Repeated Ultrasonically Guided Needle Biopsy of Small Subpleural Nodules*

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Study objective: To detect the significance of repeated ultrasonically guided needle biopsy (UGNB) for the diagnosis of nodular lesions ≤ 2 cm in diameter.

Design: Retrospective study to evaluate the diagnostic yield of UGNB.

Setting: University hospital, outpatients, and inpatients of the respiratory department.

Patients: One hundred seven cases with small nodular lesions ≤ 2 cm in diameter in contact with the pleura. Sixty-two of 107 cases were malignant, and the others were benign diseases.

Results: Initial UGNB identified 56% (35/62) of the malignant lesions and 16% (7/45) of the benign lesions, i.e., 39% (42/107) of the total. In 35 of 65 cases that were not diagnosed by the initial UGNB, it was repeated. Diagnostic yields of the second UGNB were 68% (13/19) of the malignant cases, 25% (4/16) of the benign cases, yielding a total of 49% (17/35) in those reexamined. Furthermore, 51 of 65 patients with negative findings on the initial UGNB underwent fiberoptic bronchoscopy. The resulting diagnostic yields were 22% (5/23) from the malignant lesions and 18% (5/28) from the benign lesions, 20% (10/51) in total. Thus, among the malignant cases, the repetition of UGNB increased the definitive diagnostic yield from 56% (the initial UGNB) to 77%. In these small tumors, no serious complications were caused by the procedure.

Conclusions: UGNB should be performed twice for a definitive diagnosis of small subpleural nodules before deciding on surgical biopsy or follow-up. (CHEST 1999; 116:1320–1324)

Key words: small pulmonary nodule; transthoracic needle biopsy; ultrasound

Abbreviations: FBS = fiberoptic bronchoscopy; UGNB = ultrasonically guided needle biopsy

The widespread use of CT has increased the detection of small lesions in the lung field. It is not easy to diagnose these lesions based only on the CT findings, and specimens obtained directly from the lesions are essential for definitive diagnosis.1 The pulmonary nonsurgical approaches to obtain small specimens directly are transbronchial and transthoracic.

Ultrasound can detect nodules in contact with the pleura without necessitating exposure to ionizing radiation. We employ ultrasonically guided needle biopsy (UGNB) as the first method of choice to obtain specimens from the lesion, and the usefulness of this technique has been widely acknowledged.2–4 In particular, since a curative treatment can be obtained from the surgical resection of small lung cancer, it is necessary to improve the diagnostic yield in cases with small lesions. In this study, the subjects were cases with subpleural nodules in which we had performed UGNB. We attempted to clarify the usefulness of repeated UGNB in the definitive diagnosis of small nodules (≤ 2 cm in diameter) in which negative diagnoses were initially obtained.

Materials and Methods

This study encompassed a total of 335 cases with subpleural nodules in which UGNB was performed from October 1985 through December 1995 in our department. Of these cases, there were 255 with pathologically proven pulmonary carcinoma, and 80 with benign disease that were diagnosed on the basis of pathologic and bacteriologic examinations or follow-up studies (disappearance of shadow, or absence of change for at least 4 years).

The sizes of the nodules were measured by their longest dimension on the plain chest radiographs. The relationship between the frequency of malignant disease and the size of the lesion was studied in the 335 cases. Next, we focused on 107 cases (62 of malignant disease, 45 of benign disease) that presented nodular shadows ≤ 2 cm in diameter. The diagnostic yields of UGNB and fiberoptic bronchoscopy (FBS) were surveyed, and a similar survey of the 30 cases of malignant nodular shadows ≤ 1.5 cm in longest diameter was performed.
The equipment used in this study consisted of ultrasound units (SSA-90A and SSA-270; Toshiba; Tokyo, Japan), a 4-MHz linear array transducer (GCE-406M; Toshiba), and a metallic needle (0.8-mm inner diameter, 1.0-mm outer diameter, and 150 mm long; Takei Medical & Optical; Tokyo, Japan) for UGNB. First, the puncture site was verified on the ultrasound image with the patient and operator in comfortable positions. After local anesthesia with 0.5% procaine hydrochloride, the needle was introduced and advanced into the nodule under ultrasound image guidance on a TV monitor; while observing the tip of the needle, aspiration biopsy was carried out using a one-hand grip aspirator. The puncture of the nodule by the aspiration needle was confirmed by the appearance of a high echo spot within the nodule in the ultrasound image (Fig 1). The specimens were immediately smeared on glass slides for cytologic and bacteriologic examinations. After smear preparations, the interiors of both the syringe and the needle were washed out with saline solution (about 3.0 mL), and the washings also were used for bacterial culture and cytologic examinations. If there were no tissue fragments in the washings, aspiration was repeated immediately once or twice, and the entire series was considered as a single procedure. A specific finding obtained from the cytologic or bacteriologic testing examinations was taken as positive.

