CT-Guided Agar Marking for Localization of Nonpalpable Peripheral Pulmonary Lesions*

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Background: Small pulmonary lesions with ground-glass opacity (GGO) are increasingly detected by CT; however, intraoperative localization of such lesions is difficult because these lesions are often invisible and nonpalpable.

Study objectives: To localize and resect nonpalpable and invisible small pulmonary lesions, a new marking technique that we call “agar marking” was developed.

Methods and patients: Powdered agar was dissolved in distilled water at a concentration of 5% and kept at > 50°C to maintain its liquid form. Agar was injected through an 18-gauge needle and placed near the target lesion with CT. After animal experiments, agar marking was applied to the nine patients who had lesions < 20 mm in diameter and lesions with GGO. The mean diameter of these lesions was 11 mm, with a mean depth of 19 mm from the pleural surface on CT.

Results: Agar could be detected as a hard nodule by manual palpation, and the lesion was resected during thoracotomy in all cases. There were no complications associated with the agar injection, aside from one case of slight pneumothorax.

Conclusions: Agar marking may represent a feasible alternative technique for localizing nonpalpable occult lesions located away from the pleural surface. *CHEST 1999; 116:139–143*

Key words: agar marking; CT; ground-glass opacity; occult lesion; peripheral pulmonary lesion

Abbreviation: GGO = ground-glass opacity

With recent advances in diagnostic radiology and lung cancer screening programs using CT, an increasing number of small lesions have been detected. Some of them are cloudy nodules with ground-glass opacity (GGO).1–3 GGO is defined as a hazy increased attenuation of the lung with preservation of the bronchial and vascular margin.3 A differential diagnosis for GGO includes various types of both benign and malignant diseases. Because a GGO lesion is usually fluoroscopically invisible, cytologic conformation by a fluoroscopically guided percutaneous or transbronchial approach is difficult. One alternative approach for such lesions is open or thoracoscopic lung biopsy. However, intraoperative localization of such lesions is difficult because they are nonpalpable and invisible unless the lesion is located just below the pleural surface. Therefore, special techniques to assist in localizing occult lesions are required. It has been reported4–13 that several novel techniques are able to identify the pulmonary nodules for thoracoscopic resection. As an alternative technique for localizing peripheral nonpalpable lesions with a small thoracotomy, we report the use of preoperative agar marking that converts the nonpalpable lesion to a palpable one by injecting agar near the lesion.

**Materials and Methods**

**Agar Preparation**

Purified agar, which is usually used as medium for cell culture or electrophoresis, was dissolved in distilled water and applied as a palpable marker. According to information from the manufacturer, when agar is dissolved at a concentration of 1.5%, its melting point is 80 to 95°C, and the temperature of the liquid gel is 32 to 37°C. To increase the gel intensity, agar was dissolved at a concentration of 5% in distilled water. In brief, powdered agar (Cosmo-Bio; Tokyo, Japan) was placed in a bottle with sterile distilled water and microwaved until the powder was completely...
dissolved. Liquid-form agar was kept warm and transferred into a tube (50-mL Conical Tubes; Becton Dickinson Labware; Lincoln Park, NJ) after passage through a 0.45-μm membrane (MILLEX-HA; Millipore Corp; Bedford, MA). The tube was placed in hot water (>50°C) so that the agar could maintain its liquid form until injection.

**Experimental Study**

Before clinical application, we performed an animal study (unpublished study; September 10 to September 15, 1997) and an ex vivo study (unpublished study; September 20, 1997) using the human lung. Five beagle dogs weighing 10 to 15 kg were anesthetized, agar was injected percutaneously through an 18-gauge needle under roentgenographic fluoroscopy, and localization of the agar was tested. All animals received humane care in accordance with the guidelines for animal experimentation of Niigata University. In addition, agar was injected into three resected human lungs, and manual palpation and microscopic evaluation was performed.

**Patients**

Preoperative agar marking was performed in nine patients whose lesions were thought to be difficult to identify. All patients underwent CT for lung cancer screening. The indications for agar marking were as follows: GGO lesions <20 mm in diameter and lesions located deeper than 10 mm from the pleural surface.

**Agar Injection**

All of the patients agreed to undergo this procedure and gave their informed consent. All procedures were approved by the local institutional committee. Each patient was positioned on the CT table in a suitable position. Figure 1 demonstrates the CT-guided agar injection. The GGO lesion is 8 mm in size and is located at a depth of 20 mm from the pleural surface (Fig 1 Top, A). With CT guidance, an 18-gauge needle was placed percutaneously through the chest wall into the lung parenchyma (Fig 1 Center, B). The needle tip was placed so that the agar was located a little bit deeper than the target lesion. After confirming that the needle was placed in the appropriate position with no blood backflow, warm agar was mixed with contrast media (1-to-10 dilution), and 1 mL of the mixture was injected before the agar became a hard gel (Fig 1, Bottom, C). The presence of the agar nodule was confirmed by consecutive CT scan, and the patient was transferred to the operating room.

**Intraoperative Technique**

The patients underwent surgery in the lateral position under general anesthesia with single-lung ventilation using a double-lumen tube. A 15-cm skin incision was made, and mobilization of the latissimus dorsi and serratus anterior was performed. Once thoracotomy through the auscultatory triangle was undertaken, the lung was collapsed, and a hard nodule could easily be detected by manual palpation. Because the marker was placed deeper than the target lesion, the wedge resection using a linear cutter (Proximate; Ethicon Endo-Surgery; Cincinnati, OH) was

**Figure 1.** CT-guided agar injection. **Top, A:** the tumor is 8 mm in diameter and is located at a depth of 20 mm from the pleural surface (indicated by arrow). **Center, B:** an 18-gauge needle is inserted near the tumor under CT image. **Bottom, C:** agar-containing contrast media is injected.
oriented to the marker in seven cases. To ensure a sufficient surgical margin, a stapler was placed at least 2 cm away from the lesion. In two cases, segmentectomy was performed because the lesions were located more centrally. The resected specimen was sent to the pathology laboratory, and the diagnosis was confirmed immediately (Fig 2).

