Clinical implication of pulmonary excision for undiagnosed peripheral lung cancer

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1. Introduction

Lung cancer is the leading cause of death in most industrial countries [1], and therefore we should identify an appropriate method of treatment. Recently, the size of lung cancers has decreased, and the chance of needing to surgically excise such small pulmonary nodules is increasing [2]. This is because techniques, such as biopsy using flexible fiberoptic bronchoscopy (FFB) and computed tomography (CT)-guided fine-needle biopsy have limited ability in diagnosing such small pulmonary nodules [2–4].

Although surgical excision is an accepted method for diagnosing small lung cancer, surgical manipulation may spread isolated tumor cells at the margins [5, 6] and may lead to a relapse of the malignancy. We therefore conducted a study to evaluate whether surgical excision is an optimal diagnostic technique in terms of tumor recurrence and prognosis, and to clarify the effect on the cytology at the surgical margins.

2. Methods

2.1. Patient selection

This retrospective analysis was based on records collected in a database of patients with primary lung cancer who had been histologically diagnosed and had undergone thoracotomy at the National Hospital Organization Toneyama Hospital in Japan.

Between 1998 and 2004, 590 consecutive patients underwent thoracotomy for primary lung cancer. Among them, 252 patients had had a lobectomy for clinical stage IA non-small cell lung carcinoma (NSCLC) with a diameter ≤3.0 cm. A total of 148 patients were diagnosed by FFB before surgery (group B), and 86 patients were diagnosed by surgical excision (group E). Thirteen patients diagnosed by needle biopsy (six under CT guidance and seven under open thoracotomy) and five patients diagnosed after lobectomy were excluded. Of these 234 patients, 25 patients had ground-glass attenuation (GGA) lesions (>50%) on CT-scan. Except for the 25 patients with GGA lesions, FFB was preoperatively attempted on all patients.

2.2. Procedure

During FFB, the lesions were diagnosed using a curette cytology technique followed by a lavage cytology technique...
without autofluorescence and a navigation system. During surgical excision, we designed these methods to, in principle, have a macroscopically greater safe margin than the tumor diameter [7]. Specimens taken by wedge resection using staplers were diagnosed using frozen sections. Surgical excision under open thoracotomy was performed in 24 patients, and surgical excision under video-assisted thoracic surgery (VATS) in 62.

Immediately after surgical excision but before cross-sectioning of the specimen, cytological examination of the stump was performed with the Papanicolaou method, as previously described [5]. Papanicolaou classes IV and V were regarded as positive cytological findings. A total of 67 patients had negative findings at the surgical stump (group EN), and 19 had positive findings (group EP). When the tumor was diagnosed as NSCLC, a further pulmonary resection was undertaken. Before closure, the pleural cavity was washed with >3000 ml of physiological saline solution. Pleural recurrence was defined as pleural dissemination or malignant effusion or both in the hemithorax of the operated side at first relapse.

All patients underwent staging according to the 2009 TNM classification criteria [8]. An institutional review board approved this retrospective study, and written informed consent for the surgical intervention was obtained from each patient.

2.3. Statistical analysis

The χ² method was used to compare differences between the two groups, and the Student’s t-test was used to analyze continuous variables. Survival was defined as the time between the date of operation and death. The survival rates were calculated using the Kaplan–Meier method and compared by log-rank test. A P-value <0.05 was considered significant. All statistical manipulations were performed using StatView 5.0 (Abacus Concepts Inc, Berkeley, CA, USA).

3. Results

3.1. Patient characteristics

The clinical characteristics of the patients enrolled in the study are presented in Table 1. There was no significant difference in gender, age, smoking status and the chance of detecting lung cancer. However, patients diagnosed by surgical excision had a lower performance status than those diagnosed by FFB (P=0.05).

The tumor characteristics of the patients are presented in Table 2. There was no significant difference in the primary lesion and the histological type. The mean tumor size for group E was significantly less than that for group B (1.5±0.5 cm vs. 2.2±0.6 cm; P<0.0001). In group E, there were significantly more GGA lesions than in group B (20% vs. 5%, P=0.0006). The distributions of pathological N status and pathological stage were significantly different: patients in group E had a lower pathological N status (P=0.002) and lower pathological stage (P=0.003) than those in group B.