Before the procedure, allergic reactions to local anesthetics and tendency to bleed were checked. UGNB was performed in those cases with no prolongation of bleeding time, normal coagulation tests, and a platelet count > 100 x 10^3/μL. UGNB was carried out by the same three operators in this study.

FBS was performed as follows: after the induction of local anesthesia with 2% lidocaine, a 6-mm diameter fiberoptic bronchoscope (model BF-10; Olympus Optical; Tokyo, Japan) was introduced through the mouth without endotracheal intubation, and forceps biopsy, brushing, and lavage of the lesion were performed under radiograph fluoroscopic guidance.

When a diagnosis was not obtained by the initial UGNB procedure, a second UGNB was carried out within 1 month of the first procedure. A bronchoscopic examination was usually performed between these two UGNB procedures. When no positive findings emerged from all of the above examinations, a choice was made between surgical biopsy and further follow-up observations.

For comparison of the diagnostic yields, classified by lesion size and by examination method, and for testing for significant differences in the frequency of complications, the χ² test was used.

**RESULTS**

The frequency of malignant disease in 335 cases of subpleural nodules classified by size is shown in Figure 2. Of 107 small nodules (32%) ≤ 2 cm in diameter, 62 were malignant (58%). Among 87 cases of nodules between 1.1 cm and 2.0 cm in diameter, 53 cases (61%) were malignant, whereas 9 cases (45%) were malignant of the 20 cases that were ≤ 1.0 cm in diameter. The frequency of malignancy tended to be lower in the smaller nodules.

A definitive diagnosis was obtained with the initial UGNB in 42 of 107 cases (39%) with small subpleural nodules (Table 1). The second UGNB, per-
formed in 35 of 65 cases with negative findings on the initial UGNB, yielded definitive diagnoses in 17 cases (49%). Bronchoscopy that was performed in 51 of 65 cases in which the initial UGNB finding was negative yielded a definitive diagnosis in only 10 cases (20%). In the initial UGNB, the diagnostic yield in the 62 cases of malignant disease was 56% (35/62); in the second UGNB, the diagnostic yield was 68% (13/19). It was possible to diagnose malignancy in 77% of cases (48/62) by combining the first and second UGNB procedures (Tables 1, 2). Also, bronchoscopy yielded definitive diagnoses in 22% of malignant cases (5/23).

On the other hand, the diagnostic yield among the 45 cases of benign disease was 16% (7/45) on the initial UGNB and 25% (4/16) on the second UGNB. Thus, repeated UGNB diagnosed an overall total of 11 benign cases (24%). Bronchoscopy in 28 of 38 cases with negative findings in the first UGNB yielded diagnoses in 5 cases (18%). All 16 benign lesions that were diagnosed by UGNB or bronchoscopy were mycobacteriosis. We performed a total of 142 initial and second UGNB procedures. In 4 of 142 procedures, aspiration was repeated immediately, once because of a lack of tissue fragments in the washings of the syringe and the needle.

The significance of repeated UGNB for small subpleural nodules of pulmonary carcinoma up to 2 cm in longest dimension and up to 1.5 cm in diameter is shown in Table 2. The yields of definitive diagnoses in 30 cases of pulmonary carcinoma nodules ≤ 1.5 cm in diameter were 47% (14/30) on the first UGNB and 67% (8/12) on the second, for a total 22 of 30 cases (73%). UGNB yields did not significantly differ between nodules from 1.6 cm to 2 cm and those ≤ 1.5 cm.

Complications are shown in Table 3. The incidence of complications occurring in UGNB was compared in all 335 cases of subpleural nodules, 107 cases of small nodules ≤ 2 cm in diameter, and 62 cases of small pulmonary carcinoma of ≤ 2 cm in diameter. The incidence of complications showed no significant difference between for the total of 335 cases and for small nodules ≤ 2 cm in diameter, and there was no significant difference in the data for malignant or benign nodules. These complications were minor, consisting of three cases with pneumothorax and four cases with hemoptysis, and they were improved by rest alone.

