CT-Guided Transbronchial Biopsy Using an Ultrathin Bronchoscope With Virtual Bronchoscopic Navigation*

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Study objectives: We evaluated the feasibility, safety, and efficacy of CT-guided transbronchial biopsy (TBB) using an ultrathin bronchoscope with navigation by virtual bronchoscopy (VB) for small peripheral pulmonary lesions of < 20 mm in diameter.

Design: A pilot study.

Setting: A national university hospital.

Patients: We performed CT-guided TBB after VB navigation for 25 patients with 26 small peripheral pulmonary lesions (average diameter, 13.2 mm) between June 1, 2001, and October 31, 2002. Of the 26 lesions, 10 were in the right upper lobe, 2 were in the right middle lobe, 6 were in the right lower lobe, and 8 were in the left upper lobe. Nineteen lesions were not detected on chest radiographs.

Interventions: VB images were reconstructed from helical CT scans. CT-guided TBB was performed using an ultrathin bronchoscope after studying the VB image.

Results: CT-guided TBB was performed safely without any complications for all patients. The bronchi seen under VB imaging were highly consistent with the actual bronchi confirmed using an ultrathin bronchoscope. The ultrathin bronchoscope was inserted between the fifth and eighth generation bronchi. The average durations of the initial scan, the first biopsy, and the total examination were 5.46, 12.96, and 29.27 min, respectively. Seventeen lesions (65.4%) were diagnosed from pathology examinations (primary lung cancers, 13; atypical adenomatous hyperplasia, 1; metastatic cancer, 1; sarcoidosis, 1; and nontuberculous mycobacteriosis, 1). Diagnoses were not obtained for the remaining lesions due to an insufficient number of specimens (six specimens) or to the inability to reach the lesions even using the ultrathin bronchoscope (three specimens).

Conclusions: In summary, CT-guided TBB using an ultrathin bronchoscope with VB navigation was safely performed and was effective for diagnosing small peripheral pulmonary lesions.

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Key words: benign disease; CT-guided transbronchial biopsy; primary lung cancer; small peripheral pulmonary lesion; stereotactic radiotherapy; ultrathin bronchoscope; virtual bronchoscopic navigation

Abbreviations: AAH = atypical adenomatous hyperplasia; FFB = flexible fiberoptic bronchoscope; HRCT = high-resolution CT; SRT = stereotactic radiotherapy; TBB = transbronchial biopsy; VB = virtual bronchoscopy

With recent advances in CT scan screening, an increase in the detection of faint nodules in the peripheral lung has been noted. The transbronchial approach using a flexible fiberoptic bronchoscope (FFB) remains one of the most feasible and safest methods of diagnosing those lesions. The accuracy of diagnosing peripheral pulmonary lesions from tissue samples retrieved using the FFB is reportedly 20 to 84% in cases of malignant lesions, and 35 to 56% in cases of benign lesions.1–9 The yield of FFB is lower in peripheral lesions,1,2,4–7 compared with those of central and intermediate lesions, and is lower in small lesions.1–3,6–9 Baaklini and colleagues1 reported that lesions < 2.0 cm in diameter had a diagnostic yield of 14% when located in the peripheral third, compared with 31% when located in the inner two thirds of the lung.
Some respiratory physicians prefer to diagnose small peripheral pulmonary lesions from tissue samples obtained by percutaneous needle aspiration cytology or biopsy. Although the success rates of these techniques might be very high, with 76 to 97% diagnostic accuracy, these techniques have several problems. First, they have the potential to spread malignant cells from the tumor into the pleural cavity. For patients with poor pulmonary function, these techniques result in an increased risk of pneumothorax. Moreover, systemic arterial air embolism is a rare but severe complication. Conversely, video-assisted thorascopic biopsy may be appropriate for lesions that are strongly suspected to be malignant. However, this process is invasive for elderly patients and patients with poor respiratory function. Thus, diagnosing small peripheral pulmonary lesions more effectively using the FFB is important to respiratory physicians.

