranial magnetic resonance imaging, and radionuclide bone scan, is to be repeated every 3 months for patients with an operable stage NSCLC. Therefore, we defined more than 3 months between the first detection of lung cancer on chest radiography or CT scan and the surgical resection as delayed surgery.

We conducted a retrospective analysis of patients who underwent curative surgery for operable stage NSCLC (I-IIIA) at a single institution. Part of this population experienced a broad range of delay (from 3.1 months to 12.1 years) between when the tumor was first present on the imaging and when it was resected. The most common

reason for delay in surgery was doctor-related. Our data was not able to determine whether previous delay in surgical resection is inevitably associated with poor prognosis when preoperative assessment of NSCLC is at an operable stage. Identifying barriers to early surgical resection that are within the control of patients or doctors may help reduce the percentage of patients for who surgery is delayed [11]. In patients, surgery for lung cancer is often delayed by prolonged decision making, or arranging their work or personal schedules [18]. However, the delays due to the doctors are much more common and can possibly be improved [10]. One of the most common causes for doctor delays may be contributed to missed diagnosis of lung cancer in radiology. A study performed by Quekel et al found a miss rate of 19% NSCLC on the chest film [21]. They indicated that small pulmonary lesions (less than 15 mm in diameter), and superposing anatomic structures, such as ribs, vessels, the heart, were the main reasons for missed diagnosis. The other significant issue contributing to diagnostic delay is that some radiographic abnormalities are described as benign lesions, such as pneumonia and fibrosis [22, 9]. In our series, 46 (79.3%) of 58 delays were caused by the doctors. Among them, 15 pulmonary nodules were missed on the chest radiographs and 22 were described as benign lesions. As a result, we think that considering the potential of CT to lower the miss rate in the diagnosis of lung cancer, patients who are at risk may be screened by this modality [23, 9], and biopsy may be aggressively performed in patients with an uncertain pulmonary lesion.

In the present series, there was a significantly higher proportion of patients at stage I

and II lung cancer, and lower proportion at stage IIIA in delayed group (*P*=0.046), suggesting that patients with delayed surgery had smaller tumors or earlier diseases. On the contrary, larger tumors or more advanced diseases were more commonly seen in non-delayed group. The finding seems to indicate that longer surgical delay is more frequently seen in patients with early stage lung cancer, and supports the point of view of other studies [24, 25, 5, 20]. Our study shows that the risk of pathologic upstaging, positive surgical margins, surgical complications and deaths did not significantly reduced in non-delayed group. Moreover, disease-free survival and overall survival were not significantly better in non-delayed group than delayed group. Explanation for the unexpected results might be that in non-delayed group, diagnosis is less likely to be missed because the tumor is larger [21], or patients undergo surgery more promptly due to symptoms and signs caused by advanced disease [26, 24, 25, 5, 20], but the prognosis is worse.

The study shows another unexpected result: a significant increase of lymphovascular invasion in non-delayed group. As mentioned above, the patients in non-delayed group had larger tumors or more advanced diseases. This finding supports the conclusion of a previous paper that the incidence of lymphovascular invasion increases with an increasing tumor size in lung adenocarcinoma [27]. In addition, Wang et al indicated that lymphovascular invasion was significantly associated with a higher recurrence and mortality risk in patients with NSCLC [28]. This result explains again why the prognosis of non-delayed group is not better.

There is concern that diagnostic or treatment delays may be a contributing factor in

the majority of patients presenting with advanced stages of lung cancer. In the study from Sweden [10], a diagnostic delay of median 189 days caused that the majority of the patients (66.4%) presented in stage IIIB or IV diseases, and only 11% patients were found to be operable. A study using a threshold of 8-week time point as a marker of delayed surgery suggested that delay in resection was related to increased risk of postoperative upstaging and decreased median survival in patients with clinical stage I NSCLC [11]. Another study found that surgical treatment delayed more than 12 weeks was associated with increased incidence of cancer recurrence and poorer prognosis in early-stage NSCLC [14].

However, Quarterman and colleagues [16] collected retrospective data for 84 patients who underwent surgical intervention for pathologic stage I or II NSCLC. Surgery was delayed in 38 patients at least 90 days after presentation. They found that there was no significant effect of delay on cancer-free survival or overall survival, and thought any survival analysis in which these groups were compared was subject to lead-time bias: if the tumors are older, then the patients' survival necessarily will be shorter. Additionally, another study [18] demonstrate that, when analyzing four different cancers (lung, thyroid, breast and colorectum), delays to curative surgery beyond 12 weeks were associated with increased mortality in patients with breast and colorectal cancers but not lung and thyroid cancers. This illustrates that the prognosis is significantly influenced by the biological behavior of the tumor, not necessarily by delayed surgical intervention. In fact, studies of tumor biology reveal that lung cancers initially grow slowly. It is estimated that it takes about 130 months for a lung

cancer to reach a diameter of 1 cm [29, 24].

Consistent with the prior studies [16, 24, 25, 13], our data unable to detect a significant influence of previous delay on prognosis when a lung cancer is diagnosed as an operable stage disease preoperatively. The result may imply that a limited delay (e.g., 3 months) in surgical resection for an early-stage lung cancer is acceptable in patients with other comorbidity requiring immediate treatment [18]. However, in spite of the result, such a delay should be minimized in order to improve surgical resection rate in lung cancer [30, 14].

There are important limitations to this retrospective study. First, we include stage I, II, and IIIA tumors which were regarded as suitable operation. This removes a large number of patients with stage IIIB and IV tumors who may have experienced long delays before surgery [31-33]. The impact of missed diagnosis and delayed surgery for NSCLC, therefore, cannot be precisely analyzed. However, we believe that including only patients with operable stage disease is an effective way to evaluate the reasonability of delayed surgery. Besides, the present study is of relatively small size, which might limit statistical significance. But it gives a concept about the reasons for surgical delays and made us assess where we can improve. Finally, the study is limited by including a substantial duration of time during which therapeutic approaches may have changed. However, the results hopefully help us to judge the order of treatment when lung cancer and other comorbidity coexist.

Conclusions

In summary, this study demonstrates that among patients with delayed surgery for lung cancer, the proportion of those at clinical stage I and II is higher, while the proportion at clinical stage IIIA is lower. Furthermore, due to the earlier stage of lung cancer in these patients, the incidence of lymphovascular invasion is lower. Consequently, the prognosis for patients with delayed surgery may not necessarily be worse than for those who receive timely surgery. We believe that, in patients with delayed diagnosis or surgery for lung cancer, if the preoperative clinical assessment indicates an operable stage, an aggressive surgical resection remains a crucial treatment option.

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Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Authors' contributions

Conceptualization, Yueh-Feng Tsai, Shih-Chuan Hsiao, and Chung-Jing Wang; methodology, Yueh-Feng Tsai, Meng-Ping Dai, Wen-Pin Wu, and Chien-Chih Ou; data curation, Shih-Chuan Hsiao and Mao-Te Chuang; Formal analysis, Yueh-Feng Tsai and Chiung-Lun Kao; writing—original draft preparation, Yueh-Feng Tsai and Chiung-Lun Kao; writing—review and editing, Yueh-Feng Tsai, Meng-Ping Dai, Wen-Pin Wu, Chien-Chih Ou, Shih-Chuan Hsiao, Mao-Te Chuang, and Chung-Jing

Wang; All authors have read and agreed to the published version of the manuscript.

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