Curative Wedge Resection for Non-Invasive Bronchioloalveolar Carcinoma

MOTOYASU SAGAWA, KOTARO HIGASHI, KATSUO USUDA, HIROKAZU AIKAWA, YUICHIRO MACHIDA, MAKOTO TANAKA, MASAKATSU UENO and TSUTOMU SAKUMA

1Department of Thoracic Surgery, Kanazawa Medical University, Ishikawa, Japan
2Department of Radiology, Kanazawa Medical University, Ishikawa, Japan

Pure bronchioloalveolar carcinomas have no stromal, vascular or pleural invasion, and they are candidates for curative wedge resection, although standard operative procedure for lung cancer is a pulmonary lobectomy. Most lung cancers with ground glass opacity (GGO), namely faint homogeneous shadows with sharp margin, are pure bronchioloalveolar carcinomas. This report presents the results of a pilot study on wedge resection with candidate selection by high-resolution computed tomography and positron emission tomography with 18F-fluorodeoxyglucose (FDG). The criteria for wedge resection were: 1) clinically no nodal or distant metastasis, 2) the location of the tumor was peripheral enough to undergo wedge resection, 3) the diameter of the shadow was 8-20 mm, 4) GGO% (diameter of GGO area/diameter of whole tumor) was 80% or over, 5) FDG uptake of the tumor was less than that of the mediastinum, 6) the intraoperative pathological diagnosis was non-invasive bronchioloalveolar carcinoma, and 7) informed consent was obtained. Nine tumors from 8 patients were selected in the study. The maximum diameter of the tumors was 9-18 mm and GGO% was 82-100%. All of nine tumors were treated with a wedge resection under video-assisted thoracic surgery. The postoperative courses were uneventful and no recurrence has been detected after 19-50-month follow-up. The changes in pulmonary function before and after the surgery were minimal. In conclusion, wedge resections were safely performed without any recurrence, and the postoperative pulmonary function was well preserved, suggesting the advantage of wedge resections for non-invasive bronchioloalveolar carcinomas. 

Lung cancer; Bronchioloalveolar carcinoma; Ground glass opacity; FDG PET; Limited resection.


Many lung cancers with ground glass opacity (GGO), a faint homogeneous shadow with sharp margin, are detected by thoracic computed tomography (CT) scans (Henshke 2000; Kaneko et al. 2000; Sone et al. 2001). Some of them are pure bronchioloalveolar carcinoma (BAC) without any stromal, vascular or pleural invasion (Noguchi et al. 1995; Sakurai et al. 2004). Such tumors often show little change in size over an extended period (Kodama et al. 2002). These non-invasive cancers might be candidates for a limited resection, such as a pulmonary wedge resection or a segmental resection. Because the Lung Cancer Study Group reported that the patients treated with a limited resection for the cT1N0M0 (clinically no nodal or distant metastasis; the diameter of the tumor was 3cm or smaller) peripheral lung cancer had a worse prognosis than those treated with a standard operation, a pulmonary lobectomy and a hilar/mediastinal nodal dissection (Lung Cancer Study Group 1995), it would be prudent to determine the appropriate criteria for selecting candidates to undergo a limited resection. Even in lung cancers with GGO, there are occasionally invasive adenocarcinomas (Yamato et al. 2001; Suzuki et al. 2002; Nakata et al. 2003), and chest CT findings alone cannot distinguish invasive carcinomas from non-invasive carcinomas.

Positron emission tomography (PET) imaging with 18F-fluorodeoxyglucose (FDG) provides metabolic information on pulmonary nodules (Coleman 1999; Vesselle et al. 2000; Higashi et al. 2000). FDG PET findings are helpful for the discrimination of non-invasive BACs from adenocarcinomas mixed subtype (Higashi et al. 1998). If a combination of chest CT and FDG PET findings enables to select more biologically inactive cancers, such as non-invasive BACs, then a wedge resection might be an appropriate treatment for such tumors. This report presents the results of a pilot study on wedge resection for small pulmonary adenocarcinomas using high-resolution CT (HR-CT) and FDG PET findings. The criteria for limited resection candidacy are also discussed.
PATIENTS AND METHODS

Patients referred to our hospitals with a suspicion of lung cancer underwent chest, abdominal and brain computed tomography (CT), as well as bone scintigram, pulmonary function test, bronchoscopic examination, and FDG PET.