The following three methodological problems hinder the diagnosis of small peripheral pulmonary lesions using an FFB: (1) small peripheral pulmonary lesions may not be visible under fluoroscopic radiograph guidance; (2) curettage for transbronchial cytology can reach small peripheral pulmonary lesions, but not forceps for transbronchial biopsy (TBB), given the difficulty in maneuvering within the angles of the bronchi; and (3) identifying accessible bronchial routes to reach small peripheral pulmonary lesions is not always easy during limited examination time. CT-guided TBB or cytology has been developed to overcome the first problem of incorrect positioning of the forceps or curette. To overcome the second problem, an ultrathin bronchoscope has been developed that can be inserted into more peripheral bronchi than conventional bronchoscopes under direct vision. Recently, the working channel of an ultrathin bronchoscope has become wider, so the collection of tissue specimens has become possible. This has led to the feasibility of TBB for diagnosing more peripheral small lesions of the lung. In addition, rapid progress in computer technology has resulted in advances in diagnostic imaging. Virtual bronchoscopy (VB) is the application of three-dimensional display techniques to the airways, enabling the simulation of actual bronchoscopic procedures. A new method using VB for navigation to the proper bronchi has been introduced to bronchoscopy.

In the present study, CT-guided TBB, use of an ultrathin bronchoscope, and VB navigation were combined in one procedure. The feasibility, safety, and efficacy of this procedure for diagnosing small peripheral pulmonary lesions were evaluated.

Materials and Methods

Subjects

Between June 1, 2001, and October 31, 2002, at Hokkaido University Medical Hospital, 29 patients with 30 small peripheral pulmonary lesions (mean diameter, < 20 mm) underwent chest CT scans to generate VB images for the navigation of CT-guided TBB with an ultrathin bronchoscope. Nineteen lesions were not detected on chest radiographs, but by chest CT scans performed during the follow-up of other diseases or for check-ups of the lung. No patients with small peripheral pulmonary lesions < 20 mm in diameter received TBB without information about VB during this period, but lesions deemed as displaying inflammatory or postinflammatory changes on high-resolution CT (HRCT) scans were excluded. For small peripheral pulmonary lesions of < 10 mm in diameter, only those proven to be growing were included in this study. All patients were given detailed descriptions of the examination and were informed that this was a new approach. Informed consent was obtained in all cases. Conventional and HRCT scan examinations were performed on all 29 patients before VB images were made.

VB

CT scan examinations were performed using a multidetector CT scanner (Aquilion; Toshiba; Tokyo, Japan) with the following parameters: collimation, 0.5 mm; four detectors; pitch, 5 to 7; and rotation time, 0.5 s. Helical volume data sets were acquired during single breath-hold inhalations. Images were reconstructed from helical CT scans and transferred to a computer workstation (Aлатoview; Toshiba; or Virtual Place workstation; Medical Imaging Laboratory; Tokyo, Japan). All VB images were made by one radiologist. The volume-rendering method was used for the VB algorithm. VB objects were built by autosegmentation, and a fly-through image was used. Reconstructed VB images were generated accurately to approximately the fifth generation of bronchi, as more peripheral bronchi were not visible. We therefore generated VB images using the pulmonary artery instead of invisible peripheral bronchi to predict a more peripheral route (Y. Onodera, MD; unpublished observation; May 2003).

CT-Guided TBB

Each patient was premedicated using 15 mg pentazocine hydrochloride and 0.5 mg atropine sulfates. Local anesthesia of the upper respiratory tract was achieved using 4% lidocaine. All patients were intubated orally with a 8.0-mm endotracheal tube, as a routine procedure for TBB in our institute. In this study, an ultrathin bronchoscope (BF-type XP-40; Olympus; Tokyo, Japan) with an external diameter of 2.8 mm and a biopsy channel diameter of 1.2 mm was utilized. After the VB image was generated and studied, the ultrathin bronchoscope was inserted into the target bronchus as deep as possible under direct vision. The position of the forceps inserted through a bronchoscope then was confirmed and adjusted by real-time multislice CT scan. After the position was confirmed, a biopsy was performed. The bronchoscopy procedures were performed by two pulmonary fellows, each with >5 years of training and experience in bronchoscopy, who were directly supervised and assisted by the pulmonary faculty in attendance.

Results

Twenty-nine patients with 30 small peripheral pulmonary lesions were enrolled into this study. One
patient was excluded because the lesion was no longer visible when the CT scan for VB was performed. VB images were therefore obtained from 28 patients with 29 small peripheral pulmonary lesions. Three patients with three lesions did not undergo CT-guided TBB, as the VB images suggested that the lesions would not be able to be reached using even an ultrathin bronchoscope. No bronchi reaching the lesions were seen.

