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Original Article

Feasibility of uniportal VATS in the histopathological diagnosis of the peripheral pulmonary nodules which are marked by methylene blue before resection

Volkan Karaçam[1]*, Fatma Mutlu[1], İlkay Kaya[1], Aytaç Gülcü[2], Kemal Can Tertemiz[3], Aydın Şanlı[1], Duygu Gürel[4]

[1]Department of Thoracic Surgery, Dokuz Eylul University Faculty of Medicine, İzmir, Turkey
[2]Department of Radiology, Dokuz Eylul University Faculty of Medicine, İzmir, Turkey
[3]Department of Chest Diseases, Dokuz Eylul University Faculty of Medicine, İzmir, Turkey
[4]Department of Pathology, Dokuz Eylul University Faculty of Medicine, İzmir, Turkey

ABSTRACT

Background: This study aims to reveal the diagnostic success to determine nodule localization, by marking the nodules with methylene blue, its contribution to operation time, and perioperative complications.

Materials and Methods: In 52 patients with peripheral pulmonary nodules smaller than 20 mm, the nodule was marked by injecting 0.5-1 cc methylene blue with the guidance of computed tomography (CT) with a Chiba needle (22 G), before they were taken to the operating room. A frozen section examination was done after wedge resection with VATS.

Results: The mean nodule size in the study was 8.85 mm (3-25 mm). The mean measurement distance to the chest wall at the peripheral endpoint of the nodules was 9.0 mm (1-40 mm). Of the nodules, 22 were solid, 15 were semisolid, and 15 were ground glass. Pathology subtypes were as follows, especially in ground glass lesions whose localization could not be determined without marking; 7 adenocarcinomas, 2 adenocarcinomas in situ, 4 atypical adenomatous hyperplasias, and 2 benign cytology. The pathologies for the other 37 patients resulted in 13 benign cytology, 10 metastases of known malignancy, 3 lung squamous cell carcinoma (pT1bN0, pT1aN1), 7 adenocarcinoma (pT1aN0- pT2N0), 1 adenocarcinoma in situ, 2 typical carcinoids (pT1aN0) and 1 atypical adenomatous hyperplasia.

Conclusions: Through CT-guided percutaneous methylene blue marking, the localization of peripherally located, small-sized, and non-palpable lesions can be detected easily with uVATS. In this way, unnecessary thoracotomy can be avoided, the operation can be performed quickly and with low morbidity, and the diagnosis of lung cancer can be provided at an early stage.

Keywords: videothoracoscopic surgery, methylene blue, dye, ground glass nodule, uniportal

Corresponding Author*: Volkan Karaçam, MD. İnciraltı Mah, Mithatpaşa Cad. No: 1606, Balçova, İzmir, Turkey.
E-mail: volkankaracam@hotmail.com Phone: +90 5326623426
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Introduction

Pulmonary nodules are lesions that are 3 cm or less in diameter radiologically and at least partially located in the lung parenchyma, with solid or sub-solid features [1]. With the widespread use of low-dose computed tomography (CT) and the widespread use of lung cancer screening programs all over the world and in our country, there is an increasing number of pulmonary nodules have been detected [2]. Pulmonary nodules can be observed due to malignant or benign neoplasms of the lung, infectious, vascular, traumatic, or congenital pathologies [1]. Histopathological diagnosis is required to elucidate lesions suspicious of malignancy. The indications for the histopathological diagnosis of pulmonary nodules change according to the following; radiological densities of the nodule (spiculation, solid-ground glass), smoking history over 30 p/y, size over 6 mm, growth rates, family history, emphysema, and fibrosis [3].

Anatomical resection has already been performed by thoracotomy for lesions that were invisible and palpable nodules. Video-assisted thoracoscopic surgery (VATS) provides higher efficacy and less morbidity, compared to traditional thoracotomy in the diagnosis and treatment of nodules. Resection with VATS has become a popular therapeutic modality for potentially malignant nodules [4]. Preoperative marking is important for accurate resection, especially in invisible, non-palpable, or deeply located nodules. In this way, the operation time is shortened, and morbidity and transition rates to thoracotomy are reduced [5]. Various marking methods are mentioned in the literature. These are using autologous blood, hook wire, micro coil, determination of the lesion with intraoperative ultrasound, methylene blue, etc. Each technique has advantages and disadvantages [6].