Patients suspected of having cT1N0M0 (clinically no nodal or distant metastasis; the diameter of the tumor was 3 cm or smaller) lung cancer were investigated. With HR-CT (slice thickness: 2 mm), the maximum diameter of the tumor (MDT) and that of the consolidation (MDC) were independently measured. GGO% was calculated as follows: GGO% = (MDT – MDC)/MDT.

PET scanning was performed with a PET camera, Headtome IV (Shimazu, Kyoto, Japan) or Advance (GE Medical System, Milwaukee, WI). The detail of the PET scanning was described previously (Higashi et al. 1998; Higashi et al. 2000). Transmission scans were obtained in all subjects for attenuation correction. FDG accumulation within the primary lung cancer on the attenuation- and decay-corrected images was graded independently. A 5-point visual grading system (a modified method of Vansteenkiste et al. (Vansteenkiste et al. 1998)) was used to interpret FDG uptake within the primary lesions without the pathological information; including no increased uptake (similar to background), weak uptake (lower than mediastinum), medium uptake (similar to mediastinum), strong uptake (higher than mediastinum), and very strong uptake (remarkably higher than mediastinum).

When the diameter of the tumor shadow was 8-20 mm by HR-CT, GGO% was 80% or over, and FDG uptake was weak uptake or lower, another chest CT was performed 3-4 months later. If the shadow was still suspected to be lung cancer, three therapeutic options were proposed to the patients: 1) follow-up with CT, 2) pulmonary wedge resection followed by the standard procedure (pulmonary lobectomy with nodal dissection) when the intraoperative diagnosis was carcinoma, 3) pulmonary wedge resection followed by the standard procedure when the intraoperative diagnosis was invasive carcinoma, indicating only a wedge resection would be performed when the intraoperative diagnosis was non-invasive BAC (Noguchi’s type A/B) (Noguchi et al. 1995; WHO 1999). The patients were also informed that some lung cancers of this kind might remain stable for a long time, and that it was uncertain whether a wedge resection was sufficient for such tumors. Finally, eight patients (nine tumors) chose the last option.

Pulmonary wedge resection was conducted by video-assisted thoracic surgery (VATS), with a surgical margin of at least 10 mm in the collapsed lung. If necessary, CT-guided tumor marking by a hook with a thread (Guiding Marker System, Hakko Medical, Nagano, Japan) was performed. A pulmonary function test was performed before and at 3-24 months after surgery.

Intraoperative and postoperative pathological diagnoses were made by a licensed pathologist without any radiological information. Histological typing was classified according to the WHO classification (WHO 1999). The growth pattern of the tumor was also classified according to Noguchi’s classification (Noguchi et al. 1995): A: localized bronchiole-alveolar carcinoma (LBAC), B: LBAC with fibrous septa, C: LBAC with foci of active fibroblastic proliferation, D: poorly differentiated adenocarcinoma, E: tubular adenocarcinoma, and F: papillary adenocarcinoma with compressive and destructive growth. Type A/B/C tumors show a growth pattern involving replacement of alveolar lining cells, whereas type D/E/F tumors are nonreplacement-type adenocarcinomas. Type A/B tumors are regarded as non-invasive BAC in the WHO classification, but type C tumors are adenocarcinomas mixed subtype.

The study was approved by the Institutional Review Board of Kanazawa Medical University.

RESULTS

Table 1 shows the characteristics of the nine tumors from the eight patients. Seven of eight patients were female. Six tumors were detected by mass screening CT, and the remaining three tumors were detected by CT for other diseases, such as bronchitis. The maximum diameter of the tumors was 9-18 mm, GGO% of the tumors was 82-100%, and the grade of FDG uptake was weak in 5 and no increase in 4. The CT findings and the FDG PET findings of the representative patient (Patient 7) are shown in Figure 1.