Thus, a total of 25 patients (9 men, 16 women) with 26 small peripheral pulmonary lesions received CT-guided TBB. The average age was 67.1 years (age range, 57 to 82 years). On HRCT scans, the average diameter of target lesions was 13.2 mm. Of the 26 lesions, 10 were in the right upper lobe, 2 were in the right middle lobe, 6 were in the right lower lobe, and 8 were in the left upper lobe.

CT-guided TBB was performed safely without any complications for all 25 patients with 26 small peripheral pulmonary lesions. The bronchi depicted on VB images were highly consistent with the actual bronchi, as confirmed by ultrathin bronchoscopy (Fig 1). The ultrathin bronchoscope was inserted between the fifth and eighth generation bronchi. The tip of the ultrathin bronchoscope and the tip of the forceps were visualized clearly along with each lesion on real-time multislice CT scans in all cases, confirming the lesions as the origins of the specimens. The average time for an initial scan, including anesthesia of the trachea and bronchi, using an ultrathin bronchoscope and inserting the ultrathin bronchoscope following VB, was 5.46 min. The average time for the first biopsy, including the first scan, the CT scan, and the adjustment of positions for the bronchoscope and forceps, was 12.96 min. The average total time for examination once the ultrathin bronchoscope was inserted into the endotracheal tube was 29.27 min (Table 1). Light bleeding occurred around small peripheral pulmonary lesions, but severe bleeding was not observed under CT fluoroscopy.

Adequate tissue was obtained for pathologic diagnoses in 17 of the 26 lesions (65%) [Table 2]. Lesions comprised 13 cases of primary lung cancer (adeno-
Lung cancer, 4; AAH, 1.

*Not diagnosed

Diagnosed as representing primary lung cancer, and were treated by surgical resection. Four then were diagnosed as benign lesions were monitored without intervening therapy. Of the nine lesions that could not be diagnosed by CT-guided TBB, five were treated by surgical resection. Four then were diagnosed as representing primary lung cancer, and one was diagnosed as AAH. The diagnostic sensitivity of this procedure was 65.4% for the 26 lesions in which CT-guided TBB was performed. Of the 22 lesions in which a final diagnosis was made, the sensitivity, specificity, negative predictive value, positive predictive value, and accuracy were 75.0%, 100.0%, 100.0%, and 77.3%, respectively. No significant differences were observed regarding age, sex, average diameter or size of the lesion, time of the initial scan, time of the first biopsy, total time of the examination, the number of biopsies, or the ability to obtain a diagnosis (data not shown). Of the nine lesions for which diagnoses could not be obtained, six lesions had an insufficient number of biopsy samples taken and the other three lesions were inaccessible, even using an ultrathin bronchoscope with VB navigation.

### Discussion

A transbronchial approach under radiograph fluoroscopic guidance has been the most generally accepted method for diagnosing peripheral pulmonary lesions since the 1970s. However, obtaining diagnostic samples from small peripheral pulmonary lesions <2.0 cm in diameter is difficult. In our institute, the diagnostic sensitivity of FFB for small peripheral pulmonary lesions (average diameter, <20 mm) under radiographic fluoroscopic guidance in the past year was 35%, and the rate for obtaining diagnostic biopsy samples was as low as 13% (data not shown). In the present study, we combined CT-guided TBB, an ultrathin bronchoscope, and VB navigation for diagnosing small peripheral pulmonary lesions. The diagnostic sensitivity of this procedure was as high as 65.4% in small peripheral pulmonary lesions examined in our institute during this period. Moreover, cytologic procedures using brushes or washing might enhance diagnostic sensitivity at least for malignant diseases, although these procedures were not performed in the present study. Notably, all diagnoses were made from biopsy samples, and included two lesions from benign diseases, which have typically been diagnosed from histologic, rather than cytologic, samples. An accurate diagnosis by TBB may circumvent unnecessary surgery with general anesthesia for the treatment of these benign diseases. In addition, even video-assisted thoracoscopic biopsy would retain considerable risk for elderly patients or patients with poor respiratory or cardiac function. For such patients, SRT has been recommended as an appropriate alternative. Of the 13 patients found by this procedure to have lung cancer, 5 received SRT and have shown no signs of recurrence for >1 year. Those cancers may go into complete remission without surgical treatment after accurate diagnosis by bronchoscopy.

We successfully obtained VB images from helical CT scan information, and used them for the simulation and navigation of appropriate bronchial routes to small peripheral pulmonary lesions. Several groups have reported using VB images for the simulation of major endobronchial abnormalities.