In this study, we retrospectively evaluated the peripheral pulmonary nodules which we resected by performing a uniportal VATS (uVATS) after being marked by methylene blue. This study aims to reveal the diagnostic success of this procedure, and its contribution to determining nodule localization, operation time, and perioperative complications in cases with nodules marked with methylene blue.

Materials and Methods

Between January 2017 and December 2020, 52 patients who underwent uVATS wedge resection with methylene blue marking due to peripheral pulmonary nodules were evaluated retrospectively. Cases with a nodule that has a peripheral location less than 3 cm to the visceral pleura, smaller than 3 cm in size, and have a density that could not be seen or palpated videothoracoscopically were included in the study. Cases with nodule localization close to the hilar region and large vascular structures, who have a previous history of thoracotomy, severe emphysema or severe chronic obstructive pulmonary disease, and bleeding diathesis disorders were not included in the study. This study was approved by the Dokuz Eylul University Ethics Committee (29.06.2022, 2022/22-42).

All patients were marked with methylene blue under the guidance of CT in the interventional radiology unit before the surgical procedure. The closest distance of the nodule to the thoracic wall was determined using the steepest angle possible. Marking was done on the skin with a marker pen. After appropriate sterilization measures and subcutaneous local anesthesia, the nodule was reached by a 22-gauge Chiba needle. To see that the needle was oriented correctly, control images were taken to include the sections where the nodule was located. When the needle tip reached the nodule, methylene blue was started to be given. The needle was slowly withdrawn by injecting methylene blue (0.5-1 cc) along the line up to the visceral pleura (Figures 1,2). After the marking, the patients were transported to the operating room after the final follow-up CT was seen in terms of complications and procedural success. Nasal oxygen (2-3 L/min) was given to all patients in terms of pneumothorax throughout the transport and until the start of the operation.

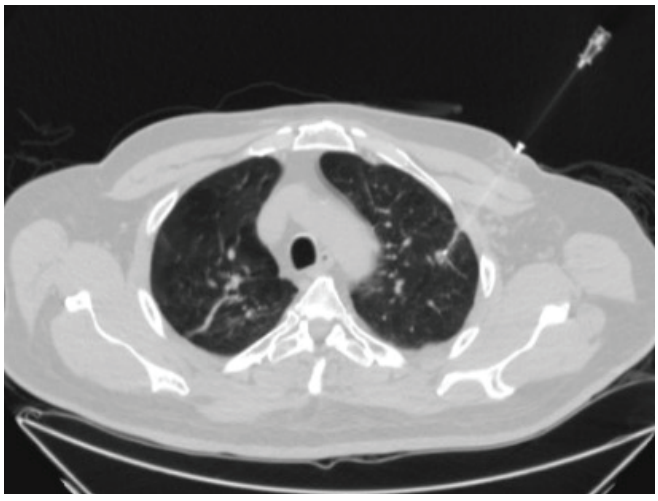

Figure 1. Methylene blue marking of the left upper lobe lesion under CT guidance.

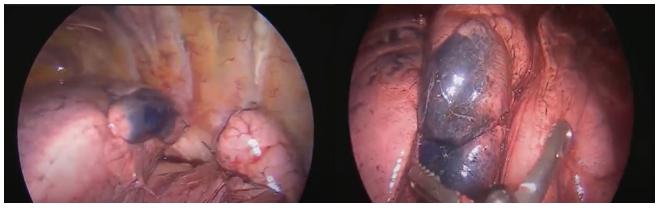

Figure 2. The parenchymal coloration during the VATS procedure.