The clinical characteristics of the patients in group E according to the cytology at the surgical margin are presented in Table 3. There was no statistical difference between groups EN and EP.

3.2. Tumor recurrence

In group B, 42 patients (28.4%) had a recurrence. At first relapse, seven had recurrences in the pleural cavity and two had pleural and distant recurrences (6.1%). In group
E, seven patients (8.9%) had recurrences; among these, all seven patients had distant metastases, while there was no recurrence in the pleural cavity (Table 4).

### 3.3. Survival rate of patients according to diagnostic techniques

The 30-day mortality was 0% (0/148) in group B and 1.2% (1/86) in group E. The mean follow-up period was 98.7 months. There was a significant difference in overall survival between groups B and E ($P=0.003$; Fig. 1). The five-year survival rate was 80.5% for group B and 91.7% for group E. To avoid any differences arising from tumor staging, we analyzed the survival rate of patients with pathological stage IA disease excluding GGA lesions. The same trend was apparent, although the difference was not significant ($P=0.17$; Fig. 2). The five-year survival rate was 80.5% for group B and 90.2% for group E.

Finally, we analyzed the survival rate of patients diagnosed by surgical excision according to the cytological status of the excision margin. There were no significant differences in overall survival between groups EN and EP, with a five-year survival of 90.8% and 94.7%, respectively ($P=0.94$; Table 3).

### 4. Discussion

Although there has been a recent increase in the number of relatively smaller sized or early-stage lung cancers, there has also been more opportunity to diagnose them intraoperatively. More than half of the indeterminate small pulmonary nodules that cannot be diagnosed using FFB are malignant, as previously reported [9]. VATS exploration methods have been documented to be both minimally-invasive and very useful [10–12]. Thus, surgical excision (especially with VATS) is considered to be useful to detect and cure early-stage lung cancer. However, whether surgical methods have been documented to be both minimally-invasive and very useful [10–12]. Thus, surgical excision (especially with VATS) is considered to be useful to detect and cure early-stage lung cancer. However, whether surgical techniques are more effective than flexible fiberoptic bronchoscopy for small pulmonary nodules needs further study. 

#### Table 4. Characteristics of patients diagnosed by pulmonary wedge resection

<table>
<thead>
<tr>
<th>Pathological stage</th>
<th>Group EN (n=67)</th>
<th>Group EP (n=19)</th>
<th>$P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>0</td>
<td>2</td>
<td>0.25</td>
</tr>
<tr>
<td>II</td>
<td>0</td>
<td>0</td>
<td>0.25</td>
</tr>
<tr>
<td>III</td>
<td>3</td>
<td>1</td>
<td>0.99</td>
</tr>
<tr>
<td>IV</td>
<td>3</td>
<td>0</td>
<td>0.99</td>
</tr>
</tbody>
</table>

#### Table 3. Characteristics of patients diagnosed by pulmonary wedge resection

<table>
<thead>
<tr>
<th>Gender</th>
<th>Group EN (n=67)</th>
<th>Group EP (n=19)</th>
<th>$P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>31</td>
<td>7</td>
<td>0.47</td>
</tr>
<tr>
<td>Female</td>
<td>36</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>61.5±10.2</td>
<td>65.3±9.5</td>
<td>0.16</td>
</tr>
<tr>
<td>Smoking status (packs/yr)</td>
<td>≤20</td>
<td>44</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>&gt;20</td>
<td>23</td>
<td>4</td>
</tr>
<tr>
<td>Performance status</td>
<td>0</td>
<td>64</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Histology</td>
<td>Adenocarcinoma</td>
<td>63</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>Squamous cell carcinoma</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Others</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Tumor size</td>
<td>Mean±S.D. (cm)</td>
<td>1.5±0.5</td>
<td>1.6±0.5</td>
</tr>
<tr>
<td>GGA&gt;50%</td>
<td>15</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

Group EN, patients had negative findings at the surgical stump; group EP, patients had positive findings. GGA, ground-glass attenuation.

Fig. 1. Overall survival rate of patients according to diagnostic techniques. Group B, patients diagnosed by flexible fiberoptic bronchoscopy before surgery; group E, patients diagnosed by surgical excision. The five-year survival rate was 80.5% for group B and 91.7% for group E ($P=0.003$). FFB, flexible fiberoptic bronchoscopy.

