Peripheral Direct Adjacent Lobe Invasion Non-small Cell Lung Cancer Has a Similar Survival to That of Parietal Pleural Invasion T3 Disease

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Introduction: The postoperative prognosis of peripheral adjacent lobe invasion non-small cell lung cancer (NSCLC) is unclear. The purpose of this study was to determine the postoperative prognosis of NSCLC with direct adjacent lobe invasion by comparing it with that of visceral pleural invasion (primary lobe) T2 disease, and parietal pleural invasion T3 disease, and hence determine its most appropriate T category.

Methods: A retrospective analysis was conducted to assess the survival of patients with peripheral direct adjacent lobe invasion NSCLC (group A), and it was compared with that of patients with visceral pleural invasion of the primary lobe (group B) and parietal pleural invasion (group C). All patients were node-negative on pathologic examination. Kaplan-Meier method was used to compare the postoperative survival between groups.

Results: A total of 263 patients were analyzed. The overall survival rates in groups A ($n = 28$), B ($n = 167$), and C ($n = 68$) at 5 years were 40.7, 54.6, and 41.9%, respectively; corresponding median survival in three groups were 53, 71, and 40 months, respectively. The survival difference among three groups was statistically significant ($p = 0.031$). A similar survival was observed between groups A and C, whereas group B had a much better survival than other groups.

Conclusions: Peripheral adjacent lobe invasion NSCLC has a similar survival prognosis with that of parietal pleural invasion T3 disease and hence should be classified as T3 rather than T2. However, further studies are warranted.

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The tumor, node, metastasis (TNM) staging system of lung cancer is used as a guide for the prognosis of patients with non-small cell lung cancer (NSCLC).[1] According to the 6th and proposed 7th revision of International Association for the Study of Lung Cancer (IASLC) staging system, direct invasion of peripheral adjacent lobe is defined as T2 disease. However, the postoperative prognosis of these patients is controversial.[2,3] The purpose of this study was to determine the postoperative prognosis of NSCLC with direct adjacent lobe invasion by comparing it with that of visceral pleural invasion (same lobe) T2 disease and parietal pleural invasion T3 disease, and hence determine its most appropriate T category.

MATERIALS AND METHODS

Patients Selection

We conducted the study using data extracted from a prospectively collected NSCLC database, which is composed of 2094 surgically managed cases at thoracic surgery department, Sun Yat-sen University Cancer Center from March 1997 to October 2006. The patients receiving complete or incomplete lung resections were included in the database. We applied the definition of complete surgical resection proposed by the IASLC Staging Committee.[4] The direct adjacent lobe invasion was defined by contiguous extension of the primary tumor across a fissure into another lobe.

Preoperative workup for patients included chest computed tomography (CT), brain magnetic resonance, B ultrasound or CT scan for abdomen, and a bone scan. Mediastinal lymph node involvement (short diameter >1 cm) was excluded preoperatively by CT scan. Mediastinoscopy was not routinely performed as part of preoperative workup. In all patients, routine biochemical profile, fibrobronchoscopy, pulmonary function tests with spirometry, and arterial blood gas analysis at rest were also required.

The patients involved in our analysis fit the criteria as follows: (1) pathologically confirmed diagnosis of primary

NSCLC; (2) peripheral NSCLC with direct pathologic adjacent lobe invasion (classified in group A), NSCLC with visceral pleural invasion of the same lobe by the primary tumor (pathologic T2 disease, classified in group B), or NSCLC with pathologic parietal pleural invasion T3 disease (classified in group C); (3) the tumor were considered resectable preoperatively and received surgical management; and (4) pathologically confirmed N0M0 disease after surgery. We defined peripheral tumors as those where the center of mass was beyond the debouchement of the segmental bronchus, and central tumors as those where the center of mass was at the proximal side of the debouchement of the segmental bronchus. We applied the proposed 7th revision of the IASLC staging system for patient selection.[3,5] Because our main concern was comparing the prognosis of adjacent lobe invasion with visceral pleural invasion of the same lobe, and with parietal pleural invasion disease, we did not involve other T2 and T3 descriptors in our analysis.

We excluded the patients with bronchioloalveolar carcinoma, small cell lung cancer, M1 disease, superior sulcus tumor, and patients with a history of concurrent malignant disease or other previous primary cancers. Cases of synchronous multiple primary lung cancer were excluded according to the criteria proposed by Martini and Melamed.[6] We excluded the central NSCLC with adjacent lobe invasion to avoid the confusion in data analysis. The tumors with adjacent lobe invasion simultaneously combined with parietal pleural invasion were also excluded. Because the purpose of this study was to assess the reasonable T stage for adjacent lobe invasion NSCLC, we excluded lymph node positive patients in this analysis.

