Preoperative Pulmonary Nodule Localization: A Comparison of Methylene Blue and Hookwire Techniques

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OBJECTIVE. Small pulmonary nodules are often difficult to identify during thoracoscopic resection, and preoperative CT-guided localization performed using either hookwire placement or methylene blue injection can be helpful. The purpose of this study is to compare the localization success and complication rates of these two techniques.

MATERIALS AND METHODS. One hundred two consecutive patients who underwent a total of 109 localization procedures performed with CT fluoroscopic guidance were analyzed. The procedures included 52 hookwire insertions and 57 methylene blue injections. The localization success and complication rates associated with the two groups were compared.

RESULTS. All nodules in both groups were identified intraoperatively, except for those in two patients in the hookwire group who did not proceed to undergo same-day surgery, including one with a massive systemic air embolus that resulted in death. Hookwires were dislodged in seven of 52 cases (13%), but the surgeons were still able to locate the nodules through visualization of the parenchymal puncture sites. The total number of complications was higher in the hookwire insertion group than in the methylene blue injection group, but this trend was not statistically significant, with all types of complications occurring in 28 cases (54%) versus 26 cases (46%) ($p = 0.45$), major complications noted in four cases (8%) versus one case (2%) ($p = 0.19$), pneumothorax observed in 20 cases (38%) versus 14 cases (25%) ($p = 0.15$), and perilesional hemorrhage occurring in six cases (12%) versus two cases (4%) ($p = 0.15$), respectively.

CONCLUSION. The present study suggests that methylene blue injection and hookwire insertion are statistically equivalent for preoperative pulmonary nodule localization; however, seven of 52 hookwires dislodged, and trends toward more frequent and severe complications were noted in the hookwire insertion group.

Keywords: air embolism, CT-guided, hookwire, lung nodule localization, methylene blue

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More than 150,000 patients with pulmonary nodules are treated by physicians annually in the United States, and this number is likely to increase with the recent approval of lung cancer screening [1]. Although practice patterns vary depending on local expertise, transbronchial biopsy is often used for central masses, whereas percutaneous biopsy has a high rate of diagnosis when used for parenchymal nodules [2]. Diagnosis is possible with the use of one of these two methods, in most cases. However, in some cases, a pathologic diagnosis is not achieved despite multiple attempts at transbronchial biopsy, percutaneous biopsy, or both [3]. In these cases, thoracoscopic resection may be needed for definitive tissue characterization [3]. Thoracoscopic resection is also required for many small nodules for which pathologic diagnoses are already established. Small deeply situated parenchymal nodules can be particularly difficult to identify at thoracoscopy, and several researchers have found preoperative localization to be helpful [4]. In one study, the rate of visual identification of pulmonary nodules at thoracoscopy was low when nodules were less than 15 mm in diameter and were located more than 10 mm below the lung surface [5].

The difficulties associated with identifying small pulmonary nodules at thoracoscopy have led to the development of multiple different techniques designed to allow accurate intraoperative identification of these nodules, including percutaneous injection of methylene blue, radiotracer, colored collagens, barium, or ethiodized oil (Lipiodol, Guerbet); intraoperative ultrasound; and the insertion of metallic coils and hookwires

TABLE 1: Demographic and Clinical Characteristics of 102 Patients With Pulmonary Nodules Who Underwent 109 Localization Procedures

Characteristic	Hookwire Insertions (*n* = 52)	Methylene Blue Injections (*n* = 57)
Mean patient age (y)	60.3	62.6
Patient sex		
Male	16 (31)	25 (44)
Female	36 (69)	32 (56)
Mean nodule size (mm)	10.0	10.6
Mean distance of nodule from pleura (mm)	9.2	14.7
Final diagnosis		
Primary lung cancer	17 (34)[a]	23 (40)
Metastatic disease	20 (40)[a]	16 (28)

Note—Except where indicated otherwise, data are no. (%) of procedures. Seven patients had two nodules localized, with each localization procedure counted as a separate procedure.
[a]Two patients in the hookwire insertion group did not undergo surgery, and therefore final pathologic diagnoses were not available for those two patients.

