Pleural Dye Marking Using Radial Endobronchial Ultrasound and Virtual Bronchoscopy before Sublobar Pulmonary Resection for Small Peripheral Nodules

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Keywords

Bronchoscopy · Radial endobronchial ultrasound · Peripheral lung nodule · Lung cancer · Minimal invasive thoracic surgery · Dye marking

Abstract

Background: Minimally invasive surgery of pulmonary nodules allows suboptimal palpation of the lung compared to open thoracotomy. **Objective:** The objective of this study was to assess endoscopic pleural dye marking using radial endobronchial ultrasound (r-EBUS) and virtual bronchoscopy to localize small peripheral lung nodules immediately before minimally invasive resection. **Methods:** The endoscopic procedure was performed without fluoroscopy, under general anesthesia in the operating room immediately before minimally invasive surgery. Then, 1 mL of methylene blue (0.5%) was instilled into the guide sheath, wedged in the subpleural space. Wedge resection or segmentectomy were guided by visualization of the dye on the pleural sur-

face. Contribution of dye marking to the surgical procedure was rated by the surgeon. **Results:** Twenty-five nodules, including 6 ground glass opacities, were resected in 22 patients by video-assisted thoracoscopic wedge resection ($n = 11$) or robotic-assisted thoracoscopic surgery (10 segmentectomies and 1 wedge resection). The median greatest diameter of nodules was 8 mm. No conversion to open thoracotomy was needed. The endoscopic procedure added an average 10 min to surgical resection. The dye was visible on the pleural surface in 24 cases. Histological diagnosis and free margin resection were obtained in all cases. Median skin-to-skin operating time was 90 min for robotic segmentectomy and 40 min for video-assisted wedge resection. The same operative precision was considered impossible by the surgeon without dye marking in 21 cases. **Conclusions:** Dye marking using r-EBUS and virtual bronchoscopy can be easily and safely performed to localize small pulmonary nodules immediately before minimally invasive resection.

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Introduction

The diagnosis and management of small pulmonary nodules (SPNs) has become increasingly challenging, with a reported prevalence of SPNs as high as 50% in lung cancer screening studies [1]. In an era of minimally invasive thoracic surgery (video-assisted thoracoscopic surgery [VATS] or robotic-assisted thoracoscopic surgery [RATS]), subcentimeter lesions or ground glass opacities (GGOs) may be difficult to localize, as these procedures allow only suboptimal palpation of the lung in comparison with open thoracotomy [2–4]. Sometimes, even larger lesions are difficult to find because of their deep location beneath the pleura. Therefore, there is frequent conversion from minimally invasive VATS to more invasive thoracotomy if the nodule cannot be located during the procedure, with a conversion rate as high as 59% in some studies [5].

To overcome this difficulty, various percutaneous techniques have been developed to localize SPNs, such as computed tomography (CT)-guided radiotracer injection [6], CT-guided wire localization [7], CT-guided fiducial placement and fluoroscopic localization [8], ultrasonography [9], or CT-guided methylene blue injection [10]. Because these percutaneous localization techniques are often performed in radiology departments located far from the operating room (OR), coordination between radiologists, anesthesiologists, and thoracic surgeons is crucial. These logistic issues can be difficult to overcome in

certain settings. In addition, the risks of CT-guided trans-thoracic localization procedures include pneumothorax (16–35%) and hemorrhage (6–16%) [11].

Recent studies on pleural dye marking using electromagnetic navigation bronchoscopy (ENB) report accurate nodule localization before minimally invasive resection in a single setting in the OR [12–14].

Another study described a new dye-marking technique using methylene blue and radial endobronchial ultrasound (r-EBUS) [15]. Our objective was to assess a simplified dye-marking technique using a combination of virtual bronchoscopy (VB) and r-EBUS performed immediately before minimally invasive resection of SPNs or GGOs.

Patients and Methods

This retrospective single-center study was performed at Rouen University Hospital between April 2016 and June 2017. All patients requiring sublobar lung resection (i.e., wedge resection or segmentectomy) for a pulmonary lesion, which was anticipated by the surgeon to be hardly palpable or barely visible intraoperatively, based on its small size, its distance from the pleura, or its GGO appearance on CT, benefited from the endoscopic dye-marking technique. When a solid primary lung cancer was suspected, cases were preferentially submitted to segmentectomy, while cases with GGO or suspicion of metastasis from extrapulmonary cancer were preferentially submitted to wedge resection, according to preoperative multidisciplinary meeting decisions. The study protocol was approved by the Institutional Review Board for Non-Interventional Research of Rouen University Hospital, France (protocol No. E2017-17).