Follow-Up of Patients

Operative death was defined as death within 1 month after surgery. A follow-up examination was, in general, done every 2 months for the first year, 3 months for the second year, and 4 months thereafter. The examination included a physical examination, blood chemistry, and chest radiography. In addition, all patients routinely received chest scan by CT, head scan by magnetic resonance or CT, and radionuclide bone scan. However, if the patient had specific symptoms, the examination was performed as soon as possible for a more careful assessment. The median time from surgery to the last contact for the entire cohort was 65.7 months, ranging from 0.7 to 101 months.

Statistical Methods

SPSS 16.0 software was used for statistical analysis. Survival was calculated by Kaplan-Meier method, and log-rank test was used to assess differences in survival between groups. A two-sided p value of less than 0.05 was considered statistically significant. Patients alive at the end of the study period were censored for the purpose of data analysis.

RESULTS

Patients Demographics and Treatment Information

There were 263 patients derived from the previously collected database according to the inclusion criteria. The patient numbers involved in groups A, B, and C were 28, 167, and 68, respectively. Twenty-one adjacent lobe invasion cases in group A were identified on CT scan before surgery, and the others were detected by examination during surgery. Table 1 gives the details of the patients.

The posterolateral thoracotomy was routinely used, and the type of lung resection is shown in Table 1. Systematic mediastinal lymph nodes dissection or sampling was performed during surgery. For patients received exploratory thoracotomy without lung resection, mediastinal sampling was performed to achieve an accurate pathologic stage. All patients in group A received complete resection with a negative resection margin (R0); whereas in other groups, some patients were with microscopically positive residue

TABLE 1. Demographic Features and Treatment Information About the Patients

Characteristics	Group A (n = 28)	Group B (n = 167)	Group C (n = 68)	p
Gender				
Male	17	98	42	0.427[a]
Female	11	69	26	
Median age/yr (range)	64 (40–77)	63 (32–82)	59 (35–78)	—
Tumor size (mean cm ± SD)	5.4 ± 1.6	4.6 ± 1.4	5.3 ± 1.6	0.683[b]
FEV1 before surgery (mean liter ± SD)	1.74 ± 0.13	1.82 ± 0.10	1.76 ± 0.12	0.752[b]
Pathology				
Squamous cell carcinoma	18	60	23	0.023[c]
Adenocarcinoma	7	84	33	
ASC	3	6	4	
Others	0	17[d]	8[e]	
Type of surgery				
Bilobectomy	3[f]	20	3	—
Lobectomy + wedge	7[g]	0	0	
Single lobe lobectomy	0	144	63	
Right pneumonectomy	11	1	0	
Left pneumonectomy	7	2	2	
Resection completeness				
R0	28	165	61	—
R1	0	2	4	
R2	0	0	3	
Postoperative chemotherapy				
Yes	20	122	52	0.638[a]
No	8	45	17	

[a] Pearson χ^2 test.
[b] Independent samples t test.
[c] Fisher exact test.
[d] Large cell carcinoma.
[e] Including six cases of large cell carcinoma, two cases of carcinosarcoma.
[f] Two cases of primary right upper lobe tumors with middle lobes invasion; one case of primary middle lobe tumor with lower lobe invasion.
[g] Two cases of primary right lower lobe tumors with right upper lobes invasion; four cases of primary left lower lobe tumors with left upper lobes invasion; one case of primary left upper lobe tumor with left lower lobes invasion.
FEV1, forced expiratory volume in 1 sec; ASC, adenosquamous carcinoma.

(R1) or gross positive residual (R2) (Table 1). The patients with incomplete resection received postoperative radiotherapy followed by platinum-based chemotherapy. The constitute ratio of adenocarcinoma in groups B and C was higher than that in group A (Table 1). The gender, age, pulmonary function before surgery (forced expiratory volume in 1 second), and administration of postoperative chemotherapy were well balanced between all groups (Table 1).

In group A, seven patients underwent left pneumonectomy and 11 patients underwent right pneumonectomy because of the large tumors both in primary and in invaded lobes.

Most patients received two to four cycles of platinum-based postoperative chemotherapy with variable compliance within the whole group (Table 1).