Fig. 2. Survival rate of patients with pathological stage IA excluding GGA lesions according to diagnostic techniques. Group B, patients diagnosed by flexible fiberoptic bronchoscopy before surgery; group E, patients diagnosed by surgical excision. The five-year survival rate was 80.5% for group B and 90.2% for group E ($P=0.17$). FFB, flexible fiberoptic bronchoscopy.

Fig. 3a). Among patients with pathological stage IA disease excluding GGA lesions, there was also no significant difference in survival between the two groups ($P=0.73$; Fig. 3b).
Accordingly, we designed the method of surgical excision as a diagnostic tool may increase the risk of local recurrence by tumor spillage remains unknown.

In this study, the tumor size of patients diagnosed by surgical excision was significantly smaller than that of those diagnosed by FFB. Furthermore, in patients diagnosed by surgical excision, the distributions of GGA lesions and pathological stage I lesions were significantly greater than those diagnosed by FFB. A lower pathological stage was mainly attributed to a lower pathological N status. These results suggest that surgical excision is a useful method to diagnose early-stage lung cancer after unsuccessful FFB. Especially for GGA lesions, surgical excision with VATS may be very useful because this category is much more difficult to diagnose by FFB.

One of the unfavorable recurrent patterns after limited resection for NSCLC is local failure, especially at the surgical margin in the pulmonary parenchyma. Cytological examination of the surgical margins of wedge-resected malignant tumors was found to be useful to detect malignant cell contamination, as previously reported [5]. In cases of limited resection, a cytologically positive margin has the potential for surgical margin recurrence [5, 6, 13, 14]. Thus, intraoperative margin cytology is clinically useful in checking for complete resection in these cases [5, 7].

With regard to the pattern of recurrence, we found that, among 79 patients diagnosed by surgical excision, there was no recurrence in the pleural cavity, even in the group with cytologically positive margins, although there were seven recurrences with distant metastasis. Surgical manipulation did not affect shedding of tumor cells into the pleural cavity in this study. With regard to prognosis, the survival rate of patients diagnosed by surgical excision was significantly better than that of patients diagnosed by FFB. The same tendency was found among patients with pathological stage IA disease excluding GGA lesions. Furthermore, survival was not significantly different between patients with cytologically positive and negative margins.

To prevent the spread of malignant cells into the pleural cavity, surgical excision with a safe margin is desirable [6, 7]. Accordingly, we designed the method of surgical excision to include a macroscopically greater margin than the tumor size. However, there is a possibility of margin cytology becoming positive. Even if the resected margin of surgical excision was cytologically positive, this did not affect the pattern of recurrence and the prognosis in cases that underwent further residual lobectomy in this series. Contaminated malignant cells may have a low potential for growth in the pleural cavity because further resection was performed following surgical excision with washing of the pleural cavity using a large volume of physiological saline solution.

Surgical excision is the most accurate technique for the diagnosis of small pulmonary nodules. Both VATS and thoracotomy have specific advantages, as a residual lobectomy can be carried out if the results of frozen-section histology lead to a diagnosis of malignancy during surgery. It is possible to treat this by surgical excision immediately after obtaining the diagnosis. Residual lobectomy was undertaken in all 86 patients of ours who were diagnosed by surgical excision. Furthermore, in our series, most cases were diagnosed during pathological stage N0 disease by surgical excision. This can therefore be recommended for a small pulmonary nodule after unsuccessful FFB.

A limitation of this study that should be noted, however, is that this analysis was retrospective and the sample of patients diagnosed by surgical excision was small. Furthermore, there is a bias in this study as the size and location of the tumors were different between the two groups: most patients in group E had small peripheral adenocarcinomas (T1aN0). Thus, a greater number of peripheral T1aN0 patients should be compared in future studies.

5. Conclusions

In conclusion, pulmonary wedge resection was a useful method to detect and cure early-stage lung cancer discovered as undiagnosed pulmonary nodules. The survival of patients diagnosed by surgical excision was significantly better than that of those diagnosed preoperatively by FFB in clinical stage IA disease. Surgical excision was beneficial as a diagnostic technique because this method did not
affect relapse and prognosis, even if the surgical margin was cytologically positive.

References