Fig. 1. Virtual bronchoscopy of a 8-mm nodule localized in RB3 (LungPoint® Planner, Broncus Medical Inc., San Jose, CA, USA). Left panel, coronal CT view; right panel, virtual bronchoscopy view. RB, right bronchus.

Each endoscopic procedure was performed immediately before surgical resection in the same OR. The nodule location was mapped using VB software in order to identify the smallest bronchus leading to the lesion (LungPoint® Planner, Broncus Medical Inc., San Jose, CA, USA) (Fig. 1). Endotracheal ventilation was carried out with a single-lumen endotracheal tube under general anesthesia. The endoscopy was performed using a BF-MP60F endoscope (Olympus®, Tokyo, Japan) with a 4-mm outer diameter and a 2-mm working channel. The ultrasound probe used was a UM-S20-17S radial probe (Olympus®) with 1.4 mm diameter that was introduced into the 1.9-mm-diameter guide sheath (Fig. 2). When the fiberscope reached the most distal subsegmental bronchus along the route previously defined in VB, the guide sheath with the r-EBUS probe was inserted into the working channel and pushed

within the smallest bronchus leading to the lesion in order to reach the subpleural space, without fluoroscopy guidance. The probe was then removed and the guide sheath left in place within the working channel. Subsequently, 1 mL of methylene blue (5 mg/1 mL) (Proveblue, Medac, France) was injected into the guide sheath and rinsed with 20 mL of air in order to clear the methylene blue from the guide sheath.

After the endoscopic procedure, the patient was intubated with a double-lumen tube and appropriately placed in a lateral decubitus position for minimally invasive resection (VATS or RATS) of the lung lesion. On inspection of the lung surface, the methylene blue dye was visualized in order to perform a wedge resection or a segmentectomy using an endoscopic stapler (Covidien Tri-Staple® or Ethicon Echelon Flex®) (Fig. 3a).

Fig. 2. A radial endobronchial ultrasound probe (r-EBUS; UM-S20-17S, Olympus®, Tokyo, Japan) was introduced into the 1.9-mm-diameter guide sheath in the 4-mm-diameter bronchoscope (BF-MP60, Olympus®).

Fig. 3. Perioperative view. **a** Methylene blue visualized on the pleural surface of the S3 segment during video-assisted thoracoscopic surgery. **b** Macroscopic aspect of the nodule right after resection in the operating room: the nodule, an 8-mm melanoma metastasis, was stained with methylene blue.

Resection of the lesion was guided both by the dye marking and by preoperative high-resolution CT scan for the depth of resection. The nodule resection was immediately evaluated by opening the specimen in the OR prior to pathology analysis (Fig. 3b). The success of the procedure was defined by the presence of the entire lesion with tumor-free margins in the resection specimen on histological analysis.

The entire resection procedure was recorded (video). The contribution of dye marking to the procedure was assessed retrospectively by the surgeon on the basis of the recorded video sequences, according to the grading system published by Sato et al. [16]: grade A, the same level of operative precision was considered to be impossible without marking; grade B, a similar level of precision was considered to be possible, but marking enabled confident performance of the operation, and grade C, the same operation was considered to be possible without marking.

Collected data included demographic information, the size of the lesion and distance from the pleural surface, radiographic characteristics of the lesion (solid vs. ground glass), contribution of the dye-marking technique, perioperative data, adverse events, type or resection needed for diagnosis, and final pathologic diagnosis.

Results

Patients' Characteristics

Twenty-two consecutive patients (11 men, 11 women; mean age 61.5 [47–70] years) with 25 lesions were included. Sixteen patients (73%) had a substantial smoking history, and 10 patients had a history of malignancy (2 with lung cancer and 8 with extrathoracic cancer).

Characteristics of the Lung Lesions

The diagnosis of the nodule was unknown preoperatively in all patients. Nineteen out of 25 nodules (72%) were solid and 6 were GGOs (Table 1). The median greatest diameter of the nodule was 8 (3–15) mm, and in 23/25 (92%) of the cases, the nodule diameter was <10 mm. The median distance between the center of the lesion and the nearest parietal pleural surface was 10 (2–27) mm (Table 1). The lesions were located in the upper lobe in 17 out of 25 cases (68%) (Table 1).