**Results**

In the animal experiment, 1 mL of agar injected into the beagle lung parenchyma hardened within 1 min and could be detected as a hard nodule in all cases. In addition, histologic examination using the resected human lung indicated that agar might not interrupt pathologic examination for the histologic diagnosis. Agar was also tested for bacterial culture, and it was confirmed that there was no contamination.

As of August 1997, agar has been used in patients with GGO lesions that are <20 mm in size and located deeper than 10 mm below the pleural surface. The characteristics of nine patients are summarized in Table 1. The maximum diameter of the tumor ranged from 8 to 17 mm on the CT scans. The distance from the pleural surface to the tumor ranged from 10 to 32 mm. All lesions had GGO density, and two of them had a small high-density area in the middle of the tumor. In all cases, agar was placed successfully near the target lesion but not within the lesion. The average time needed to complete the marking procedure was 1 h. In all cases, agar could be detected as a hard nodule, whereas cloudy lesions were nonpalpable. Occult lesions were resected by wedge resection in seven cases, and by segmentectomy in two cases in which the tumor was located too centrally to resect by wedge resection. The confirmed histology showed bronchioloalveolar adenocarcinoma without active fibrotic proliferation in eight cases and atypical adenomatous hyperplasia in one case. The histologic diagnosis using paraffin-embedded sections completely coincided with the intraoperative frozen-section diagnosis. To exclude the possibility of tumor dissemination associated with this technique, intraoperative pleural lavage was performed, and no tumor cells were identified.

The postoperative course was uneventful in all cases, and no complications were observed.

![Figure 2](http://publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21927/)
DISCUSSION

Recently, small peripheral pulmonary lesions with GGO have been increasingly detected by CT. Most of these lesions are fluoroscopically invisible, and preoperative histologic or cytologic diagnosis by a fluoroscopically guided approach is difficult. Although CT-guided percutaneous lung biopsy is one option for such lesions, the diagnosis may remain unclear in some cases. In addition, Koizumi et al\(^1\) reported that a cloudy nodule is often a well-differentiated adenocarcinoma. Therefore, surgeons are frequently consulted to resect such lesions for the purpose of diagnosis or treatment. It is reasonable to first resect the lesion by wedge resection for histologic diagnosis. However, unlike common pulmonary nodules, it is difficult to localize the lesion and determine the resectional line because these lesions are invisible and nonpalpable. In fact, we were unable to localize the lesions even with the aid of hook-wire marking in two early cases, which led us to develop the technique outlined here.

Several methods of localization have been reported\(^4–13\) for resecting small nodules under thoracoscopy. However, each technique has some limitations for deep and nonpalpable lesions. The preoperative injection of methylene blue\(^4,7,8\) does not indicate the depth of the lesions, and it might be difficult to determine the resectional line. Ultrasound techniques require the lesions to be somewhat hard, which is not common in GGO lesions. The hook-wire technique\(^8,9\) is also of limited use for deep lesions because the hook-wire sometimes dislodges from its initially inserted position. Nomori and Horio\(^11\) have reported the use of CT-guided bronchoscopic barium marking for resection of invisible lesions. It is not clear, however, that these two techniques would be useful for deep lesions. All of these techniques were developed based on either direct or fluoroscopically assisted visualization.

On the other hand, agar marking depends on "touch feeling" by a surgeon's hands and provides a palpable marker. Agar is a gelatin-like product made from certain seaweeds that is used for solidifying culture media and as a thickening agent for foods. Because the metabolism of agar within lung tissue has not been tested, it should be resected completely, as with other types of markers. Compared with other marking techniques, agar marking is especially useful for nonpalpable lesions located away from the pleural surface. The surgeon can palpate the agar marker placed near the lesions and determine with confidence how deep the resectional line should be. Even when the lesion is located in the central part of the lung near the hilum, making an anatomic resection such as a segmentectomy necessary, an agar marker provides a certain localization of the tumor and an appropriate resectional line. Agar is cheap (< $1 per case), and it can be injected easily because of its liquid form. Furthermore, agar is easily cut and does not interrupt a pathologic examination. The only change brought about by an agar injection is an enlargement of the alveolus of the injected site. The disadvantage of this technique, however, is the need for thoracotomy to palpate the marker. Because the marker contains contrast media, however, it is possible to resect the lesion under roentgenographic fluoroscopy without thoracotomy. As experience grows with this technique, it may be possible to complete the procedure under thoracoscopy alone for the next step.

No complications have been observed in association with agar injection, aside from one case of slight pneumothorax. In addition, no cancer dissemination has occurred, as confirmed by cytopathologic examination of pleural lavage fluid. Because intravessel injection with distal embolization of the agar is a possible serious complication associated with this technique, it is important to place the tip of the needle away from vessels and to make sure there is no blood backflow. Therefore, this procedure is not without risk, and a large series is needed to prove its safety. In the present study, we simultaneously required both the CT and the operating room to resect the agar marker as soon as possible. Because this agar marker remained in place for > 2 weeks in the animal studies, it is possible that this procedure can be performed some days prior to the operation.

In conclusion, agar marking is a simple and useful method for localizing and resecting occult pulmonary lesions with GGO. Agar marking may represent a feasible alternative technique for the localization of the following lesions: (1) lesions located some depth from the pleural surface; and (2) nonpalpable and invisible lesions with GGO.

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