All cases were intubated with a double-lumen endotracheal tube. Wedge resection was performed by uVATS with a 3-4 cm incision from the 4-5th intercostal space in the lateral decubitus position under general anesthesia (Figure 3). The frozen section was studied in all cases. UVATS lobectomy and mediastinal lymph node dissection were performed in the same session in cases without distant organ metastasis and mediastinal lymph node involvement, and frozen resulted in primary lung malignancy. Limited resection with wedge resection was performed in cases with benign, uncertain, or metastasis of primary malignancy as a result of frozen. After the operation, a 24-28 F thoracic drain was applied into the thorax, and the operation was terminated.

The cases included in the study were evaluated according to age, gender, size of the nodule, the density of the nodule on imaging (solid, semisolid, ground glass), histopathological diagnosis, distance to the chest wall, surgery performed (lobectomy with mediastinal lymph node dissection or wedge resection), complications, duration of operation, duration of follow up with a drain, time of hospitalization and one-year survival retrospectively.

Statistical Analysis

Statistical analyzes were performed using SPSS 19.0 software (SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as mean ± std. Categorical variables were expressed as deviation, frequency, and percentage. The student's t-test and Mann-Whitney-U test were used depending on the situation of the variables i.e. normally distributed or not.

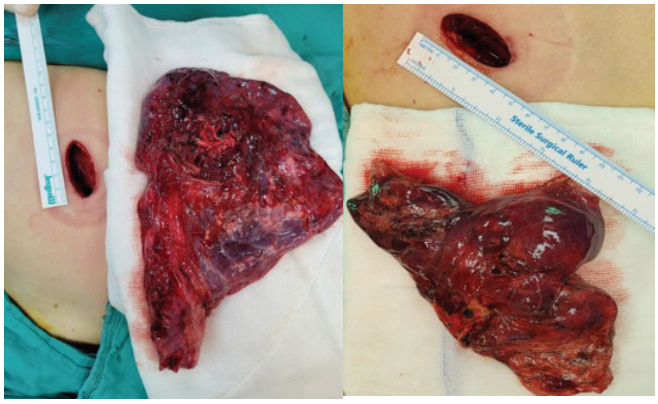

Figure 3. Four cm incisions for uVATS and lobectomy specimens.

Results

Thirty of the cases were male and 22 were female. The mean age was 58.9 ± 10.8 years (25-77 years). The mean size of the nodules measured by computed tomography (CT) was 8.9 ± 3.3 mm (4-20 mm), and the mean pathological size was 8.56 ± 4.3 mm (3-25 mm). The mean distance of the nodule to the visceral pleura was 9 ± 5.9 mm (4-29 mm). Of the nodules, 22 (42.3%) were solid, 15 (28.8%) were semisolid, and 15 (28.8%) were ground glass. The marking process was performed in 17 ± 3.1 minutes on average (13-24 minutes).

Pneumothorax developed in 13 (25%) cases after marking; however, none of them required tube thoracostomy. Perilesional hemorrhage was reported in two (3%) cases and the pain was reported in 23 (44.2%) cases. According to the frozen result, 30 (57.6%) of the nodules were malignant, 15 (28.8%) were benign, and 7 (13.4%) were indeterminate. The mean time from the beginning of the surgery to the end of the wedge resection was 20 ± 6.8 (13-25) minutes. The results according to the final histopathological diagnosis are shown in table 1.

UVATS lobectomy and mediastinal lymph node dissection were performed in the same session in 7 (13.4%) cases that were diagnosed as primary lung malignancy according to the frozen result and were suitable for surgery. Complementary resection and mediastinal lymph node dissection with uVATS were performed in 6 (11.3%) cases whose frozen pathology results were uncertain but the final pathology result was evaluated as primary lung cancer (Table 2).

Table 1. Histopathological diagnoses according to the final pathology result.

Histopathology	N	(%)
Adenocarcinoma	15	28.8
Atypical adenomatous hyperplasia	5	9.6
Squamous cell carcinoma	3	5.7
Typical carcinoid tumor	2	3.8
Adenocarcinoma in situ	2	3.8
Metastatic lung lesions	10 (5 colon, 3 rectum, 1 breast, 1 larynx, 1 bladder)	19.2
Benign histology	15	28.8

Table 2. Localization, the structure of nodules, histopathological diagnosis, and TNM stages of cases who underwent uVATS lobectomy.