Perioperative and Postoperative Outcomes

These results are displayed in Table 2. No complications due to dye marking were reported. The mean time of the endoscopic procedure, including injection of the methylene blue dye, was 10 (5–15) min. There was no difference in terms of size, distance from the pleura, solid nature or GGO, or bronchus signs between the 12 nodules that were visualized using r-EBUS and the 13 that were not (Table 3). A bronchus sign was seen in only 2

Table 1. Characteristics of the pulmonary nodules ($n = 25$)

Type of nodule, solid/GGO	19/6
Median greatest diameter (min.–max.), mm	8 (3–15)
Median distance between nodule and pleura (min.–max.), mm	10 (2–27)
<i>Location of the nodule</i>	
Right upper lobe	14 (56%)
RB1	9
RB2	1
RB3	4
Left upper lobe	3 (12%)
LB1	2
LB5	1
Right lower lobe	6 (24%)
RB6	1
RB8	2
RB9	2
RB10	1
Left lower lobe	2 (8%)
LB7	1
LB10	1

min.–max., minimum–maximum; RB, right bronchus; LB, left bronchus; GGO, ground glass opacities.

cases, and an ultrasound image of the nodule was found in only 12 cases (48%).

The mean time between endoscopic dye marking and visualization of the lesion by the surgeon was 37 (20–60) min. This included the change of tracheal tube, the positioning of the patient, the preparation of equipment for VATS or RATS, and the thoracoscopic examination of the pleural surface.

Fifteen lesions were resected by wedge using VATS in 14 cases and RATS in 1 case. All 10 segmentectomies were performed using RATS.

In all but 1 of the 25 cases (96%), the dye was visible on the pleural surface. The contribution of dye marking was rated by the surgeon as grade A in 21 cases and as grade B in 3 cases.

For robotic segmentectomy, the median operating time (skin to skin) and the OR time were 90 (80–170) and 210 (210–260) min, respectively. The median operating time (skin to skin) and the OR time of video-assisted wedge resections were 40 (25–70) and 120 (90–200) min, respectively. No conversion to open thoracotomy was needed.

A definitive diagnosis was obtained by pathological evaluation in all the 25 nodules. This included 11 with primary lung cancer, 6 with metastatic cancer, and 8 benign nodules (4 granulomas, 3 inflammations, and 1 am-

Table 2. Perioperative and postoperative outcomes

Mean navigation time (min.–max.), min	10 (5–15)
Mean time between dye marking and surgery (min.–max.), min	37 (30–45)
Median operating time, skin to skin (min.–max.), min	
Video-assisted wedge resection	40 (25–70)
Robotic segmentectomy	90 (80–170)
Median operating room time (min.–max.), min	
Video-assisted wedge resection	120 (90–200)
Robotic segmentectomy	210 (210–260)
Type of surgery	
VATS	11 (50%)
RATS	11 (50%)
Type of resection	
Wedge resection	15
Segmentectomy	10
Surgeon rating of dye marking	
Grade A	21
Grade B	3
Grade C	1
Definitive diagnosis	
Malignant	17
Lung cancers	11
Gastric cancer metastases	2
Melanomas	1
Lymphomas	2
Kidney cancer	1
Benign	8
Granulomas	4
Inflammations	3
Amyloidosis	1
Surgical complication	
Conversion to open surgery	0
Other complications	0
Median length of hospital stay (min.–max.), days	3 (1–8)

min.–max., minimum–maximum; VATS, video-assisted thoracoscopic surgery; RATS, robotic-assisted thoracoscopic surgery.

Table 3. Nodule features according to ultrasound results

	Ultrasound image		<i>p</i> *
	Yes: 12 (48%)	No: 13 (52%)	
Solid nodule	10	9	0.64
GGO	2	4	
Median size (min.–max.), mm	8 (5–15)	8 (3–10)	1
Median distance between nodule and pleura (min.–max.), mm	10 (2–35)	10 (2–27)	1
Bronchus signs	2	0	0.22

GGO, ground glass opacities; min.–max., minimum–maximum. * Fisher exact test.

yloidosis). All malignant lesions were completely resected with negative microscopic resection margins.

The median length of hospital stay was 3 days, with a prolonged air leak in 2 cases leading to an extended stay of 7 and 8 days, respectively. No other complications occurred during the hospitalization.

Discussion

In this series, we showed that VB and r-EBUS for methylene blue marking of SPNs appear easy and safe to use and efficiently target the area of sublobar resection. The mean navigation time was low (10 min), and a single operative setting was used for both the dye-marking technique and for the surgical procedure. There were no complications related to the preoperative procedure in the present series. All nodules were successfully localized and fully resected with tumor-free margins in all malignant lesions.