### Table 1—Diagnostic Yields of Biopsy From Small Subpleural Nodules (≤2 cm)*

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Diagnostic Yield (n = 107)</th>
<th>Malignant (n = 62)</th>
<th>Benign (n = 45)</th>
</tr>
</thead>
<tbody>
<tr>
<td>First UGNB</td>
<td>42/107 (39)</td>
<td>35/62 (56)</td>
<td>7/45 (16)</td>
</tr>
<tr>
<td>Second UGNB</td>
<td>17/35 (49)</td>
<td>13/19 (68)</td>
<td>4/16 (25)</td>
</tr>
<tr>
<td>FBS after first UGNB</td>
<td>10/51 (20)</td>
<td>5/23 (22)</td>
<td>5/28 (18)</td>
</tr>
<tr>
<td>Total</td>
<td>69/107 (64)</td>
<td>53/62 (85)</td>
<td>16/45 (36)</td>
</tr>
</tbody>
</table>

* Data are presented as No. of cases/total cases (%).

### Table 2—Overall Diagnostic Yield of UGNB From Malignant Nodules From 1.6 to 2 cm and 1.5 cm or Less in Diameter*

<table>
<thead>
<tr>
<th>Diagnostic Yield</th>
<th>UGNB</th>
<th>≤2 cm</th>
<th>1.6 to 2.0 cm</th>
<th>≤ 1.5 cm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 62)</td>
<td>(n = 32)</td>
<td>(n = 30)</td>
<td></td>
</tr>
<tr>
<td>First UGNB</td>
<td>35/62 (56)</td>
<td>21/32 (66)</td>
<td>14/30 (47)</td>
<td></td>
</tr>
<tr>
<td>Second UGNB</td>
<td>13/19 (68)</td>
<td>5/7 (71)</td>
<td>8/12 (67)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>48/62 (77)</td>
<td>26/32 (81)</td>
<td>22/30 (73)</td>
<td></td>
</tr>
</tbody>
</table>

* Data are presented as No. of cases/total cases (%).

### Table 3—Complications due to UGNB*

<table>
<thead>
<tr>
<th>Complications</th>
<th>All Nodules (n = 335)</th>
<th>Small Nodules ≤ 2 cm (n = 107)†</th>
<th>Small Malignant Nodules ≤ 2 cm (n = 62)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumothorax</td>
<td>11 (3)</td>
<td>3 (3)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Bloody sputum</td>
<td>9 (3)</td>
<td>4 (4)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Total</td>
<td>20 (6)</td>
<td>7 (7)</td>
<td>3 (5)</td>
</tr>
</tbody>
</table>

* Data are presented as No. (%).
† ≤ 2 cm in diameter.
discussion

Opportunities to discover small lesions in the lung field have increased with the growing frequency of CT examinations of the chest. Noninvasive approaches have been tried in order to distinguish between benign and malignant small lesions by techniques such as high-resolution CT,\textsuperscript{5,6} three-dimensional CT,\textsuperscript{7} and nuclear medicine examinations,\textsuperscript{8} but the preoperative diagnostic yields have not been at all satisfactory. There has been a recent trend toward the increased use of thoracoscopy as a method of obtaining specimens directly from these small lesions. However, since these thoracoscopic lung biopsies\textsuperscript{9} have to be conducted under general anesthesia, less invasive procedures such as bronchoscopic examination and percutaneous biopsy are more frequently performed before surgical biopsy.

Bronchoscopy has contributed greatly to the diagnosis and evaluation of lung cancer originating from the bronchus. However, the diagnostic yield in cases of small peripheral nodules (\(\leq 2\) cm in diameter), while varying slightly among institutions, is hardly in the satisfactory range.\textsuperscript{1,10,11} In pulmonary adenocarcinoma arising in the peripheral lung parenchyma, the smaller that the primary lesion is, the lower the frequency of advanced stage.\textsuperscript{12} To improve the patient’s prognosis, therefore, it appears necessary to differentiate between benign and malignant disease while the lesion is still small. Many institutions have consequently turned to percutaneous biopsy techniques using fluoroscopic\textsuperscript{13–15} or CT guidance.\textsuperscript{16,17}

The small nodules (\(\leq 2\) cm in diameter) in this report accounted for approximately one third of all subpleural nodules (335 cases), and some 60% of them were malignant. Moreover, 20% of the lesions were \(\leq 1.5\) cm in diameter. It is foreseeable that to increase the diagnostic yield for small subpleural lesions, a percutaneous approach will become more of a routine procedure than bronchoscopic examinations.\textsuperscript{18} In the present study, the results for the first UGNB yielded 42 diagnoses in a total of 107 small nodules. However, in cases for which negative results are obtained with the first UGNB, it is difficult to decide whether to proceed by carrying out a surgical biopsy or a bronchoscopic examination, or to repeat the percutaneous biopsy.