The intraoperative pathological diagnoses of the tumors were Noguchi’s type B in 4, type A or B in 3, and type A or atypical adenomatous hyperplasia (AAH) in 2, respectively. No tumor was intraoperatively diagnosed as invasive carcinoma. The final diagnoses of some tumors were different from the intraoperative ones, i.e., eight of nine tumors were non-invasive BACs (Noguchi’s type A/B) and the remaining one was adenocarcinoma mixed subtype (Noguchi’s type C).

All of the patients underwent only a wedge resection by video-assisted thoracic surgery. The postoperative courses of all patients were uneventful. Until June 2008, the duration of the follow-up ranged from 19 to 50 months (median 38), and no evidence of recurrence was observed in any of the patients.

Table 2 shows the changes in the pulmonary function tests. The preoperative vital capacity (VC) of the patients ranged 2.02-3.77 L, and the postoperative VC ranged 1.83-3.90 L. (Postoperative VC/preoperative VC) ranged 84.6-112.0%, with an average value of 99.2%. The preoperative and postoperative forced expiratory volume in one second (FEV1) of the patients ranged 1.41-2.82 L and 1.22-2.88 L, respectively. (Postoperative FEV1/preoperative FEV1) ranged 86.3-115.5%, with an average value of 95.2%.
TABLE 1. The clinical and pathological characteristics of the patients.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Gender</th>
<th>Method of detection [mm]</th>
<th>Size</th>
<th>GGO%</th>
<th>FDG uptake</th>
<th>Location of tumor</th>
<th>Diagnosis (Noguchi’s class.)</th>
<th>Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>57</td>
<td>F</td>
<td>Mass screening CT</td>
<td>11</td>
<td>100</td>
<td>No increase</td>
<td>Right S(^1)</td>
<td>AAH or BAC (A) BAC (A)</td>
<td>50M NED</td>
</tr>
<tr>
<td>(1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>59</td>
<td>M</td>
<td>Mass screening CT</td>
<td>11</td>
<td>82</td>
<td>Weak</td>
<td>Left S(^3)</td>
<td>BAC (A or B) BAC (B)</td>
<td>45M NED</td>
</tr>
<tr>
<td>3</td>
<td>61</td>
<td>F</td>
<td>Mass screening CT</td>
<td>15</td>
<td>87</td>
<td>Weak</td>
<td>Right S(^1)</td>
<td>BAC (B) BAC (B)</td>
<td>43M NED</td>
</tr>
<tr>
<td>4</td>
<td>76</td>
<td>F</td>
<td>CT for other disease</td>
<td>12</td>
<td>85</td>
<td>Weak</td>
<td>Left S(^{1+2})</td>
<td>BAC (A or B) Mixed (C)</td>
<td>38M NED</td>
</tr>
<tr>
<td>5</td>
<td>66</td>
<td>F</td>
<td>CT for other disease</td>
<td>10</td>
<td>100</td>
<td>No increase</td>
<td>Left S(^{1+2})</td>
<td>AAH or BAC (A) BAC (A)</td>
<td>35M NED</td>
</tr>
<tr>
<td>6</td>
<td>64</td>
<td>F</td>
<td>Mass screening CT</td>
<td>18</td>
<td>100</td>
<td>Weak</td>
<td>Right S(^2)</td>
<td>BAC (B) BAC (B)</td>
<td>34M NED</td>
</tr>
<tr>
<td>7</td>
<td>65</td>
<td>F</td>
<td>Mass screening CT</td>
<td>10</td>
<td>100</td>
<td>Weak</td>
<td>Left S(^{10})</td>
<td>BAC (B) BAC (B)</td>
<td>21M NED</td>
</tr>
<tr>
<td>8</td>
<td>66</td>
<td>F</td>
<td>Mass screening CT</td>
<td>10</td>
<td>100</td>
<td>Weak</td>
<td>Right S(^2)</td>
<td>BAC (B) BAC (B)</td>
<td>19M NED</td>
</tr>
</tbody>
</table>

Patient 1 had two tumors.
Mass screening CT: Chest computed tomography for the purpose of early detection of lung cancer
CT for other disease: Chest computed tomography for other diseases, such as bronchitis
GGO%: percentage of ground-glass opacity/whole tumor
AAH, atypical adenomatous hyperplasia; BAC, bronchioloalveolar carcinoma; Mixed, adenocarcinoma mixed subtype;
Noguchi’s class., Noguchi’s classification
(A), Noguchi’s type\(^1\) A; (B), Noguchi’s type\(^1\) B; (C), Noguchi’s type\(^1\) C
NED, no evidence of disease

Fig. 1. The CT and FDG PET findings of a representative patient. The CT findings (left) reveal that the diameter of the tumor is 18 mm and GGO% is 100%. The FDG PET findings (right) reveal the tumor to have a weak FDG uptake.

