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Review Article

Sublobectomy involving the use of methylene blue staining combined with medical glue to locate small pulmonary nodules pre-operation

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Abstract: To investigate the efficacy of sublobectomy involving the use of methylene blue staining combined with medical glue to locate small pulmonary nodules pre-operation. A total of 87 patients with small pulmonary nodules undergoing sublobectomy at the Department of Thoracic Surgery in Hohhot First Hospital of Inner Mongolia between January 2014 and July 2017 were randomly assigned to two groups, including the preoperative localization with methylene blue staining group (simple localization group) (n=45 patients) and the preoperative localization with methylene blue staining combined with medical glue group (combined positioning group) (n=42 patients). The accuracy of localization of small pulmonary nodules, surgical effect, extubation time, operation time, as well as postoperative drainage volume and complications were compared between the two groups. In the simple localization group, there were three cases of localization failure caused by methylene blue staining in thoracic cavity, and the success rate was 93.33%. Successful localization was achieved in all 42 patients in the combined localization group, and the success rate was 100%. The operation time in the combined localization group was significantly shorter than that in the simple localization group ($p<0.05$). There were no significant differences in extubation time, length of hospital stay, volume of intraoperative bleeding and postoperative drainage volume between the two groups. The incidence of postoperative complications, such as pulmonary infection, early atelectasis and subcutaneous emphysema, were significantly lower in the combined localization group than in the simple localization group ($p<0.05$). There was no significant difference in air leakage and bleeding between the two groups. Hence, the injection of methylene blue combined with medical glue under the guidance of CT before video-assisted thoracoscopic surgery (VATS) could improve the success rate of the excision of small pulmonary nodules by VATS. Besides, the incidence of complications was low, especially for ground glass opacity (GGO) pulmonary nodules, indicating clinical value for the diagnosis and treatment.

Keywords: Methylene blue staining, medical glue, preoperative positioning, small pulmonary nodules, sublobectomy

Introduction

Lung cancer is the most common cause of cancer-related deaths in China. Studies have shown that the cure rate of lung carcinoma in situ is nearly 100%. The 5-year survival rate of patients with stage I lung cancer is 60-90%, while the survival rate of patients with stage IIIb and stage IV lung cancer is only 5-20%, indicating that early diagnosis and treatment are essential to improve the prognosis of lung cancer patients. Solitary pulmonary nodule (SPN) refers to isolated circular lesions of <3 cm diameter in the whole lung. According to the diameter, SPN is divided into micronodule (3-5 mm), small nodule (5-10 mm), and nodule (≥10 mm). With the wide application of low-dose spiral CT and popularization of regular physical examination, the detection rate of small and even micronodules is steadily increasing every year. However, CT cannot accurately distinguish between benign and malignant pulmonary nodules, and follow-up observation would delay the treatment. A study [1] reported that when the diameter of SPN is <5 mm, the possibility of malignancy is 0-1%; when the diameter is 5-10

mm, the possibility is 6-28%; and when the diameter of SPN is >20 mm, the possibility is 64-82%. The ACCP evidence-based clinical practice guideline in 2007 reported that the detection rate of SPN is 8-51%, of which 59-73% of pure ground glass opacity (pGGO) nodules are malignant. The nature of SPN is difficult to determine. Although the sensitivity of PET-CT is 88%, the specificity is only 67%. Moreover, the sensitivity of PET for the diagnosis of GGO nodules is poor [2]. Biopsy and pathological examination of lesion are used as the diagnostic gold standard. Video-assisted thoracoscopic surgery (VATS) enables safe and minimally invasive wedge-shaped resection of the lung, and facilitates complete resection of the lesion for obtaining a pathological diagnosis. In addition, total thoracoscopy or video-assisted thoracoscopic lobectomy using a small incision combined with lymph node dissection for primary lung cancer have the same short and long-term effects for early lung cancer as thoracotomy, with the obvious advantage of minimally invasive procedure as compared to traditional thoracotomy [3, 4]. So VATS is increasingly accepted by patients and clinicians, and is widely used in the diagnosis and treatment of SPN. However, a small number of nodules cause difficulties in finger palpation during VATS because of their small diameters, deep location or low density, which could affect operation mode, prolong operation time, and increase unnecessary pain to patients. The incidence of thoracotomy due to the failure of localization in thoracoscopic surgery is up to 46% [5]. Therefore, the precise localization of small pulmonary nodules before operation is closely related to the success rate of thoracoscopic surgery [6]. Hence, there is a critical need for a superior method of preoperative positioning in clinical practice. In this study, methylene blue staining combined with medical glue was used for the localization of small pulmonary nodules before VATS, followed by sublobectomy in order to improve the success rate of VATS in the treatment of small pulmonary nodules, and precisely locate microlesions in the lung during surgical resection and postoperative pathological examination.