Survival

Survival data was collected on each patient from the date of surgery. There were 11 deaths in group A at the end of follow-up, including one operative death patient who lived 29 days after surgery. The perioperative death was in a 66-year-old man who underwent right pneumonectomy and died of pneumonitis caused by bronchopleural fistula. The other deaths in group A were caused by brain metastases (five cases), local recurrence (three cases), and multiple organ metastases (two cases). The overall survival rates including the operative deaths in group A at 2, 3, and 5 years were 68.7, 61.1, and 40.7%, respectively, with a median survival of 53 months (Figure 1). The operative mortality in groups B and C was 0.6% (1 of 167) and 1.5% (1 of 68), respectively. The

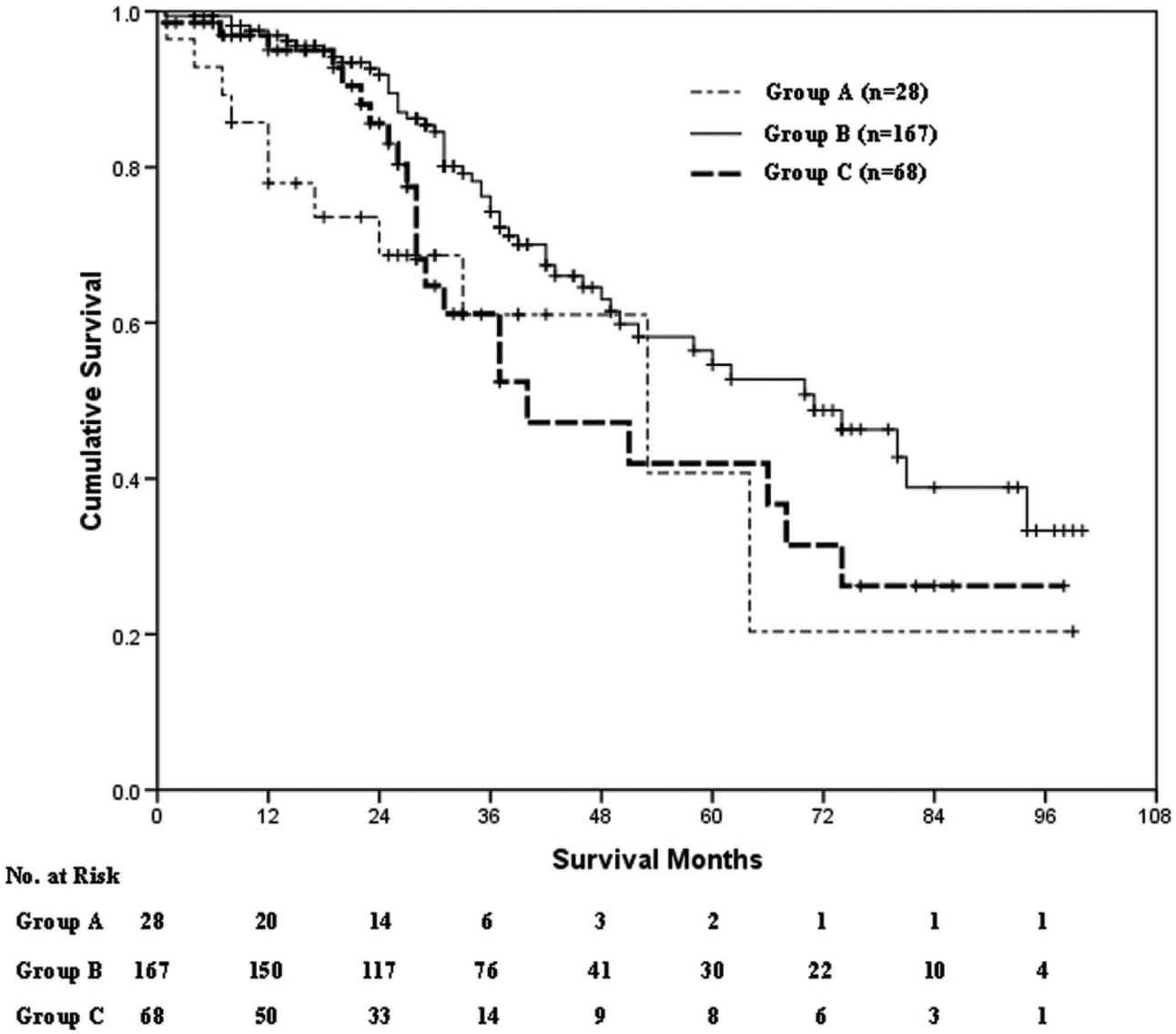

FIGURE 1. Survival curves of patients for all groups. The survival difference among three groups was statistically significant ($p = 0.031$). Between groups A and B, $p = 0.032$; between groups A and C, $p = 0.501$; and between groups B and C, $p = 0.039$.

overall survival rates for group B and group C at 2, 3, and 5 years were 91.9, 74.3, 54.6%, and 85.6, 61.2, 41.9, respectively; corresponding median survival in two groups were 71 and 40 months, respectively (Figure 1). Among the three groups, the survival difference was statistically significant (between groups A and B, $p = 0.032$; between groups A and C, $p = 0.501$; and between groups B and C, $p = 0.039$; Figure 1). A similar survival was observed between groups A and C, whereas group B had a much better survival than other groups.