[4, 6]. Each localization method has its own risks and benefits, but two of the more successful methods that do not require specialized equipment or expertise are percutaneous injection of methylene blue and hookwire placement. To our knowledge, these two techniques have not been directly compared in terms of safety and efficacy. The purpose of the present study is to compare the localization success and complication rates of preoperative CT-guided hookwire insertions and methylene blue injections.

Materials and Methods

Patient Population

This study was approved by the institutional review board at the University of Wisconsin–Madison and was HIPAA compliant. The requirement for informed consent was waived. This is a single-institution retrospective cohort study of 102 consecutive patients who underwent a total of 109 CT-guided localization procedures between October 2006 and August 2012. The 109 procedures included 52 hookwire insertions and 57 methylene blue injections. Seven patients had two nodules localized, with each localization procedure counted as a separate procedure. The demographic characteristics of the two groups were similar, with the exception that the pulmonary nodules in the patients who received methylene blue injections tended to be deeper below the lung surface (14.7 vs 9.2 mm; $p = 0.01$) (Table 1).

Procedures

All procedures were performed with the use of CT fluoroscopic guidance (Optima, GE Healthcare). Hookwire insertion was the localization method used at our institution until a patient had an air embolism develop, after which time methylene blue injection became the preferred localization method. The relative position of the localizing wire or methylene blue stain in relation to the underlying nodule was confirmed using limited unenhanced CT at the conclusion of the procedure and was discussed by the performing radiologist directly with the thoracic surgeon. All procedures were performed by one of seven radiologists with between 1 and 24 years of experience in performing CT-guided procedures.

Hookwire Localization

The most commonly used breast localization needles were 20-gauge needles (Kopans, Cook Medical; and Accura, Angiotech). The hookwires were positioned so that the wires traversed the pulmonary nodule and the tips were placed just deep to the nodule (i.e., the hook was wrapped around the nodule) (Figs. 1 and 2). Once the hookwire was in position, the excess was trimmed and the hookwire was fixed in position externally with an overlying sterile dressing and tape. The patients were then transferred to the preparation area for same-day surgery.

Methylene Blue Injection

Twenty- to 25-gauge spinal needles were used for the methylene blue injections. CT fluoroscopic guidance was used to place the needle into the superficial aspect of the pulmonary nodule. Methylene blue was injected as the needle was removed, with the majority of the stain injected into the subpleural parenchyma directly overlying the nodule (Figs. 3 and 4). Half a milliliter was the most commonly injected volume of methylene blue, but the

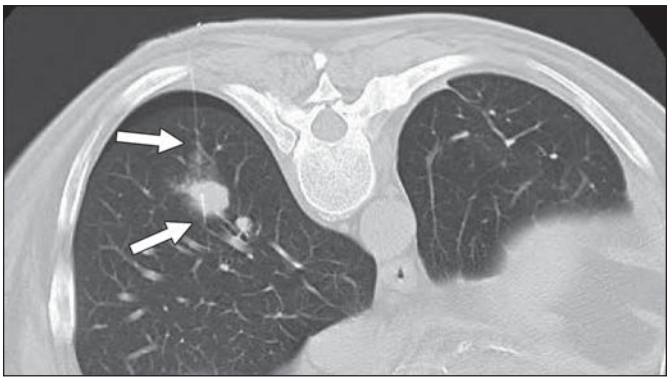

Fig. 1—56-year-old woman with pulmonary nodule who underwent hookwire insertion localization procedure performed with CT fluoroscopic guidance. CT image shows that hookwires were positioned such that hookwire (*arrows*) traversed pulmonary nodule and tip was placed just deep to nodule (i.e., hook was wrapped around nodule).