	Histopathological diagnosis	Surgery	Pathological stage	Radiological density
1	Adenocarcinoma	Right lower lobectomy	pT1bN0	Solid
2*	Adenocarcinoma	Right middle lobectomy	pT1aN0	Ground Glass
3*	Typical Carcinoid	Right upper lobectomy	pT1aN0	Solid
4*	Typical Carcinoid	Right middle lobectomy	pT1aN0	Semi-solid
5*	Adenocarcinoma	Left lower lobectomy	pT1aN0	Ground Glass
6	Squamous cell carcinoma	Right lower lobectomy	pT1bN0	Solid
7*	Adenocarcinoma	Left lower lobectomy	pT1aN0	Semi-solid
8	Squamous cell carcinoma	Right lower lobectomy	pT1bN0	Solid
9	Adenocarcinoma	Right lower lobectomy	pT2N0	Solid
10	Adenocarcinoma	Right upper lobectomy	pT1bN0	Ground Glass
11	Squamous cell carcinoma	Left upper lobectomy	pT1aN1	Solid
12*	Adenocarcinoma	Right lower lobectomy	pT1aN0	Ground Glass
13	Adenocarcinoma	Left upper lobectomy	pT2N0	Solid

**Cases whose frozen results were uncertain but whose final pathology was evaluated as primary lung cancer.*

Out of 39 cases who did not undergo anatomic resection, wedge resection was performed on the right upper lobe in 12 patients (23%), right lower in 12 patients (23%), left upper in 7 patients (13.4%), left lower in 7 patients (13.4%) and right middle in 1 patient (1.9%). Resection was completed with uVATS in all cases. Thoracotomy was not required in any case.

Of the 15 cases with ground glass nodules were resulted as 7 were lung adenocarcinoma (46.6%), 4 were atypical adenomatous hyperplasia (26.6%), 2 were benign (13.3%) and 2 were (13.3%) adenocarcinoma in situ. Of the 37 cases with solid or semi-solid features, 10 (27%) were metastatic, 14 (37.8%) were lung primary malignancies or precancerous, and 13 (35.1%) were benign.

Mean follow-up time with drain after the operation was 1.9 ± 1.2 days (1-5 days); the mean hospitalization time was 3.1 ± 1.3 days (1-7 days). Two (3.8%) cases have died after one year of follow-up. Pathology results of these cases were one of them was with extrapulmonary malignancy, and the other was benign. The 6-month survival rate was 100%, and the 1-year survival rate was 96.2%. One of the cases dead was oligometastatic advanced extrapulmonary malignancy, and the other one was a patient who has benign pathology but died of cardiac problems.

In malignant cases, the radiological (malignant: 9.51 mm benign: 7.40 mm p = 0.038) and pathological (malignant: 9.46 mm benign: 6.33 mm p = 0.018) sizes of the nodules were found to be significantly larger than the benign cases. No statistically significant correlation was found between whether the nodule was solid, semisolid, or ground glass and whether the nodule was malignant or benign. (p = 0.232)

Discussion

Diagnosis provides great prognostic benefits in cases with suspected primary pulmonary malignancy [7,8]. Performing VATS wedge resection for small or non-palpable lung nodules is a difficult procedure, especially for uVATS [9,10]. Suzuki et al reported the unfindable nodule rate as 63% without marking (diameter ≤10 mm or at a depth of more than 5 mm in the lung parenchyma) [11]. Correct preoperative marking not only increases the efficacy of the surgery but also helps the pathologist to identify the lesion in the resected specimen [8]. For this reason, various marking methods are used as hook wire, methylene blue, spiral wire, bronchoscopic barium marker, colored collagens, micro coil (especially in pediatric cases), lipiodol marker, and fluoroscopy, Tc99-labeled albumin macroaggregates [12-14]. The most important advantages of methylene blue compared with the other methods are low cost, easy to find, and easy to apply. [7,8]. In this study, regardless of the size of the semisolid or ground glass nodules and their distance from the visceral pleura, we marked all the cases with methylene blue under CT guidance just before surgery.