Importantly, our dye-marking technique was considered useful by the surgeon in the majority of cases. Moreover, we recorded a median operating time (skin to skin) for RATS segmentectomy of 90 min, which appears lower than in our previous series without marking (140 min) [17]. Similarly, we report a median operating time for VATS wedge resection of 40 min, compared to 69 min in other studies [18, 19]. Furthermore, the overall occupation time of the OR in our series for VATS wedge resection (125 min) also compared favorably with previous reports (150 min) [20].

To date, CT-guided wire placement (including hook wires, microcoils, and spiral wires) is the most common procedure used to localize small, nonpalpable pulmonary lesions, with a high rate of successful localization [11]. However, this technique has several limitations, including pneumothorax (16–35%) and hemothorax (6–16%) [7, 11, 21, 22], as well as dislodgement of the guide wire, which can lead to the failure of localization. A few cases of air embolism have also been reported [22–24]. CT-guided localization can be difficult to implement with a reported median procedure time of about 40 min in awake patients [25]. CT-guided wire placement is performed in a dual setting, as the patient must be transferred from the radiology suite to the OR for the surgical procedure. Preoperative transthoracic CT-assisted methylene blue staining has recently shown a good sensitivity for small nodule localization. The procedure is less costly than wire-related techniques and obviates wire-related complications, but the coloration of the targeted area ap-

pears significantly affected by the time between tumor marking and thoracoscopy [26, 27].

Few data have been published on bronchoscopy dye-marking techniques, most of them concerning ENB-guided localization followed by minimally invasive resection [12–14]. r-EBUS associated with a VB dye-marking technique uses a thinner bronchoscope (4 mm) compared to ENB (6 mm), which results in a more distal progression of the endoscope and a more selective catheterization of the subsegmental bronchus. r-EBUS also appears to be more cost-effective than ENB, which requires specific preparation of the OR and more expensive disposable material. On average, r-EBUS costs 5 times less than ENB.

The technique presented here alleviates the loss of accuracy linked to the resorption of methylene, as both the mean time of the dye-marking technique and the time to surgical localization of the lesion are very low. Another advantage of our dye-marking technique is that there is no exposure to radiation as fluoroscopy was not used [28], whereas fluoroscopy was used in the 3 published studies using ENB [12–14].

As opposed to a recent study [15], a characteristic EBUS image of the peripheral nodule was obtained in only 12 cases (48%), whereas methylene blue was visible at the surface of the pleura in 95% of the cases in our series. This may be explained by the large proportion of GGOs among the patients explored (28%), by the very small size of the lesions, and by the absence of a bronchus sign in 92% of the cases. This suggests that VB may be the most useful part of the technique, while the role of r-EBUS may be essentially that of a guide to reach and to visualize the pleural surface. It is possible that future studies will demonstrate that a simplified procedure using only VB and a catheter, without r-EBUS or other imaging devices, is as accurate as the procedure presented in this study.

Sato et al. [16, 29] also reported the use of VB and a bronchoscopic multi-spot dye-marking technique using 3-dimensional virtual imaging for precise thoracoscopic sublobar lung resection with safe surgical margins. However, their procedure appears difficult to implement, as the procedure was not performed immediately before the surgery or during the same surgical procedure but 2 days preoperatively. Therefore, a second CT scan had to be performed to confirm the location of markings within 2 hours of the mapping procedure [16]. The authors also reported a mean time of 59 min for mapping and 20 min for the bronchoscopy.

In our series, a malignant lesion was diagnosed in 61% of patients, which appears higher than in a reported series of sublobar resection of pulmonary nodules, with a prev-

alence of malignancy varying from 6 to 28% for solid nodules of 5–10 mm in size and from 59 to 73% for GGOs [30]. The high rate of malignancy reported in our series may be explained by the size of the present series. It may also reflect the selection of patients based on multidisciplinary meeting decisions, including patients with either a nodule detected during CT screening or a metastatic nodule detected during follow-up for other cancers.

Besides its retrospective nature, the principal limitation of our study is related to a possible selection bias as procedures were performed by a single surgical team. Moreover, the absence of a control group did not allow any comparison of either the operating times or the rates of thoracotomy among patients with similar nodules that were not dye marked before minimally invasive surgery. However, we believe that the results presented here compare favorably with previous techniques designed to help surgical resection during video- or robotic-assisted sublobar resections.

Conclusion

Methylene blue dye marking using r-EBUS and VB seems to be an easy and safe technique to guide minimally invasive resection of small peripheral lung nodules and GGOs.

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Financial Disclosure and Conflicts of Interest

The authors declare no conflict of interest related to the submitted work. The authors have reported that no funding was received for this study.

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