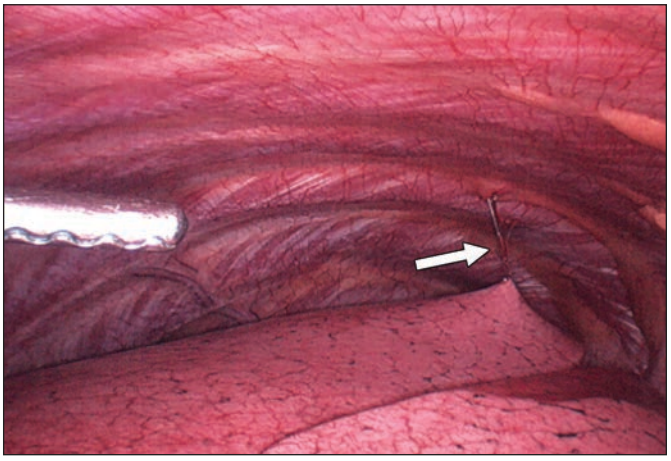

Fig. 2—48-year-old man with pulmonary nodule who underwent hookwire insertion localization procedure performed with CT fluoroscopic guidance. Surgical photograph shows hookwire (*arrow*) traversing pleural space and entering lung parenchyma.

Fig. 3—72-year-old woman with pulmonary nodule who underwent methylene blue injection localization procedure performed with CT fluoroscopic guidance. CT image shows that methylene blue was injected as needle was removed, with majority of stain injected into subpleural parenchyma directly overlying nodule.

volume range was 0.1–4 mL. In 16 of the 57 cases, small amounts of lidocaine and iodinated contrast medium were admixed with the methylene blue. The addition of lidocaine was intended to decrease the discomfort associated with the injection, and the iodinated contrast medium was intended to improve delineation of the injection on the postprocedure CT scan. The methylene blue admixture evolved over time, but the admixture that was most frequently used contained 1 mL of 1% methylene blue, 0.2 mL of iohexol (Omnipaque 300, GE Healthcare), 0.2 mL of 1% lidocaine hydrochloride with epinephrine, and 0.2 mL of 8.4% sodium bicarbonate. Once again, all surgeries were planned for the same day that the injection occurred.

A review of the PACS and the medical record system was performed. Data that were extracted included patient age and sex, preoperative diagnosis, final diagnosis, nodule location, nodule size, distance of the nodule from the pleura, localization technique used, complications, procedure time (defined as the period from the time that the scout image was obtained to the time that the final CT image was acquired), localization success (as described in the surgical report), time until the surgical procedure was completed (defined as the time from the end of the localization procedure to the time that the postoperative chest radiograph was obtained), the number of days that the chest tube remained (hereafter referred to as "chest tube–days"), the number of days until patient discharge from the hospital, and the mortality rate at 30 days after the surgical procedure was performed. The most commonly encountered complications were pneumothorax, perilesional hemorrhage, and pain. Pulmonary nodule size was expressed as the mean of the anterior-posterior and transverse axial measurements.

Statistical Analysis

Major and minor complications were defined using the Society of Interventional Radiology classification system [7]. The complication rates for the two groups were compared using a two-tailed Fisher exact test. Poisson regression was used to evaluate how patient age and sex, nodule size, the distance of the nodule from the pleura, the time required for the localization procedure, the time between the localization procedure and the completion of the surgical procedure, the localization method used, and the diagnosis related to localization complications, the number of chest tube–days, and the length of hospitalization.

Ordinary least squares regression was used to model procedure time (expressed in minutes) as a function of the aforementioned predictors. All models were univariate. Statistical significance was defined as $p < 0.05$ (two-sided). Statistical computing and graphics software (R, version 3.1.0, R Foundation) was used for the statistical analyses.

Results

Localization

One hundred seven of the 109 nodules (98%) were localized during same-day surgery, including all 57 nodules (100%) treated with methylene blue injection and 50 of the 52 nodules (96%) treated with hookwire insertion ($p = 0.23$). Two patients who underwent hookwire insertion had their surgeries canceled. During hookwire placement, one of these patients had a massive systemic air embolus develop that resulted in death; the other patient had ECG changes that could not be causally related to the hookwire localization procedure but precluded the patient from undergoing same-day surgery. Thirteen percent of the hookwires (7/52) became dislodged between the time of placement and the time of surgery, either because of patient motion or interval development of a pneumothorax. In all cases, when the hookwires dislodged, the surgeons were still able to localize the nodules as a result of visualization of the parenchymal puncture site.