TABLE 2. Changes in the pulmonary function of the patients.

<table>
<thead>
<tr>
<th>Patient</th>
<th>PreVC (l)</th>
<th>PreFEV1 (l)</th>
<th>PreFEV1%</th>
<th>PostVC (l)</th>
<th>PostFEV1 (l)</th>
<th>PostFEV1%</th>
<th>PostVC/PreVC</th>
<th>PostFEV1/PreFEV1</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-1</td>
<td>2.25</td>
<td>1.68</td>
<td>81.9 %</td>
<td>2.52</td>
<td>1.94</td>
<td>82.2 %</td>
<td>112.0 %</td>
<td>115.5 %</td>
</tr>
<tr>
<td>1-2</td>
<td>2.52</td>
<td>1.94</td>
<td>82.2 %</td>
<td>2.50</td>
<td>1.83</td>
<td>79.2 %</td>
<td>99.2 %</td>
<td>94.3 %</td>
</tr>
<tr>
<td>2</td>
<td>3.77</td>
<td>2.82</td>
<td>81.0 %</td>
<td>3.90</td>
<td>2.88</td>
<td>72.7 %</td>
<td>103.4 %</td>
<td>102.1 %</td>
</tr>
<tr>
<td>3</td>
<td>2.76</td>
<td>2.04</td>
<td>72.8 %</td>
<td>2.85</td>
<td>1.76</td>
<td>71.5 %</td>
<td>103.3 %</td>
<td>86.3 %</td>
</tr>
<tr>
<td>4</td>
<td>2.02</td>
<td>1.41</td>
<td>71.6 %</td>
<td>1.83</td>
<td>1.22</td>
<td>73.5 %</td>
<td>90.6 %</td>
<td>86.5 %</td>
</tr>
<tr>
<td>5</td>
<td>2.30</td>
<td>1.68</td>
<td>75.7 %</td>
<td>2.50</td>
<td>1.63</td>
<td>70.9 %</td>
<td>108.7 %</td>
<td>97.0 %</td>
</tr>
<tr>
<td>6</td>
<td>3.08</td>
<td>2.35</td>
<td>78.6 %</td>
<td>2.66</td>
<td>2.08</td>
<td>80.6 %</td>
<td>86.4 %</td>
<td>88.5 %</td>
</tr>
<tr>
<td>7</td>
<td>2.13</td>
<td>1.54</td>
<td>77.0 %</td>
<td>1.99</td>
<td>1.37</td>
<td>74.5 %</td>
<td>93.4 %</td>
<td>89.0 %</td>
</tr>
<tr>
<td>8</td>
<td>2.78</td>
<td>2.38</td>
<td>85.6 %</td>
<td>2.66</td>
<td>2.32</td>
<td>89.9 %</td>
<td>95.7 %</td>
<td>97.5 %</td>
</tr>
</tbody>
</table>

Patient 1 underwent a pulmonary wedge resection twice.
PreVC, preoperative vital capacity; PreFEV1, preoperative forced expiratory volume in one second;
PreFEV1%, (preoperative forced expiratory volume in one second/preoperative forced expiratory volume) × 100;
PostVC, postoperative vital capacity; PostFEV1, postoperative forced expiratory volume in one second;
PostFEV1%, (postoperative forced expiratory volume in one second/postoperative forced expiratory volume) × 100
**DISCUSSION**

Lung cancer is the leading cause of cancer death in Japan as well as in most developed countries. Recently thoracic CT screening for the detection of early lung cancer is regarded as a possible tool to decrease lung cancer mortality (Henshke 2000; Kaneko et al. 2000; Sone et al. 2001). Small size pulmonary adenocarcinomas can be detected with CT screening. Especially in Japan, numerous lung cancer patients with a GGO-like shadow have been detected (Kaneko et al. 2000; Sone et al. 2001; Kodama et al. 2002), which was different from US. Most of those tumors had no lymph node metastasis, rare vascular involvement, and an excellent prognosis (Noguchi et al. 1995; Sakurai et al. 2004). Lung cancer with a GGO-like shadow might therefore be candidates for limited resection.