In this study, the mean nodule size was 8.85 mm. The mean distance of the nodules to the visceral pleura was 9 mm. The technical success of our study was 100%, and the diagnosis was obtained from all cases after the final histopathological examination. This result is similar to other studies in the literature [8,15,16]. The disadvantages of marking with methylene blue are its rapid diffusion and poor visibility in severe anthracosis lung [8]. The time between marking and surgery should be kept below 120-150 minutes to get the highest efficiency from methylene blue marking [17]. Therefore, the operations are performed immediately as soon as possible after marking with methylene blue. During the marking, a surgeon of the surgical team accompanied the interventional radiologist, making sure that the appropriate amount of methylene blue is given to the appropriate localization. Cases with invisible methylene blue marking according to anthracosis lung, Chiba needle entry hole or air bubble should be visualized in the lung parenchyma by performing an air leak test. In this study, the marking was completed in as little as 17 minutes. In this way, complications such as pneumothorax, hemorrhage, and pain were seen at a lower rate and the procedure could be completed more safely.

Many studies have compared the marking technique with methylene blue and hook wire which is the second most commonly used method [18,19,20]. Chu et al showed that the marking procedure with methylene blue was performed in a shorter time, and surgery time and hospitalization were reduced. In this study, the mean time from the beginning of the surgery to the end of the wedge resection was 20 ± 6.8 min. The mean hospitalization time was 3.1 ± 1.3 days. Also, the rate of complications such as hemoptysis and pneumothorax were lower in methylene blue, compared with hook wire. In this study, the pain was the most common complaint and pneumothorax was the most common complication. Chu et al reported that the administration of tissue adhesive with methylene blue reduces the risk of hemoptysis and pneumothorax [18]. The major limitation of our study is that we are not able to compare methylene blue administration with the other methods.

Another advantage of using the marking method at semisolid or ground glass lesions (which have highly malignancy rate) is diagnosing and resectioning the lesion in an early stage with uVATS. Ground-glass lesions may be due to benign causes such as hemorrhage, pneumonia, and fibrosis, or malignant histopathology, especially early-stage lung adenocarcinoma or precancerous adenocarcinoma [21]. Ha et al reported that 81% of ground glass lesions were bronchoalveolar carcinoma or precancerous histopathology [22]. In this study, 86.6% of the ground glass lesions were adenocarcinoma or precancerous-noninvasive pathology. In this study, the radiological and pathological sizes of the malignant nodules were found to be significantly larger than the benign nodules. In this study, we terminated the operation with wedge resection if the frozen result is uncertain. In cases with final pathology as primary lung cancer, we performed a second surgery for complementary lobectomy and mediastinal lymph node dissection. Considering this possibility, unnecessary dissection must be avoided during frozen waiting for the need for a safe second surgery, especially uVATS.

The major limitation of our study is that we did not compare methylene blue administration with the other marking methods.

In conclusion, using the marking method, it is faster and easier to detect the localization of the nodule, and resection is possible with VATS. In this way, morbidity, unnecessary thoracotomy, and parenchymal resection are reduced. Through VATS, the postoperative period is more comfortable for the patient. In addition, drain follow-up and hospital stay are shortened compared to thoracotomy.

Methylene blue is more advantageous than other marking methods, as it is the cheapest, easiest to reach and apply, and least complicated marking option. It should be the first choice to be used for the percutaneous pulmonary nodule localization method.

Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

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Ethics approval

Approval was obtained from the Local Ethics of Dokuz Eylül University Committee (29.06.2022, 2022/22-42).

Authors' contribution

VK; conceptualized and drafted the article, wrote the paper FM,KCT; drafted the article, collected and analyzed data, İK; collected data, AG; marking the nodule, DG; pathologic analysis.

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