CT Fluoroscopy-Guided Bronchoscopic Dye Marking for Resection of Small Peripheral Pulmonary Nodules*

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Study objective: To determine the diagnostic reliability and safety of a new marking technique using transbronchoscopic dye injection under CT fluoroscopy for preoperative localization of a small pulmonary nodule.

Design: Prospective study.

Setting: Hyogo Medical Center for Adults and Shizuoka Cancer Center in Japan.

Patients: Seventeen patients who had a peripheral pulmonary nodule < 15 mm in size on CT scans that was suspected to be difficult to localize by visual inspection and manual palpation at our institutes between April 2000 and October 2002.

Interventions: After a bronchoscope was inserted orally under local anesthesia and was introduced into the related bronchus of the target nodule, a Teflon sheath catheter with metal tip was inserted transbronchoscopically and was advanced into the visceral pleura. By monitoring CT fluoroscopy, the catheter tip was positioned at the nearest pleural surface of the nodule, and 0.5 mL indigo carmine was injected under deep inspiratory breathhold. CT scans were obtained to confirm the relationship between the injected dye area and the nodule.

Measurements and results: The dye injections were performed completely in all 17 patients, who subsequently underwent lung resection guided by the dye staining. There were no complications or harmful effects of the surgery. The area of injected dye was demonstrated as a hazy focal lesion about 10 mm beneath the pleura on the high-resolution CT scan, and was clearly visible as a patchy dark blue area about 20 mm in size on the visceral pleura at surgery. The mean distance between the nodule and the dye was 20 mm on the CT scan (distance range, 0 to 30 mm). The mean examination time with this technique was approximately 35 min (range, 25 to 45 min). The mean CT fluoroscopic time was 60 s (range, 30 to 120 s).

Conclusions: Our transbronchial “tattooing” technique is safe and reliable. We think it is superior to previous marking methods.

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Key words: bronchoscopy; CT fluoroscopy; high-resolution CT; indigo carmine; lung cancer; preoperative marking

Abbreviations: BAC = bronchioloalveolar carcinoma; GGA = ground glass attenuation; HRCT = high-resolution CT

Small peripheral lung lesions have been detected more frequently as the prevalence of CT scanning has grown. Some of those lesions show a localized area of ground glass attenuation (GGA) on high-resolution CT (HRCT) scans, and most of them are invisible on conventional chest roentgenograms. The differential diagnoses of these small lesions with GGA include not only bronchioloalveolar carcinoma (BAC) but also benign lesions such as atypical adenomatous hyperplasia or bronchioloalveolar adenoma. As these lesions are small, present at the periphery, and detected only by CT scanning, conventional diagnostic modalities and techniques are not useful for their histopathologic diagnosis, and video-assisted thoracic surgery has come to play an important role in the diagnosis and treatment of such peripheral, small, faint lesions. Since these lesions are usually not palpable or visible at surgery, preop-
erative marking of the lesion is necessary to perform an accurate resection. For this purpose, the several following marking methods have been attempted: hook-wire placement; methylene blue injection; metallic coil injection; colored collagen insertion from the transthoracic approach; and CT-guided bronchoscopic barium marking. But all of these methods have some limitations and complications. The transthoracic approach has complications such as pneumothorax and intravascular injection of the substances, and is thus usually performed just before surgery, which would rarely be fatal. Metallic materials and barium sulfate require intraoperative fluoroscopic imaging and could not be repeated in a missed marking case.

We have preliminarily reported a new preoperative marking technique using bronchoscopic dye injection under CT fluoroscopy guidance for the localization of small pulmonary nodules during thoracoscopic surgery. In this article, we describe the more precise technical aspect, diagnostic reliability, and safety of this technique, and we review additional cases in which this technique has been applied.

**Patients and Methods**

The enrollment criteria of this study were as follows: (1) location of peripheral pulmonary nodules in the outer one third of the lung field and an approximate size of <15 mm on HRCT scan; (2) presence of nodules that are suspected to be difficult to localize by visual inspection and manual palpation; and (3) provision of informed consent by the patient. Our institutional review boards approved this study.