Methods

General data

A total of 87 patients with small pulmonary nodules undergoing sublobectomy at the Department of Thoracic Surgery in Hohhot First Hospital of Inner Mongolia between January 2014 and July 2017 were randomly assigned to two groups, including the preoperative localization with methylene blue staining group (simple localization group) (n=45 patients) and the preoperative localization with methylene blue staining combined with medical glue group (combined localization group) (n=42 patients) (**Table 1**).

All the lesions were GGO, semi-solid or solid micro-lesions, difficult to locate in VATS. Selection criteria for preoperative positioning of small pulmonary nodules: (1) The location of nodule was relatively close to periphery; (2) The diameter of nodule was 8-20 mm; (3) The nodule was not surrounded by major tissues, such as cardiac large vessels or trachea; (4) Nodule was not directly connected to the visceral pleura, the distance was >10 mm.

Surgical instruments and equipment

Video-assisted thoracoscopic system (Olympus Corporation), CT (Siemens Corporation), Endo GIA, conventional surgical instruments, blood gas analyzer, and lung function test instrument were used in this study.

Specific localization method

Puncture needle (HAKKO Corporation, 12 G × 100 mm or 12 G × 150 mm), methylene blue injection (Hubei Jumpcan Pharmaceutical Co., Ltd, 2 ml: 20 mg), medical glue (Beijing Compont Medical Devices Co., Ltd, 1.5 ml/branch) were used. First, chest CT scan was performed to determine the position of nodule, and the direction, angle and depth of needle insertion. Then 2% lidocaine was used for local anesthesia after skin disinfection. After infiltration anesthesia reached the parietal pleura, the needle was retained in muscle tissues, and local scanning with a distance of 1.25 mm was performed in small pulmonary nodules. The anesthesia needle was used as a reference, and the angle and depth of needle insertion were confirmed according to image adjustment. According to CT images, puncture path was selected to avoid major organs such as cardiac large vessels, trachea and liver; and the shortest puncture path was selected. The needle was punctured into lung tissue and retained till it reached within 5 mm of the periphery of lesion. After confirmation of no blood while pump-

Table 1. General data of the two groups

Groups	n	Gender		Aver-age Age	Aver-age diameter	Location					Distance to pleura	CT Characteristics		
		Male	Fe-male			Right upper	Right middle	Right lower	Left upper	Left lower		Solid nodule	Semi-solid nodule	GGO
Combined localization group	42	22	20	68	12.5	15	1	9	9	8	20.6±4.1	11	12	19
Simple localization group	45	26	19	56.6	13	9	5	4	17	10	18.9±4.5	14	10	21

Table 2. Comparison of general data of the two groups

Groups	Localization success rate	Hematopneu-mothorax	Operation mode (VATS)				Pathological diagnosis results	
			Thoracotomy	Wedge-shaped resection	Pulmonary lobectomy	Segmental resection of lung	Benign	Malignant
Combined localization group	100%	4 (8.88%)	0	19	20	6	21 (46.66%)	24 (53.33%)
Simple localization group	93.33%	4 (9.52%)	3	22	17	3	19 (45.24%)	23 (54.76%)
p-value	0.003	>0.05	<0.05	>0.05	>0.05	>0.05	>0.05	>0.05

Table 3. Comparison of surgical indexes between the two groups

Groups	Extubation time (minutes)	Postoperative drainage volume (ml)	Operation time (minutes)*	Volume of intraoperative bleeding (ml)	Length of hospitalization (days)
Combined localization group	3±0.45	434±56.9	21±9.12	68±29.5	8±1.98
Simple localization group	4±0.22	478±67.3	29±17.76	128±38.4	8±2.12
p-value	>0.05	>0.05	<0.05	<0.05	>0.05

*Time interval between starting operation for the local resection of tumor and sending specimen for frozen section examination.

