Usefulness and complications of computed tomography-guided lipiodol marking for fluoroscopy-assisted thoracoscopic resection of small pulmonary nodules: Experience with 174 nodules

Ken-ichi Watanabe, MD,[a] Hiroaki Nomori, MD, PhD,[b] Takashi Ohtsuka, MD, PhD,[a] Masahiro Kaji, MD, PhD,[a] Tsuguo Naruke, MD, PhD,[a] and Keiichi Suemasu, MD, PhD[a]

Objective: Several techniques have been reported for the localization of small pulmonary nodules in thoracoscopic resection. In the present study we examined the usefulness and complications of computed tomography-guided lipiodol marking for thoracoscopic resection in our experience of 174 nodules.

Methods: Computed tomography-guided lipiodol marking was performed on 174 nodules less than 30 mm in size. Of these nodules, 45 showed ground-glass opacity images and 129 showed solid images on computed tomography. The mean size of the nodules was 10 ± 6 mm (range, 2-30 mm), and their mean depth from the pleural surface was 10 ± 7 mm (range, 0-30 mm). One to 7 days before thoracoscopy, all of the nodules were marked with 0.4 to 0.5 mL of lipiodol by using computed tomography. The marked nodules were grasped with a ring-shaped forceps during fluoroscopy and resected by means of thoracoscopy.

Results: All the nodules could be marked and localized by means of fluoroscopy as a clear spot during thoracoscopic surgery. Complications of the marking were chest pain requiring analgesia in 16 (11%) patients, hemosputum in 11 (6%) patients, pneumothorax in 30 (17%) patients, and hemopneumothorax in 1 (0.6%) patient. Eleven (6%) patients with pneumothorax required drainage, and the patient with hemopneumothorax required an emergency operation. No other complications were observed.

Conclusion: Lipiodol marking is a useful, safe, and inexpensive procedure for localizing ground-glass opacity lesions, small pulmonary nodules, or both for thoracoscopic resection.

From the Department of Thoracic Surgery, Saiseikai Central Hospital Tokyo,[a] Tokyo, Japan, and the Graduate School of Medicine, Kumamoto University,[b] Kumamoto, Japan.

Received for publication Feb 22, 2006; revisions received April 2, 2006; accepted for publication April 20, 2006.

Address for reprints: Hiroaki Nomori, MD, Department of Thoracic Surgery, Graduate School of Medicine, Kumamoto University, 1-1-1 Honjo, Kumamoto 860-8556, Japan (E-mail address: hnomori@qk9.so-net.ne.jp).

J Thorac Cardiovasc Surg 2006;132:320-4

0022-5223/$32.00

doi:10.1016/j.jtcvs.2006.04.012

Recently, small pulmonary nodules have been frequently detected with high-resolution computed tomography (CT).[1,2] Performing a percutaneous or transbronchial biopsy for small pulmonary nodules is often difficult, and hence thoracoscopic surgical techniques have been used in diagnostic excisional biopsies, as well as in therapeutic resection. However, a major factor that limits the success of thoracoscopic resection in the case of small or deeply situated pulmonary nodules is the difficulty in localizing the target nodule because of the lack of digital palpation. Furthermore, a bronchioloalveolar carcinoma with a ground-glass opacity (GGO) finding on CT cannot be palpated or visualized frequently, even in the case of lesions that are located just beneath the visceral pleura. Therefore several techniques have been reported for localization of such small nodules or GGO lesions.[3-18] However, these techniques can result in complications, such as pneumothorax, hemorrhage, and air embolism. Since 1999, we have used CT-guided

Abbreviations and Acronyms
CT = computed tomography
GGO = ground-glass opacity
TTNA = transthoracic needle aspiration

lipiodol marking for the thoracoscopic resection of such lesions. The purpose of our study is to examine the usefulness and safety of this procedure.