Complications

Overall complication, pneumothorax, and perilesional hemorrhage rates were all higher in the hookwire insertion group, but these trends were not statistically significant (Table 2). The overall complication rate in the methylene blue injection group, compared with the hookwire insertion group, was 46% (26/57) versus 54% (28/52) ($p = 0.45$), whereas the pneumothorax rate was 25% (14/57) versus 38% (20/52) ($p = 0.15$) and the perilesional hemorrhage rate was 4% (2/57) versus 12% (6/52) ($p = 0.15$). Minor periprocedural pain was statistically significantly more common in the methylene blue injection group (11% [6/57] vs 0% [0/52]; $p = 0.03$). Coughing also occurred more commonly in the methylene blue injection group (7% [4/57] vs 0% [0/52]; $p = 0.12$). The only episode of hemoptysis that occurred in either group was in a patient in the hookwire insertion group who had a massive systemic air embolism develop.

Major complications were less common and less severe in the methylene blue injection group than in the hookwire insertion group (2% [1/57] vs 8% [4/52]; $p = 0.19$). The major complications in the hookwire insertion group included a tension pneumothorax that required emergent chest tube placement, a small but enlarging pneumothorax that was successfully treated with a pleural blood patch

TABLE 2: Overall Complication, Pneumothorax, and Perilesional Hemorrhage Rates for 102 Patients With Pulmonary Nodules Who Underwent 109 Localization Procedures

Rate Assessed	Hookwire Insertions ($n = 52$)	Methylene Blue Injections ($n = 57$)	*p*
Pneumothorax	20 (38)	14 (25)	0.15
Perilesional hemorrhage	6 (12)	2 (4)	0.15
Pain	0 (0)	6 (11)	0.03
Overall complications	28 (54)	26 (46)	0.45

Note—Except where indicated otherwise, data are no. (%) of procedures. Seven patients had two nodules localized, with each localization procedure counted as a separate procedure.

TABLE 3: Poisson Regression Analysis of Association of Increasing Age and Increasing Nodule Size With an Increased Number of Days When Chest Tube Insertion Was Required

Variable	Outcome: Chest Tube–Days					
	Estimate	SE	*p*	Rate Ratio (95% CI)	Adjusted Estimate	Estimated Hospital Days
Age						
Intercept	–1.60	0.43	< 0.01	0.20 (0.09–0.48)		
Age (y)	0.04	0.01	< 0.01[a]	1.04 (1.03–1.05)		
Nodule size						
Intercept	0.13	0.18	0.48	1.14 (0.79–1.63)		
Size (mm)	0.06	0.02	< 0.01[a]	1.07 (1.03–1.10)		
Final diagnosis						
Benign	1.03	0.11	< 0.01[a]		1.03	2.79
Metastasis	–0.88	0.19	< 0.01[a]		0.15	1.16
Lung cancer	–0.03	0.15	0.83		0.99	2.70
Premalignant nodule	0.52	0.29	0.08		1.54	4.67

Note—SE = standard error.
[a]Statistically significant.

at the time that the localization procedure was performed, a hookwire that dislodged into the subcutaneous fat and required that a separate cut-down procedure be performed under CT guidance for removal, and a massive systemic air embolus that resulted in death (Fig. 5). This was the only periprocedural death that occurred in the present study. The major complication that occurred in the methylene blue injection group was a moderate pneumothorax that was successfully aspirated using a centesis catheter (Yueh, Cook Medical) at the time of the localization.

Procedural and Surgical Factors

No statistically significant difference was noted between the hookwire insertion group and the methylene blue injection group with respect to the mean time between the start of the localization procedure and the time that the postoperative chest radiograph was obtained (332 vs 325 minutes; $p = 0.78$). In addition, no statistically significant difference was noted in the mean time between the start of the localization procedure and the time that the postoperative chest radiograph was acquired, when the hookwire dislodged compared with when it did not dislodge (297 vs 340 minutes; $p = 0.29$). The duration of the localization procedure did not vary significantly between the methylene blue injection and hookwire insertion groups, at 33.8 and 33.3 minutes, respectively. In a regression analysis, the only factor that was associated with an increased procedure time was smaller nodule size ($p = 0.02$).