The likelihood of a malignancy is relatively low with smaller-sized lesions, and nearly half of the nodular shadows \(\leq 2\) cm in diameter in our series turned out to be benign lesions (Fig 2). When it is not possible to judge whether these small lesions are malignant or benign after the first noninvasive procedures, it would be too aggressive to carry out surgical biopsies in all such cases, because about half of them will be benign lesions quite adequately treatable by conservative treatment, including follow-up studies.

In the present study, the diagnostic yield obtained by bronchoscopic examination of small subpleural nodules \(\leq 2\) cm in diameter was significantly lower than that for the second UGNB (\(p < 0.01\)). It was therefore suggested that the diagnostic yield would be improved by repetition of UGNB if the initial procedure finding is negative. In particular, when looking at malignant cases, the diagnostic yield of initial UGNB for small pulmonary carcinoma was 56%. However, with repetition of UGNB in cases with negative findings on the initial UGNB, the overall diagnostic yield for small malignant tumors increased to 77%. Furthermore, in the present study, since not all of the cases with negative findings on the first UGNB underwent a second UGNB, it is likely that UGNB repetition in all of the cases with negative findings would have raised the positive rate above 77%.

On the basis of a report that pulmonary carcinomas with a diameter \(\leq 1.5\) cm have fewer distant metastases,\textsuperscript{19} UGNB is desirable for such lesions. The present results of UGNB suggested that there was no significant difference between the diagnostic yield in pulmonary carcinoma up to 1.5 cm and from 1.6 cm to 2.0 cm in diameter, and the diagnostic yield in the former lesions was improved by the repetition of UGNB.

Among the cases that were analyzed in this report, there were nine cases of pulmonary carcinoma that were not diagnosed by UGNB and FBS examination. Two of these cases were bronchioloalveolar cell adenocarcinoma, but the other cases showed no particular tendency in terms of specific histologic type, degree of cell differentiation, or presence of small necrotic foci. There were 13 cases that were diagnosed by the second UGNB. Three of these 13 cases had low cellularity, and the others did not show diagnostic atypism of cells. In cases with mycobacteriosis, the diagnostic yield may be improved by combined use of the polymerase chain reaction method in order to investigate the presence of tubercle bacilli.\textsuperscript{20}

In the widely used percutaneous aspiration biopsy-guided fluoroscopy and CT method, pneumothorax is reported in 6 to 33% of cases, bloody sputum in 5 to 19%, and intrapulmonary hemorrhage in 21 to 35%.\textsuperscript{1,13–17} Moreover, in bronchoscopic biopsies, pneumothorax occurs in approximately 5% of cases, and bloody sputum or hemoptysis occurs in about 1% of cases each.\textsuperscript{21} The complications of UGNB include pneumothorax, bloody sputum, hemothorax, and the vasovagal reflex. In the present series of small lesions, such complications were mild in de-
gree and low in incidence (pneumothorax, 3%; bloody sputum, 4%), but their incidence did not differ according to lesion size or to whether the lesion was malignant or benign. The small nodular shadows are in contact with the pleura, and the opportunity to monitor the needle tip while watching high resolution and real-time images facilitates effective avoidance of such mishaps. Accordingly, from the low frequency of complications and the mild complications, repetition of UGNB is an acceptable procedure.

Moreover, 39 of 62 patients (63%) in this study who had small carcinomatous tumors were 65 years old. This fact suggests that as long as the patients are in good overall physical condition and can maintain the desired posture and hold their breath, thus permitting a clear depiction of the lesion on the ultrasound image, there is no age-related limitation on the UGNB procedure. The UGNB can be carried out repeatedly in cases with small nodules on an outpatient basis. In the coming years, the elderly, who have more malignant tumors, will increase in number, and the UGNB is a safe technique with great clinical advantage in such patients.

ACKNOWLEDGMENT: The writers thank Professor J. Patrick Barron of the International Medical Communications Center, Tokyo Medical University for contributing to the revision of the manuscript.

REFERENCES