Between April 2000 and October 2002, 17 patients with a peripheral pulmonary lesion were enrolled in this study. In the study, there were 12 women and 5 men, with a median age of 56 years (age range, 42 to 83 years). Fourteen lesions were detected by CT scan, and of these, 10 had been discovered by follow-up of other diseases, and 4 had been found during routine medical checkups. Lesions in the three other patients were detected by conventional chest radiograph as part of the health survey, and because of a cough in one patient. Among the 17 lesions, 11 lesions could not be detected on chest radiograph, even by retrospective reexamination. The mean size of pulmonary nodules on HRCT scans was 10 mm (size range, 5 to 15 mm). Thirteen lesions appeared only as an area of GGA, and the others appeared as a peripheral GGA with small high attenuating area.

Our localization technique was as follows: all procedures were performed in an interventional CT scan suite. CT fluoroscopic images were acquired during continuous scanning with radiograph exposure (Astion Multi; Toshiba Medical Systems; Tokyo, Japan), which was controlled by an integrated foot switch and hand-held controller. The technical parameters of CT fluoroscopy were a 120-kV peak, 30 to 40 mA, and a 256 × 256 pixel matrix with a 5-mm section thickness. Images were reconstructed at 6 frames per second with a 0.75-s delay after scanning, which provided real-time guidance to facilitate patient positioning and bronchoscopic marking. The CT fluoroscopy was displayed on a monitor suspended from the ceiling.

Pharyngeal anesthesia with 2% lidocaine spray, and premedication using 1 mg atropine and 5 mg of diazepam was administered. The bronchoscope (BF-30; Olympus; Tokyo, Japan) was inserted orally under local anesthesia and introduced into the related bronchus of the target lesion after the tracheobronchial lumen was examined. A Tellon (DuPont; Wilmington, DE) sheath catheter with a metal tip at the top (PW-6P-1; Olympus) was inserted into the related bronchus through the channel of the bronchoscope and was advanced into the visceral pleura. After these procedures, the patient was moved into the gantry of the CT scanner. By monitoring the CT fluoroscopy in real time, the position of the catheter tip was confirmed. When the tip was positioned at the nearest pleura of the nodule, 0.5 mL indigo carmine was injected under a deep inspiratory breathhold with the patient under CT fluoroscopic monitoring. After these procedures were performed, HRCT images were immediately obtained to confirm the relationship between the injected area and the lesion. The bronchoscopic procedures were performed by one interventional bronchoscopist (M.E.) supported by two or three pulmonologists.

A diagnostic chamber (180-mL diagnostic chamber, model 9015; Radcal; Monrovia, CA) was used to measure the scatter radiation exposure of interventional bronchoscopists. Scatter radiation exposure during the procedure was directly measured at a distance of 1 m from the center of the CT scanner gantry and 1 m above the floor in two cases. The position of the chamber was almost identical to that of the interventional bronchoscopist.

**Results**

The dye injections using CT fluoroscopic monitoring were completely performed for all 17 lesions (Table 1, Fig 1, 2). There were no complications such as pneumothorax or hemoptysis related to this procedure or the indigo carmine, and there were no harmful effects on surgery from the procedure.

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**Table 1—CT Fluoroscopy-Guided Bronchoscopic Dye Marking Results in Pulmonary Lesions**

<table>
<thead>
<tr>
<th>Patient No./Age, yr/ Sex</th>
<th>Lesion Size, mm</th>
<th>Distance Between Lesion and Pleura, mm</th>
<th>Distance Between Lesion and Mark, mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/44/F 15</td>
<td>17</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>2/42/M 7</td>
<td>30</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>3/54/F 5</td>
<td>5</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>4/83/F 6</td>
<td>10</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>5/72/F 12</td>
<td>15</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>6/58/M 7</td>
<td>22</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>7/66/M 13</td>
<td>20</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>8/52/F 6</td>
<td>18</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>9/44/M 8</td>
<td>10</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>10/57/M 15</td>
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<td>15</td>
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<tr>
<td>11/56/F 10</td>
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<td>0</td>
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</tr>
<tr>
<td>13/50/F 14</td>
<td>18</td>
<td>15</td>
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<td>14/63/F 9</td>
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</tr>
<tr>
<td>17/63/F 8</td>
<td>15</td>
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</tr>
</tbody>
</table>