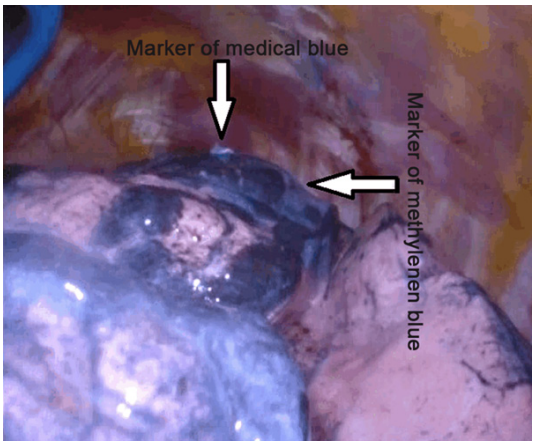

Figure 1. Markers of medical glue and methylene blue. The crumpled surface of lung after injection of methylene blue combined with medical glue is clearly seen, which could be used for localization in VATS.

ing with repeated chest CT scan, methylene blue (0.5-1.0 ml, strictly controlled) was injected by a skin test syringe (1 ml) after retracting the needle core. A small volume of medical glue was slowly injected into the parietal pleura, and then the needle was removed. After the puncture site was covered by medical gauze, the patient was transferred to the operation room, and anesthesia was induced within 30 minutes for the VATS.

Operation method

Single-port VATS method was adopted. Double-lumen tube tracheal intubation was performed, with the patient in lateral recumbent position, and contralateral single lung ventilation was used. A main operation hole was made (about 3-5 cm long) in the anterior line axillary of the fourth rib. The markers of methylene blue and medical glue could be seen on the surface of lung tissue in the thoracic cavity (**Figure 1**). The location and scope of lesion were further confirmed by finger palpation. The area stained with methylene blue was gently lifted, and a wedge-shaped resection of lung was made 2 cm outside the lesion using an endoscopic surgical cutting stapler. After the lesion was removed, a specimen was sent for frozen section examination. If the pathological diagnosis was benign lesion, metastatic tumor or patients with poor lung function, and some early malignant lesions with poor basic conditions, sublobectomy (wedge-shaped, segmental resection of lung) was performed. If the pathological diagnosis was primary lung cancer, total thoracoscopic lobectomy, systematic lymph node dissection or thoracoscopic assisted lobectomy with small incision was performed depending on the difficulty of surgery. If the pathological diagnosis was precancerous lesion, segmental resection of lung was performed. If it was bilateral pulmonary nodules, contralateral operation was performed after the operation on one side was completed.

Observation of curative effects

The accuracy of the localization of small pulmonary nodules, surgical effect, extubation time, operation time, postoperative drainage volume, intraoperative bleeding volume, length of hospitalization and postoperative complications were compared between the two groups.

Statistical analysis

Measurement data were analyzed by t-test and expressed as mean ± standard deviation. χ^2 test was used for enumeration data. $P<0.05$ was considered as significant difference.

Results

The patients in the two groups recovered smoothly with satisfactory outcomes. There were no surgical deaths, recurrence or serious complications. The operation time in the combined localization group was significantly shorter than that in the simple localization group ($p<0.05$). There were no significant differences in extubation time, length of hospitalization and postoperative drainage volume between the two groups. The postoperative complications, such as pulmonary infection, early atelectasis and subcutaneous emphysema, were significantly lower in the combined localization group than those in the simple localization group ($p<0.05$). There was no significant difference in air leakage and bleeding between the two groups (**Tables 2**-**4**).

Discussion

The prognosis of lung cancer is affected by many factors, of which tumor stage is the most important. Peripheral lung carcinoma (diameter <30 mm) is the best indication for surgical treatment, and the 5-year survival rate of patients is 60-80% [6]. CT is the best method