### Table 1—Duration of CT-Guided TBB

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean ± SD, min</th>
<th>Range, min</th>
</tr>
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<tbody>
<tr>
<td>Time to first scan*</td>
<td>5.46 ± 2.25</td>
<td>0.85–10.45</td>
</tr>
<tr>
<td>Time to first biopsy†</td>
<td>12.96 ± 8.57</td>
<td>3.33–30.58</td>
</tr>
<tr>
<td>Total time†</td>
<td>29.27 ± 13.09</td>
<td>9.90–55.45</td>
</tr>
</tbody>
</table>

*Including time to anesthetize bronchi using bronchoscope and insert bronchoscope following VB imaging.
†Including time for CT scanning and adjusting position of bronchoscope and forceps.
‡Including time for inserting ultrathin bronchoscope into endotracheal tube.

### Table 2—Diagnosis and Treatment of Examined Lesions

<table>
<thead>
<tr>
<th>CT-Guided TBB Procedure</th>
<th>Lesions, No.</th>
<th>Lesions, Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung cancer</td>
<td></td>
<td>Surgery, 11</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>12</td>
<td>Radiotherapy, 4</td>
</tr>
<tr>
<td>Large cell carcinoma</td>
<td>1</td>
<td>Observation, 2</td>
</tr>
<tr>
<td>Metastasis of colon</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Non tuberculous</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Mycobacterium</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Sarcoidosis</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>AAH</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>17 (65%)</td>
<td>17 (65%)</td>
</tr>
<tr>
<td>Not diagnosed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery*</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Observation</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>9 (35%)</td>
<td></td>
</tr>
</tbody>
</table>

*Including time to anesthetize bronchi using bronchoscope and insert bronchoscope following VB imaging.
†Including time for CT scanning and adjusting position of bronchoscope and forceps.
‡Including time for inserting ultrathin bronchoscope into endotracheal tube.
and for the assessment of tracheobronchial stenosis\textsuperscript{26} and bronchial malignant disease.\textsuperscript{27} To navigate cases of thoracic disease, several investigators\textsuperscript{28,29} have used VB images for guidance in transbronchial aspiration biopsies of mediastinal lymph nodes. For peripheral lesions, Moriya and colleagues\textsuperscript{21} have reported using VB images as a guide for conventional TBB. Furthermore, Asano and colleagues\textsuperscript{22} have reported a case of small peripheral pulmonary lesions diagnosed using ultrathin bronchoscopy under VB imaging for bronchoscopic navigation. In cases of TBB using an ultrathin bronchoscope, the bronchoscopists would have to explore many bronchi to reach the lesions, and patients could not tolerate a lengthy procedure. Although HRCT scanning can demonstrate the optimal bronchial path to the lesions, a three-dimensional understanding of the complicated bronchial bifurcation based on axial images is difficult. In this study, VB images were made by a radiologist, but the upcoming development of new software and strategies making VB imaging more convenient will allow respiratory physicians and bronchologists to make VB images from information obtained by helical CT scanning.

Several improvements also may be made to increase the yield of TBB and would bring this procedure into wide use. First, ultrathin bronchoscopes are slightly limp and somewhat difficult to control in the peripheral lung after being bent and turned. In addition, biopsy channels are narrow (diameter, 1.2 mm) and the forceps is small (diameter, 1.0 mm). In this study, six of the nine undiagnosed lesions could not be diagnosed because insufficient tissue specimens could be obtained by biopsy. Brush cytology or bronchial washing may need to be performed together to increase diagnostic sensitivity. CT-guided TBB in combination with VB navigation was performed in an examination time similar to that for conventional TBB. However, the exact radiation exposure to patients and physicians is unknown. Preliminarily, the dose of radiation exposure was measured during an examination of CT-guided TBB. The main operator and three assistants received < 200 microsievert of radiation exposure, which is 1/1,000 less than the dose causing cataracts. A detailed study of radiation exposure and radiation contours in CT scan rooms has to be performed. Moreover, although the total examination time was < 30 min, patients and physicians occupied the CT scan room for approximately 1 h, so the cost of occupying a CT scan room must be considered in terms of hospital economy.

In summary, CT-guided TBB using an ultrathin bronchoscope after VB navigation was performed safely and was very effective for diagnosing small peripheral pulmonary lesions. CT-guided TBB was combined with an ultrathin bronchoscope and VB navigation into one procedure. To clarify the efficacy of each of the three components and the cost/benefit ratio of diagnosing small peripheral pulmonary lesions, randomized trials must be performed.

**References**