*F = female; M = male.
Sixteen patients underwent this procedure on the day before surgery, and the remaining patient underwent the procedure 3 days before surgery. The area of injected dye was shown as a hazy focal lesion, about 10 mm in diameter, just beneath the pleura on subsequent HRCT scans, and was clearly visible as a patchy dark blue area about 20 mm in diameter on the visceral pleura during surgery in all cases. The mean distance between the lesion and the stained area was 20 mm on CT scan (range, 0 to 30 mm). The mean time between the induction of anesthesia and the end of subsequent CT scan examination was about 35 min (range, 25 to 45 min). The mean CT fluoroscopic monitoring time was 60 s (range, 30 to 120 s). The scatter exposure rates were 28.8 and 35.6 µGy/min at 1 m from the center of the gantry of the CT scanner.

All patients subsequently underwent lung resection, guided by dye staining on the visceral pleura. Eleven lesions were barely palpable as a slight solid mass during surgery, but the remaining 6 lesions could not be detected. Five wedge resections and six segmentectomies were performed in 11 patients with palpable cases. Of six patients with impalpable

**Figure 1.** A 50-year-old woman with a small nodule identified by medical check-up. **Top, left, a:** HRCT scan shows a hazy small nodule (arrow) adjacent to the pulmonary vein in the right upper lobe. **Top, right, b:** image obtained at the moment of dye injection under CT fluoroscopy. The metallic tip (arrow) surrounding the GGA caused by the injected dye is seen just under the pleura. The high metallic attenuation in the right main bronchus (arrowhead) is a bronchoscope. **Bottom, left, c:** HRCT scan after the procedure shows the relationship between the hazy focal region of dye adjacent to the pleura and the nodule. **Bottom, right, d:** photograph of the thoracostomy shows a patchy dark blue area on the visceral pleura. The final pathologic diagnosis was BAC.
cases, segmentectomy was performed in five with negative margins. The remaining patient with an impalpable case underwent lobectomy of the right upper lobe because of an uncertain border of the lesion on the preoperative CT scan.

Pathologic examinations revealed the 17 lesions to be primary pulmonary adenocarcinoma in 15 patients and atypical adenomatous hyperplasia in 2 patients. The margins of the specimens were all negative. The preoperative staining procedure did not hamper the pathologic examination. Of 15 patients with primary pulmonary adenocarcinoma, 10 revealed localized BAC without invasive components on permanent sections. Since it was considered that the prognosis after the resection of stage I BAC was quite good, no additional treatment was performed. The remaining five adenocarcinomas were diagnosed as localized BAC with vascular invasion or proliferative active fibroblasts on permanent sections. As these patients may have some risk of recurrence, they have been closely observed, with informed consent, to date.

**Discussion**

It has become possible to detect small peripheral lung nodules by CT scan examination. Some of these lesions are shown as localized areas of GGA on HRCT scan. If the GGA is pathologically BAC and is completely resected, the prognosis is quite good, but small lesions appearing as GGAs include not only lung carcinoma but also benign lesions such as focal pneumonia or adenomatous hyperplasia. It is difficult to differentiate these lesions even on HRCT scans. Furthermore, because these lesions are present at the periphery and attenuation is faint on chest CT scans, conventional biopsy techniques such as percutaneous needle aspiration or transbronchial biopsy are not effective.

Video-assisted thoracic surgery has been accepted as a minimally invasive procedure with which to diagnose and/or treat such peripheral small lesions. However, since such lesions appearing as GGAs are not palpable and are invisible at surgery, intraoperative localization often is difficult. To reveal the location of the lesion at surgery, the following several marking techniques have been attempted: hook-wire placement, methylene blue injection, metallic coil injection, and colored collagen injection. Since these procedures are percutaneous approaches, they carry a risk of pneumothorax, which occurred maximally in 50% of the cases. Additionally, fatal air embolisms and latent tumor implantation along the needle tract were reported. With transthoracic hook-wire injection, wire dislodgement occurred in 4 to 20% of cases, and failure of the intraoperative identification occurred in 0 to 5% of cases. As marking materials, contrast media such as barium sulfate also have been used. Okumura et al emphasized the superiority of bronchoscopic barium marking, but in half of their cases the injected barium was invisible at surgery and fluoroscopic imaging was required to detect the marker.

We have made a preliminary report on bronchoscopic dye injection for the localization of small pulmonary nodules during thoracoscopic surgery.