The pulmonary nodules in the hookwire insertion group tended to be more superficial than those in the methylene blue injection group (14.7 vs 9.2 mm; $p = 0.02$). Decreasing distance of the nodule from the pleura was the only parameter that was statistically significantly associated with an increase in the total number of procedure-related complications. Older patient age ($p < 0.01$) and increased nodule size ($p < 0.01$) were associated with an increase in the number of postoperative chest tube–days. Patients with a final diagnosis of metastatic disease were found to have fewer chest tube–days and a shorter hospital stay, compared with patients with benign conditions and lung cancer diagnoses ($p < 0.01$). Older age ($p = 0.01$), increased distance of the nodule from the pleura ($p = 0.02$), increased procedure time ($p = 0.01$), and increased number of chest tube–days ($p < 0.01$) were all associated with a statistically significant increase in the length of hospitalization (Tables 3 and 4).

Discussion

The results of the present study show that methylene blue injection and hookwire insertion can both be successful for intraoperative localization of small parenchymal pulmonary nodules; however, they also reveal that hookwire placement was associated with more frequent and severe complications. Although these differences were not statistically significant, these findings are likely

TABLE 4: Poisson Regression Analysis of Association of Increasing Age, Increasing Distance From Nodule to Pleura, Increased Localization Procedure Time, and Increased Number of Days When Chest Tube Insertion Was Required With Increased Length of Hospitalization

Variable	Outcome: Hospital Days					
	Estimate	SE	*p*	Rate Ratio (95% CI)	Adjusted Estimate	Estimated Length of Hospitalization
Age						
Intercept	–0.32	0.40	0.42	0.73 (0.33–1.60)		
Age (y)	0.02	0.01	0.01[a]	1.02 (1.00–1.03)		
Pleural distance						
Intercept	0.57	0.09	< 0.01	1.77 (1.47–2.14)		
Distance (mm)	0.01	0.01	0.02[a]	1.01 (1.00–1.02)		
Procedure time						
Intercept	0.32	0.16	0.05	1.38 (1.00–1.91)		
Time (min)	0.01	< 0.01	0.01[a]	1.01 (1.00–1.02)		
Chest tube days						
Intercept	0.41	0.08	< 0.01	1.51 (1.28–1.78)		
Chest tube–days	0.10	0.01	< 0.01[a]	1.10 (1.08–1.13)		
Final diagnosis						
Benign	0.80	0.13	< 0.01[a]		0.80	2.21
Metastasis	–0.41	0.18	0.03[a]		0.39	1.47
Lung cancer	0.02	0.16	0.91		0.81	2.26
Premalignant nodule	0.82	0.29	0.01		1.61	5.00

Note—SE = standard error.
[a]Statistically significant.

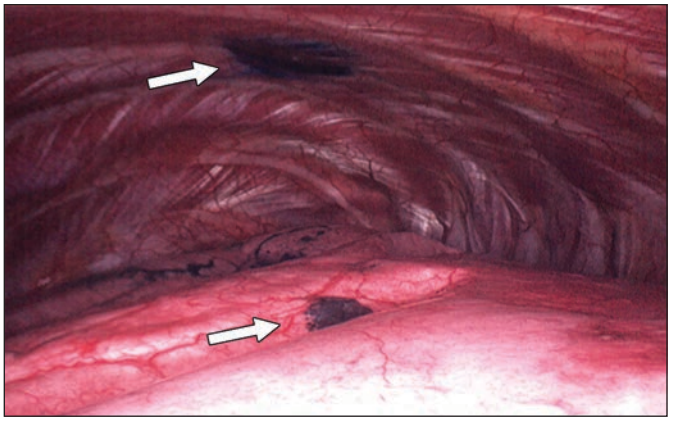

Fig. 4—76-year-old woman with pulmonary nodule who underwent methylene blue injection localization procedure performed with CT fluoroscopic guidance. Surgical photograph shows methylene blue stains (*arrows*) on visceral and parietal pleural surfaces.

Fig. 5—66-year-old woman with pulmonary nodule who underwent hookwire insertion localization procedure performed with CT fluoroscopic guidance. CT image shows small amount of hemorrhage is present along track of hookwire that had already been removed (*arrowhead*) and also shows air embolism in left ventricle (*arrow*). This air embolism ultimately resulted in death of patient.

a reflection of the relatively small numbers of patients and major complications. Considering that the methylene blue injections showed consistent efficacy, with a localization success rate of 100%, and were associated with a better safety profile, the findings of the present study suggest that methylene blue injections should be preferred over hookwire placement for the preoperative localization of small pulmonary nodules.