In group A, the median survival time was 33 months for patients who had less than pneumonectomy (lobectomy plus wedge resection), and 53 months for patients who had pneumonectomy, but the difference was not statistically significant ($p = 0.244$).

DISCUSSION

The TNM staging system for lung cancer is used to help select the most appropriate treatment for patients on the basis of the prognosis of different stages of NSCLC.

Direct invasion of peripheral adjacent lobe is currently T2 (pleural visceral invasion) under the 6th and proposed 7th revision of IASLC staging system.[2,3,5] However, the prognosis for NSCLC with adjacent lobe invasion through the fissure have seldom been reported, and the results are controversial.[7,8] In this analysis, our data suggested that the postoperative survival for patients with adjacent lobe invasion was comparable with that of parietal pleural invasion T3 patients and lower than other type of T2 (pleural visceral invasion of the same lobe) patients. Because the TNM staging system for NSCLC is based on the different prognosis of patients, comparable prognosis is related to similar stage. In our study, lung cancer with adjacent lobe invasion had a similar survival prognosis compared with that of parietal pleural invasion T3 disease. This finding provides possible evidence that the patients in group A may be classified as T3. Demir et al.[7] assessed 60 patients had T2 NSCLC that showed a limited growth through the interlobar fissure into the adjacent lobe. The prognosis of their patients was found to be similar with that of T3 tumors,[7] which was comparable with that of our series. However, different result had also been reported by other institution. Nonaka et al.[8] assessed the survival of 50 NSCLC with interlobar pleural invasion. The 5-year survival rate of 28 patients with squamous cell carcinoma with interlobar pleural invasion was 69%, similar to 54% with T2 and hence concluded that tumors with interlobar pleural invasion should be classified as T2 in squamous cell carcinoma.[8] The discrepancies may be due to the small number, or different inclusion criteria among studies, suggesting further study with much larger number is essential to make it clear.

As far as the operation was concerned, the survival curve of group A seemed to show a better survival prognosis for patient who underwent pneumonectomy than that of those receiving less than pneumonectomy (lobectomy plus wedge resection), although the survival difference was not statistically significant. The previous data from neoadjuvant chemoradiotherapy had shown that the extent of surgery determined the postoperative mortality and that patients receiving lobectomy had a better survival than that of receiving pneumonectomy.[9,10] The patients receiving pneumonectomy were usually with more advanced disease than those receiving lobectomy or bilobectomy (right lung), and meant much loss of pulmonary reserve, so our result in group A seems hard to explain. This result was interesting, but may not be surprising, because it may suggest that direct adjacent lobe invasion should be treated as two primary tumors in different lobes, and pneumonectomy or at least bilobectomy (right lung) is more reasonable than lobectomy plus wedge for a complete resection. Nevertheless, the case of operative death in group A received right pneumonectomy, and this indicates a more careful selection before surgery and more intensive care after surgery should be given to patients receiving pneumonectomy. In our study, the sample size was small, this fact must be considered when interpreting our data.

Nodal status is generally considered to be an important prognostic factor in NSCLC.[1,11–15] In this retrospective study, we excluded lymph node positive patients because the purpose of this study was to assess the reasonable T stage for adjacent lobe invasion NSCLC. Mediastinoscopy is not a routine procedure in our institute, unless there is suspected contralateral hilar or mediastinal lymph node involvement. However, a systematic review of the medical literature relating to the accuracy of noninvasive staging of the mediastinum involving 5111 patients with lung cancer showed that the pooled sensitivities and specificities for staging the mediastinum for CT scanning, positron emission tomography scanning, and endoscopic ultrasound were 0.57 and 0.82, 0.84 and 0.89, 0.78 and 0.71, respectively.[16] This suggests that noninvasive methods for evaluation of the mediastinal lymph node are not accurate enough for NSCLC staging before treatment. Nevertheless, a systematic review of cervical mediastinoscopy involving 6505 lung cancer cases showed that the sensitivity and specificity was 78 and 100% respectively.[17] Therefore, invasive staging strategy such as mediastinoscopy examination should be recommended before surgery afterward for a careful patient selection in our institute.

In conclusion, our data suggests a similar survival prognosis of NSCLC with direct adjacent lobe invasion compared with that of parietal pleural invasion T3 disease. Therefore, direct adjacent invasion NSCLC should be classified as T3 rather than T2. However, this result should be interpreted with caution because of the small size, and further studies are warranted to assess the rationality of considering these patients as T3 disease.

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