Materials and Methods

Eligibility

The CT-guided lipiodol marking was approved by the ethics committee of Saiseikai Central Hospital in January 1999. Written informed consent was obtained from all patients after they discussed the risks and benefits of the procedure with the surgeons. The nodules that were thought to be difficult to localize during thoracoscopy, such as GGO lesions, nodules situated at a considerable depth from the pleural surface, and nodules smaller than 1 cm, were candidates for this procedure. The following nodules were excluded: (1) nodules larger than 30 mm in size; (2) nodules located within the inner two third of the lung; and (3) solid nodules that were larger than 10 mm in size and located within 10 mm from the pleural surface.

Patients

Between January 1999 and June 2005, CT-guided lipiodol marking was performed on 174 pulmonary nodules in 150 patients. The mean age of the patients was 62 ± 11 years (range, 35-84 years). Table 1 shows the characteristics of the nodules. The mean size of the nodules was 10 ± 6 mm (range, 2-30 mm). Their mean distance from the pleural surface was 10 ± 7 mm (range, 0-30 mm). There were 45 GGO lesions and 129 solid lesions. All the nodules were detected with chest CT; however, they could not be detected clearly with chest roentgenograms.

Marking Technique

The procedure used for marking was as follows. After 0.5 mg of atropine and 15 mg of pentazocine was injected, the patients were placed on the CT table in a suitable position (supine or prone). A scaled paper with metal wires was placed firmly on the patient, and the CT scan was performed. The shortest distance from the nodule to the thoracic wall was selected as the injection site (Figure 1, *A*). The site for marker injection was marked on the skin, and the angle and depth of the needle required to reach the nodule were determined. After local anesthesia was administered to the thoracic wall, a 22- or 23-gauge needle was introduced from the point marked on the skin to the nodule, in keeping with the angle and depth measured. The syringe was withdrawn to confirm that no blood had flowed backward, and 0.4 to 0.5 mL of lipiodol (Lipiodol Ultrafluid; Laboratoire Guerbet, Aulnay-Sous-Bois, France), which is generally used as a contrast medium for lymphatic vessels, was then injected in a single shot. The presence of the injected materials was confirmed by means of CT after the marking (Figure 1, *B*). Thoracoscopic surgery was performed 1 to 7 days (mean, 1.7 ± 1.1 days) after marking.

TABLE 1. Characteristics of the nodules

Mean size, mm (range)	10 ± 6 (2-30)
Mean distance from the pleura, mm (range)	10 ± 7 (0-30)
Location	
Right upper lobe	42
Right middle lobe	21
Right lower lobe	37
Left upper lobe	34
Left lower lobe	40
CT findings	
Ground-glass opacity	45
Solid	129

CT, Computed tomography.