The safety of both techniques has been previously established but, to our knowledge, has not been previously directly compared in a similar patient population with the same operators [8, 9]. In the present study, the overall complication, pneumothorax, and perilesional hemorrhage rates were all higher in the hookwire insertion group. However, these trends did not prove to be statistically significant, likely because of the small numbers of complications noted overall. Methylene blue injection did result in more patient complaints of pain (11% [6/57] vs 0% [0/52]; $p = 0.03$). This finding was thought to occur secondary to the agent irritating the pleura. The addition of lidocaine to the methylene blue injection reduced the frequency of this complaint, according to anecdotal reports, although we did not have adequate data to prove this assertion. Hookwire dislodgement, a well-known complication, was encountered in 13% of cases (7/52). Previous studies have documented similar dislodgement rates of 4–20% [10]. However, in the present study, surgeons were still able to localize the nodules because of visualization of the parenchymal puncture site. In one obese patient, both the external and the internal components of the wire were dislodged, necessitating the use of a CT-guided cut-down procedure to identify and remove the wire.

Previous researchers have reported that diffusion of methylene blue in the lung parenchyma has resulted in difficulty identifying the location of the methylene blue and the demarcated nodule intraoperatively. This has led to the recommendation that surgery should be performed within 3 hours of methylene blue injection [4]. All of our patients underwent same-day surgery, and we did not encounter a problem with methylene blue diffusion in our study.

Perhaps the most disturbing trend was that major complications were more common in the hookwire insertion group and included one death occurring secondary to the development of an air embolus. There have been multiple case reports of hookwires causing massive systemic air emboli [4]. It is thought that the rigid wire traversing the lung and remaining in place increases the susceptibility to air embolism, although not enough data exist to confirm that air embolism is more common with hookwire placement than with biopsy or other lung interventions. To our knowledge, no reports of methylene blue injection causing a systemic air embolus have appeared in the literature, and we have not seen this occur in our own clinical experience. A desire to decrease the risk of significant complications was a primary factor affecting our decision to discontinue performing hookwire localization procedures.

Procedural and patient factors can also be important. For example, a shorter distance from the pleura to the nodule was associated with an increase in the overall complication rate associated with the localization procedure, regardless of the method used. This was largely caused by a higher rate of pneumothorax, which was not unexpected because this relationship has also been noted in patients undergoing biopsy. Of interest, the nodules in the hookwire insertion group tended to be more superficial than did those in the methylene blue injection group (9.2 vs 14.7 mm; $p = 0.01$). The reason for this finding is not entirely clear, but it can be theorized that the surgeons requested localization procedures only for deeper nodules after the patient had the catastrophic air embolism and that we transitioned to performing localization procedures with methylene blue injection.

Deeper nodules were associated with a longer hospitalization period, presumably because of the need to perform larger parenchymal resections. Not surprisingly, older age and increased nodule size were associated with an increased number of chest tube–days. Increased age, longer localization procedure time, and an increased number of chest tube–days were also factors that were found to be associated with longer hospitalization times. In addition, patients with a final diagnosis of metastatic disease spent less time in the hospital than did patients with final diagnoses of benign conditions and lung cancer, presumably because they were usually treated with wedge resections and because they had less underlying pulmonary disease in general. Although interesting, these observations were not directly associated with the technique used, and none would preclude the use of procedure or change patient management.

The present study is limited by its sample size and statistical power, especially in terms of showing a statistically significant difference in major complications between the

hookwire insertion and methylene blue injection groups. A larger study would be helpful for verifying our conclusions.

Conclusion

The findings of this study suggest that methylene blue injection and hookwire insertion are equivalent means of preoperative pulmonary nodule localization. However, a trend was noted toward more frequent and severe complications occurring in association with hookwire insertion. Considering the equivalent efficacy of the two options and the suggestion that methylene blue injection has a better safety profile, methylene blue injection should be preferred over hookwire placement for preoperative pulmonary nodule localization.

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