A randomized controlled trial conducted by the Lung Cancer Study Group revealed that the prognoses of the patients who underwent limited resection for the cT1N0M0 peripheral lung cancer was worse than those who underwent standard operation (Lung Cancer Study Group 1995). Therefore, it is important to determine the criterion of the candidates for the limited resection. Although there have been a few reports of limited resection for lung cancers with a GGO-like shadow, some GGO-like shadows are not non-invasive BACs, but adenocarcinomas mixed subtype (Yamato et al. 2001; Nakata et al. 2003), which are biologically more invasive. In order to exclude such active carcinomas from the pilot study on wedge resection, FDG-PET, intraoperative pathological examination and CT were all used to evaluate the lesions. In this study, the candidates were; 1) clinically no nodal or distant metastasis, 2) the location of the tumor was peripheral enough to perform a wedge resection, 3) the diameter of the shadow was between 8 mm and 20 mm by HR-CT, 4) GGO% was 80% or over by HR-CT, 5) FDG uptake of the shadow was classified as weak uptake or lower, 6) intraoperative pathological diagnosis was non-invasive BAC (Noguchi’s type A/B), and 7) informed consent was obtained from the patient.

As a result of the pilot study, nine tumors were treated with a wedge resection under VATS. Their postoperative courses were uneventful and no recurrence has been detected to date. The postoperative pulmonary function was well preserved. Although it was unclear why postoperative lung function was sometimes better than preoperative one, perioperative respiratory training may have affected the results.

There are two issues which remain to be fully discussed. First, there are two methods to measure GGO%, the ratio of the maximum area of cross section (Asamura et al. 2003, Nakata et al. 2003) and the ratio of the maximum diameter (Suzuki et al. 2002). The latter method was employed because the former method had more intraobserver difference.

Second, a 5-point visual grading system was used to interpret FDG uptake within the primary lesions, and the standard uptake value (SUV) threshold was not used. Vansteenkiste and colleagues reported that a visual scale was as accurate as the use of an SUV threshold for lymph nodes in the distinction between benign and malignant nodes (Vansteenkiste et al. 1998). SUV is affected by many factors, including the period between FDG administration and the start of an emission scan, and whether the image is attenuation-corrected or not (Keyes 1995, Chin et al. 2002). Moreover, two different kinds of PET cameras were used in this study. Therefore, a visual scale was found to be more adequate.

Although the final pathological diagnoses of eight tumors were non-invasive BACs, the remaining one was adenocarcinoma mixed subtype. There was a small region of invasive adenocarcinoma in the tumor, which was unlikely to cause recurrence. The patient was a 76 year-old female with bronchial asthma, and she did not want to undergo an additional pulmonary lobectomy when the final pathological diagnosis was notified.

Some investigators reported that AAHs were sometimes resected during surgical treatment of GGO-like shadows, (Watanabe et al. 2002; Nakata et al. 2003; Ohtsuka et al. 2006). However, in the present study, no AAH was resected and all of the tumors were carcinomas. The average value of the maximum diameter of resected AAH in their series was 6-7 mm (Nakata et al. 2003; Ohtsuka et al. 2006). The criteria of the present study, in which tumors smaller than 8 mm in diameter would not be enrolled, might be appropriate for ruling out an unnecessary surgical resection.

This report presented a pilot study on wedge resection of lung cancer using HR-CT and PET findings. Although the number of patients in this study was limited, the results were informative. A wedge resection was done safely without any recurrence, and postoperative pulmonary function was well preserved. Even using these strict criteria, one adenocarcinoma mixed subtype was observed, but the invasiveness of the tumor was very limited. The results of the pilot study were regarded as satisfactory and a new larger clinical trial should therefore be conducted in the future.

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**References**