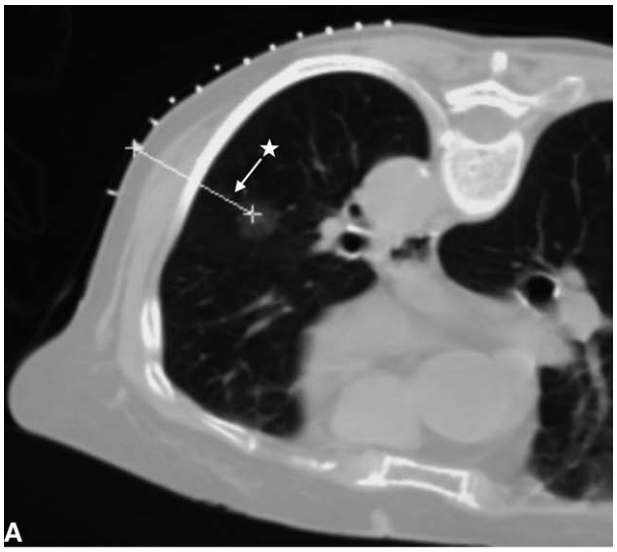
Thoracoscopic Resection Technique

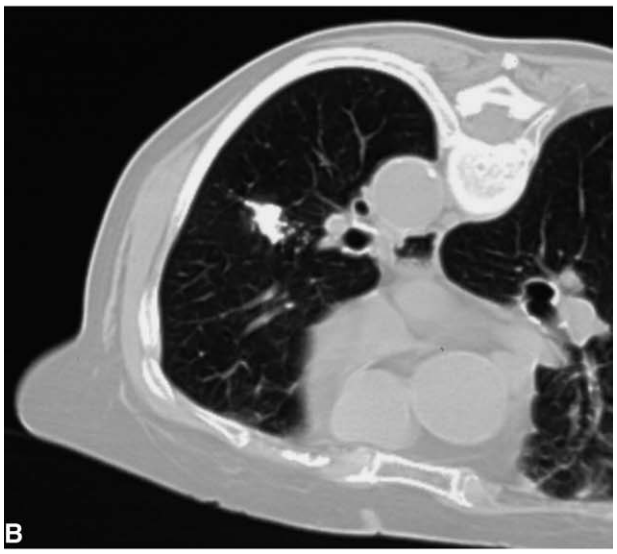
Thoracoscopy was performed during one-lung anesthesia by using a double-lumen tube. A C-arm–shaped fluoroscopic unit was used to detect the radiopaque nodules, and the radiopaque nodule was grasped with a ring-shaped forceps during fluoroscopy in multiple projections (Figure 1, *C*). The forceps was then moved in several directions to confirm that the nodule was grasped within a ring of the forceps. The grasped nodule was resected with an endostapler. The resected specimens were removed with a surgical bag. Successive resection of the nodules was confirmed by viewing the radiopaque nodule within the resected specimen during fluoroscopy. The nodules were histologically diagnosed by means of routine intraoperative pathologic examination, with the exception of the GGO lesions that were less than 10 mm in size; these were histologically diagnosed by a permanent section.

Results

All the nodules could be marked with lipiodol on the CT images. Even when the lipiodol could not mark within the nodules, it marked within 10 mm from the nodules, which caused no difficulty in their localization. All the nodules were successfully localized and resected during thoracoscopy without conversion to open thoracotomy. Even a nodule that was marked 7 days before the thoracoscopy could be detected during fluoroscopy as a clear spot. Of the 174 nodules, 107 (61%) were diagnosed as malignant, and 67 (39%) were diagnosed as benign (Table 2). For the 81 patients with primary lung cancers, 48 were followed with thoracoscopic lobectomy, and 10 were followed with thoracoscopic segmentectomy. The other 23 patients did not undergo the additional resection because of bronchioloalveolar cell carcinoma of the intraoperative frozen section, poor risk of the patients, or both. All of the surgical margins in patients treated with thoracoscopic wedge resection showed no malignancy.

Table 3 shows the complications accompanying lipiodol marking. Sixteen (11%) patients had chest pain that required analgesia. Eleven (6%) patients had a little hemosputum. Thirty (17%) patients had pneumothorax, and 11 (6%) of these patients required drainage. One (0.6%) patient had





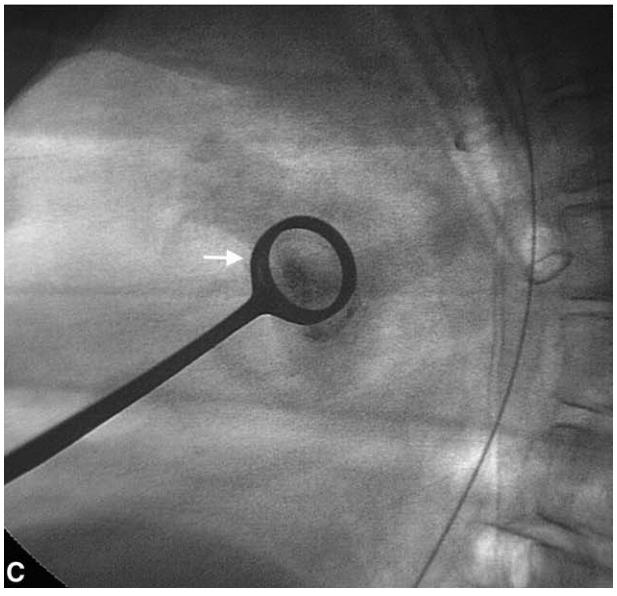


TABLE 2. Pathologic diagnosis of the nodules

Malignant (n = 107)	
Primary lung cancer	81
Metastatic lung cancer	26
Benign (n = 67)	
Tuberculosis	36
Old inflammation	11
Pulmonary lymphoid tissue	9
Atypical adenomatous hyperplasia	8
Hamartoma	3

hemopneumothorax caused by peeling off of the pleural adhesion, including blood vessels.