![Figure 2. A 52-year-old woman who had a history of breast cancer. Left, a: HRCT scan shows a nodule 6 mm in size that appeared as a GGA in the left upper division. Right, b: image obtained at the moment of dye injection under CT fluoroscopy. Ground glass opacity of the dye injected from the catheter tip was seen between the pleura and the nodule.](image)
With these additional 17 cases, we can confirm the safety and reliability of this technique.

Since we used the transbronchial approach with the use of a flexible catheter, complications such as pneumothorax, bleeding, or intravascular injection of dye did not occur in this series. While no complications occurred during this period, CT fluoroscopic monitoring and subsequent CT scanning would make possible the early detection of pneumothorax and hemorrhage. For the percutaneous approach, lesions behind the scapula and near the vertebra are often difficult to be applied. However, this technique can be applied to any lesion site except, for example, a daughter branch area. Indigo carmine dye is commonly used in GI endoscopic examinations and does not have any harmful effects on the mucosa. It was possible to inject the dye just beneath the surface of the visceral pleura, which was confirmed at surgery in all 17 cases. Although Vandoni et al.\textsuperscript{13} reported that methylene blue injected transbronchially rapidly disappeared, a clear, dyed spot was observed even 3 days after the injection of the indigo carmine dye in our series. The dye remained on the visceral pleural surface without being vulnerable to respiratory movement. We supposed that this was due to it having been injected just on the visceral pleura, not near the lesion. Although it is difficult to estimate how long the dye would remain on the pleura, the staining is certainly not permanent, and this procedure could be repeated. In contrast, barium sulfate remains permanently in the lung even if incorrectly positioned.

The position of the catheter tip and the spread area of dye could be monitored by CT fluoroscopy in real time. The bronchoscope caused a substantial artifact but did not interfere with the identification of the catheter tip or the pulmonary nodule, because the nodules were peripheral and the artifact induced by the bronchoscope did not affect the periphery. The subsequent HRCT scan obtained just after the procedure revealed both the localization of the injected dye as a hazy lesion, and the relationship between the dye and the pulmonary lesion. This information was very useful for preoperative planning. Some limitations of previous dye methods have been reported. The failure of intraoperative identification occurred because of the wide spreading and the color of the dye, which was often indistinguishable from that of the anthracotic pleura. Okumura et al.\textsuperscript{17} reported that barium sulfate instilled in the central side of a nodule was clearly monitored by intraoperative fluoroscopy. But in our series, all dye markings could be confirmed as dark blue patchy lesions measuring about 2 cm in diameter at surgery, and wedge resection or segmentectomy was safely performed guided by the dye marking without fluoroscopic guidance.

The standard of care for a patient with stage I lung cancer is a lobectomy. However, in some surgical trials,\textsuperscript{24–26} limited resections such as segmentectomy or thoracoscopic limited resection have the same curability as the standard lobectomy had for patients with small BAC. Our marking method assists surgeons in doing such limited surgery for GGA that is thought to be a small BAC.

Our technique requires an experienced interventional bronchoscopist and CT fluoroscopy. Daly and Templeton\textsuperscript{27} investigated the skin dose of thoracoabdominal interventional procedures with CT fluoroscopy and found maximum skin doses ranging from 0.8 to 41 cGy. To adjust their data to our dose factors and fluoroscopic time, the skin dose levels in our series were approximately 3 to 12 cGy. The scatter exposure of the physician standing approximately 1 m distant from the CT scanning plane was approximately 30 μGy/min. This dose was less than those from other reports of interventional procedures using single-plane CT fluoroscopy,\textsuperscript{28,29} and the radiation exposure might be further reduced by a lower current and a shortening of the fluoroscopic time using a quick-check technique\textsuperscript{20} (ie, sparing use of fluoroscopy after catheter insertion). To reveal the exposure dose during CT fluoroscopy more precisely, a larger number of cases will need to be studied.

In conclusion, our tattooing technique using a bronchoscope, thin metallic tip catheter, indigo carmine dye, and CT fluoroscopy is safe and reliable for preoperative lesion marking. We think this technique is superior to previous marking techniques because of fewer complications, the use of visible and temporary material, and the preservation of the interval between marking and surgery.

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