Table 4. Comparison of complications between the two groups

Results	Groups		Total	χ^2	*p*-value
	Simple localization group	Combined localization group			
Atelectasis					
Yes	12	7	19	13.275	0.0000
No	33	35	68		
Pulmonary infection					
Yes	11	6	17	15.467	0.0000
No	34	36	70		
Subcutaneous emphysema					
Yes	9	3	12	16.275	0.0000
No	34	39	73		

to detect small pulmonary nodules in the early stage. However, it is often impossible to distinguish between benign and malignant pulmonary nodules based on CT images, so the detection is often dependent on histopathological examinations. For small pulmonary nodules (diameter ≤10 mm), only a small amount of tissues is obtained by fine-needle biopsy, so it is often impossible to make an accurate pathological diagnosis [7]. In the last decade, total thoracoscopic surgical resection has played an important role in the diagnosis and treatment of small pulmonary nodules. Previously, intraoperative localization of pulmonary nodules relied on digital palpation by the surgeon. With the advancement of CT technique, smaller pulmonary nodules can be found, and the proportion of GGO nodules detected in lungs is increasing, leading to identification of lesions that could not be seen by naked eyes during surgery, which led to several complications during VATS, such as opening the chest or enlarging the incision. Therefore, it is particularly important to precisely locate small pulmonary nodules before the operation.

Although many methods of preoperative localization have been reported worldwide, including intraoperative ultrasound localization, preoperative CT-guided injection of dye and sclerosing agent, and hook-wire localization under the guidance of CT, there is no universally accepted localization technique for small pulmonary nodules in clinical practice. All these methods have their advantages and disadvantages [5-10]. Given the relatively low accuracy, it is difficult to locate smaller or lower density nodules by intraoperative ultrasound. Besides, the operation is tedious, the technical requirements of operators are higher, and experienced technicians are needed. Moreover, the lobes of the lung completely collapse when performing ultrasound, which takes 30-150 minutes. In addition, intraoperative ultrasound cannot be used in patients with diffuse emphysema. Preoperative CT-guided percutaneous injection of dye [9], iodine contrast agent [10], barium agent [11], radionuclide [12], and adsorbent for color removal [13], have the risk of sensitization. Furthermore, these agents easily diffuse into lung tissue and localization is not precise, so it is difficult to observe diffuse lesions in lungs. The agents might also cause toxicity to lesions and affect the accuracy of pathological examination results, while some agents could cause cerebral embolism after entering the pulmonary vein [14, 15]. Preoperative hook-wire localization is more accurate for small nodules in deep location that are difficult to palpate. In lung parenchyma, hook-wire could completely lift the lesions in deep location, which is more beneficial for the application of cutting stapler, but causes greater injury to lung tissue. Moreover, hook-wire is unstable in lung tissue [16], and displaced marker leads to pneumothorax after the implantation. The incidence of pulmonary hemorrhage and pleural pain are very high, and serious patients might also have gas embolism or die from the injury to lung tissue [2, 17-19].

In this study, satisfactory outcomes were obtained by injecting methylene blue combined with medical glue to locate small nodules under the guidance of CT before VATS. The localization success rate was 100%, and the success

rate of VATS lung wedge-shaped resection after localization was 100%. No patient had to undergo open-chest operation. Preoperative localization differs from general lung puncture, since it does not require very accurate puncture of lesion, the localization effect is related to the success of VATS when the pinpoint is within 10 mm of the lesion [20, 21]. The localization with methylene blue combined with medical glue could overcome the shortcomings of rapid dispersion of methylene blue and difficulty in identifying the lesion on the pigmented lung surface [22-24]. Besides, this precise localization method can avoid possible localization failure by single method. Slow dispersion of methylene blue and precise localization can preliminarily determine the location, depth and scope of lesion. Hence, wedge-shaped resection can be accurately performed. This procedure has fewer complications, and only four patients developed hematopneumothorax in this study.

The localization of the nodules in the deep position of lung parenchyma was relatively poor, and superficial location was selected. After precise localization with puncture needle, skin test syringe (1 ml) was used to inject methylene blue (0.5-1.0 ml) combined with medical glue (1 ml). Within 30 minutes after puncture, the patients were sent to the operation room for VATS. The skin test syringe could be more accurately controlled than an ordinary syringe [25], which avoided localization failure caused by excessive injection of methylene blue in the thoracic cavity [26]. Given the minuscule size of GGO pulmonary lesions, sometimes surgeons need to assist pathologists to locate the lesions [27].

Injecting methylene blue combined with medical glue for the localization of small pulmonary nodules before VATS could improve the success rate of VATS. Besides, the incidence of complications was low. Therefore, for small pulmonary nodules, especially GGO pulmonary lesions, the injection of methylene blue combined with medical glue before VATS has clinical value for diagnosis and treatment. The results of this study demonstrated that this method was very effective and safe.

Disclosure of conflict of interest

None.

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