One patient had bilateral pulmonary nodules, both of which were marked by lipiodol; the patient was given a diagnosis of metastatic colon cancer by means of an ipsilateral thoracoscopy. Therefore the marked contralateral nodule was followed by CT, which had been marked by lipiodol for 3 months.

Discussion

Several methods have been reported for the localization of small pulmonary nodules. These include the hook-wire technique,[3-7] endoscopic ultrasonography,[8,9] barium marking through bronchoscopy,[10,11] and percutaneous injections of dyes,[12,13] colored collagen,[14] lipiodol,[15,16] agar,[17] and barium.[18] The original dye method, because of rapid diffusion around the lung tissue after injection, has the following drawbacks: (1) the marking must be performed within 3 hours before the thoracoscopy to enable dye detection, and therefore both CT and the operating room must be used simultaneously, and (2) the injection site appears blurred because of the diffusion. With the agar marking procedure, it is difficult to localize a deeply situated nodule because the palpation of the marked nodules is requisite. The ultrasound technique requires complete collapse of the lung, which is often impossible in patients with emphysema, resulting in a failure rate of 40% in localizing the nodules.[9] The hook-wire technique has been recently reported to cause massive air embolism,[19-23] which led to its prohibition in Japan. Barium marking with a CT-guided bronchoscopy is complicated because it requires simultaneous use of bronchoscopy and CT, and marking one nodule with this procedure

Figure 1. A, Computed tomographic *(CT)* scan showing a nodule with ground-glass opacity *(GGO)* in the left lower lobe. ****The shortest distance from the nodule to the thoracic wall was selected as the injection site. The several lines on the chest wall reveal the metal wires of scaled-paper.* **(B) CT showing the tumor marked with lipiodol. C, Intraoperative fluoroscopic imaging showing the radiopaque nodule grasped within a ring-shaped forceps. The nodule is indicated with an *arrow*.

Table 3. Complications of lipiodol marking

	No. of patients (%)
Chest pain requiring analgesia	16 (11)
Hemosputum	11 (6)
Pneumothorax	30 (17)
No treatment	19 (11)
Drainage	11 (6)
Hemopneumothorax	1 (0.6)

requires approximately 30 minutes (range, 15-60 minutes).[11] In addition, barium itself can be seen as a lesion in hematoxylin and eosin–stained sections and also can cause an inflammatory change of the lung tissue, which might make a histologic diagnosis difficult.

We previously marked a nodule with lipiodol and the pleural surface with colored collagen; this enabled a comparatively easier localization of the nodules than when only lipiodol was used.[16] However, 1 mL of collagen costs approximately $80.00. Therefore since March 2002, we started using only lipiodol to mark pulmonary nodules. Thus without using colored collagen, the nodules marked with lipiodol could be localized during fluoroscopy without great difficulty, resulting in a success rate of 100% for thoracoscopic biopsy. The marking procedure with lipiodol has the following advantages: (1) overresection of the normal lung tissue around the nodules was prevented because lipiodol marked the nodules as clear spots that were less than 1 cm in size during fluoroscopy; (2) the lipiodol remained for a long time, up to 3 months after the marking, which solves the problem of requiring both CT and the operating room simultaneously; (3) although the barium marking procedure affects pathologic findings caused by the inflammatory response and barium itself, lipiodol did not affect the pathologic findings; and (4) even in the case of deeply situated nodules (ie, up to 30 mm from the pleural surface in the present study), the lipiodol marking could easily localize the nodules as a clear spot because it diffused only to a small extent.

Transthoracic needle aspiration (TTNA) is also effective in the diagnosis of pulmonary nodules.[24-26] Although TTNA has been reported to have a false-negative rate of 3% to 11%,[24] Layfield and colleagues[25] reported that its diagnostic accuracy decreased to 60% for lesions smaller than 10 mm. Kashiwabara and associates[26] reported that the positive diagnostic rate for nonmalignant lesions by using TTNA was only 56%. All the nodules in the present study were GGO lesions or small nodules deeply situated within the lung, which were not only difficult to diagnose with TTNA but also difficult to locate by means of thoracoscopic inspection without marking. We therefore believe that GGO lesions or small nodules that are deeply situated should be diagnosed by means of thoracoscopic biopsy with preoperative marking.

Although the complications of lipiodol marking included temporary pain, a little hemosputum, pneumothorax, and hemopneumothorax, all of them arose because of the insertion of the needle into the lung and not because of the lipiodol itself. Although we did not encounter air embolism during the lipiodol marking, the frequency of massive air embolism during percutaneous needle insertion into the lung has been reported to be 0.02% to 0.07%.[21] There have been reports of 6 patients who experienced a massive air embolism during percutaneous marking procedures.[19-23] In 5 of the 6 patients, it was caused by the hook-wire technique and in 1 patient by the needle-marker procedure. The massive air embolisms could have occurred because of simultaneous injury of the bronchiole and the adjacent pulmonary vein.[23] Because all 6 patients with massive air embolism had nodules in the lower lobe, we believe that the lung tissue of the lower lobe could be injured more easily by the hook wire or needle marker than that of upper lobe because the former moves more with respiration during insertion of these apparatuses than the latter. Therefore we usually inject lipiodol immediately after needle insertion without confirming the location of the needle tip by means of CT scanning, enabling the time of placing the needle in the lung tissue to be less than 10 seconds, which could decrease the lung damage caused by the needle.

Lipiodol itself poses a potential risk of embolism because it is water insoluble. We therefore take the following precautions: (1) before injection of lipiodol, the syringe is withdrawn to confirm that blood has not flowed backward, and (2) a minimum amount of lipiodol, up to 0.5 mL, is injected.

Although the lipiodol marking procedure showed some complications caused by the needle insertion, they were not of a serious nature. Because it is a simple, safe, and inexpensive method for localizing GGO lesions, small and deeply situated pulmonary nodules, or both, we believe that lipiodol marking is one of the gold standard procedures for localization of these nodules during thoracoscopy.

References

1. Kaneko M, Eguchi K, Ohmatsu H, et al. Peripheral lung cancer: screening and detection with low-dose spiral CT versus radiography. *Radiology.* 1996;201:798-802.
2. Swensen SJ, Jett JR, Hartman TE, et al. CT screening for lung cancer: five-year prospective experience. *Radiology.* 2005;235:259-65.
3. Dendo S, Kanazawa S, Ando A, et al. Preoperative localization of small pulmonary lesions with a short hook wire and suture system: experience with 168 procedures. *Radiology.* 2002;225:511-8.
4. Wicky S, Dusmet M, Doenz F, et al. Computed tomography-guided localization of small lung nodules before video-assisted resection: experience with an efficient hook-wire system. *J Thorac Cardiovasc Surg.* 2002;124:401-3.
5. Mack MJ, Gordon MJ, Postma TW, et al. Percutaneous localization of pulmonary nodules for thoracoscopic lung resection. *Ann Thorac Surg.* 1992;53:1123-4.

6. Plunkett MB, Peterson MS, Landreneau RJ, Ferson PF, Posner MC. Peripheral pulmonary nodules: preoperative percutaneous needle localization with CT guidance. *Radiology.* 1992;185:274-6.
7. Shah RM, Spirn PW, Salazar AM, et al. Localization of peripheral pulmonary nodules for thoracoscopic excision. *Am Roentgenol Surg.* 1992;161:1279-83.
8. Sortini D, Feo CV, Carcoforo P, et al. Thoracoscopic localization techniques for patients with solitary pulmonary nodule and history of malignancy. *Ann Thorac Surg.* 2005;79:258-62.
9. Shennib H, Bret P. Intraoperative transthoracic ultrasonographic localization of occult lung lesions. *Ann Thorac Surg.* 1993;55:67-9.
10. Asano F, Shindoh J, Shigemitsu K, et al. Ultrathin bronchoscopic barium marking with virtual bronchoscopic navigation for fluoroscopy-assisted thoracoscopic surgery. *Chest.* 2004;126:1687-93.
11. Okamura T, Kondo H, Suzuki K, et al. Fluoroscopy-assisted thoracoscopic surgery after computed tomography-guided bronchoscopic barium marking. *Ann Thorac Surg.* 2001;71:439-42.
12. Endo M, Kotani Y, Satouchi M, et al. CT fluoroscopy-guided bronchoscopic dye marking for resection of small peripheral pulmonary nodules. *Chest.* 2004;125:1747-52.
13. Kerrigan DC, Spence PA, Crittenden MD, Tripp MD. Methylene blue guidance for simplified resection of a lung lesion. *Ann Thorac Surg.* 1992;53:163-4.
14. Nomori H, Horio H. Colored collagen is a long-lasting point marker for small pulmonary nodules in thoracoscopic operations. *Ann Thorac Surg.* 1996;61:1070-3.
15. Moon SW, Wang YP, Jo KH, et al. Fluoroscopy-aided thoracoscopic resection of pulmonary nodule localized with contrast media. *Ann Thorac Surg.* 1999;68:1815-20.
16. Nomori H, Horio H, Naruke T, et al. Fluoroscopy-assisted thoracoscopic resection of lung nodules marked with lipiodol. *Ann Thorac Surg.* 2002;74:170-3.
17. Tsuchida M, Yamato Y, Aoki T, et al. CT-guided agar marking for localization of nonpalpable peripheral pulmonary lesions. *Chest.* 1999; 116:139-43.
18. Iwasaki Y, Nagata K, Yuba T, et al. Fluoroscopy-guided barium marking for localizing small pulmonary lesions before video-assisted thoracic surgery. *Respir Med.* 2005;99:285-9.
19. Kamiyoshihara M, Sakata K, Ishikawa S, et al. Cerebral arterial air embolism following CT-guided lung needle marking. Report of a case. *J Cardiovasc Surg (Torino).* 2001;42:699-700.
20. Horan TA, Pinheiro PM, Araujo LM, et al. Massive gas embolism during pulmonary nodule hook wire localization. *Ann Thorac Surg.* 2002;73:1647-9.
21. Sakiyama S, Kondo K, Matsuoka H, et al. Fatal air embolism during computed tomography-guided pulmonary marking with a hook-type marker. *J Thorac Cardiovasc Surg.* 2003;126:1207-9.
22. Sato K, Miyauchi K, Shikata F, et al. Arterial air embolism during percutaneous pulmonary marking under computed tomography guidance. *Jpn J Thorac Cardiovasc Surg.* 2005;53:404-6.
23. Ohi S, Itoh Y, Neyatani H, et al. [Air embolism following computed tomography-guided lung needle marking; report of a case]. *Kyobu Geka.* 2004;57:421-3.
24. Sisler GE. Malignant tumors of the lung: role of video-assisted thoracic surgery. *Chest Surg Clin North Am.* 1993;3:307-17.
25. Layfield LJ, Coogan A, Johnston WW, et al. Transthoracic fine needle aspiration biopsy: sensitivity in relation to guidance technique and lesion size and location. *Acta Cytol.* 1996;40:687-90.
26. Kashiwabara K, Nakamura H, Fukai Y, et al. Availability of diagnosis by percutaneous needle aspiration cytology of the lung in cases who showed a peripheral solitary tumorous shadow on chest Xp and diagnostic rate of transbroncial approach. *Jpn J Thorac Dis.* 1993;31: 1426-31.

GTS