Editorial

Progress in preoperative localization for small pulmonary nodules

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Video-assisted thoracic surgery (VATS) is associated with reduced postoperative pain, shorter hospital stay, and fewer perioperative complications than thoracotomy, and its application in surgery for both primary lung cancer and metastatic lung tumors is increasing. Lung cancer screening with annual low-dose computed tomography (CT) has reduced morality from lung cancer, as compared with chest radiography (1), while 24.2% of screened cases were positive in the low-dose CT group. The current guidelines recommend surgical biopsy if a lung nodule is ≥8 mm in size and the probability of malignancy is high (2). Furthermore, VATS wedge resection is recommended to obtain diagnosis for an indeterminate nodule. The increased use of CT screening for lung cancer will increase the number of cases where VATS is necessary for small pulmonary nodules.

By definition, VATS is a form of thoracic surgery performed under videoscopic guidance, with one access incision of maximum length of 8 cm and two port incisions of 0.5 cm, without rib spreading (3). Identification of nodule in the lung parenchyma by finger palpation is often hindered by the small skin incision and the limited access. Suzuki *et al.* reported in 1999 that the probability of failure to detect a nodule was 63% if the nodule is <10 mm and the distance to the pleural surface was ≥5 mm (4). When identification of a nodule during VATS is likely to be uncertain, preoperative localization will help surgeons to identify small pulmonary nodules. In one randomized controlled study by Finley *et al.* (5), patients with nodules of <15 mm were randomized to either no preoperative localization (n=27), or preoperative microcoil localization (n=29). They found that preoperative localization with a microcoil was associated with a higher rate of successful VATS wedge resection, decreased operative time, and fewer staples used, without increasing the total costs. The study was limited in that it was a single-institutional study and treatment arms were not blinded to the surgeons. Surgeons should make an informed decision about the indication for preoperative localization of nodules, based on (I) the characteristics of the nodule, including the size, the distance to the pleural surface, and whether it is a ground glass nodule; (II) the availability of equipment for localization in their institution; and (III) their skill in performing the procedure.

To date, only a few studies have evaluated preoperative localization using cone-beam CT (6) and ultrasonography (7). Two representative procedures include a trans-thoracic approach under CT guidance and a trans-bronchial approach using flexible bronchoscopy. Important factors when evaluating each technique are efficacy and safety for localization. Efficacy includes successful identification of markers on the surface of the lung, without dislodgment, during VATS, and successful wedge resection, without the need for conversion to thoracotomy. Cost analysis has rarely been reported. Furthermore, many studies in the literature are retrospective and single-institutional, and some studies include only a small number of patients, which may induce some bias.

For localization of a nodule, markers need to be located on the pleural surface of the lung, in order for markers to be recognized visually during VATS. In previous studies, markers have been evaluated using various means, including hook-wire, microcoil, lipiodol, radiolabelled technetium, and dye markers. Some markers (i.e., lipiodol) require fluorescence during VATS to identify markers and confirm

complete resection, while a gamma-probe is necessary for radio-guided surgery. Barium causes allergic reactions in the lung parenchyma and might preclude a precise pathological evaluation of the nodule and surgical margin. Dye markers are considered to diffuse easily and lead to overresection, although recent studies using dye markers have reported promising results. Zaman *et al.* concluded that radiolabelled technetium is a highly accurate and preferable method, with minimal complications and operator-dependence, for detecting nodules as compared to other techniques (8). However, their study has been criticized because they only reviewed 19 studies, with only two studies that used radiolabelled technetium for 56 patients (9). Park *et al.* evaluated the efficacy and safety of three marking methods, i.e., hook-wire, microcoil, and lipiodol, in trans-thoracic approaches under CT guidance (9). In their meta-analysis, all three methods had similarly high success rates, with lipiodol showing the highest success rates, and microcoils the lowest complication rates, respectively. In contrast, hook-wire had a lower success rate during VATS, because of dislodgement of markers, in addition to the highest rates of pneumothorax and hemorrhage. These unfavorable results with the hook-wire approach may be because this approach has been most frequently studied and reported in literature. Seo *et al.* examined 174 patients who underwent trans-thoracic localization of hook-wires under CT guidance (10). The study included eight cases with dislodgment of wires, and the distance between the tip of the hook-wire and pleural surface was a significant factor for successful localization. They concluded that in localization by means of a hook-wire, sufficient depth from the pleural surface is important.

Representative complications related to nodule localization include pneumothorax and hemorrhage, and most studies have reported that the procedures were safe. However, the rare but serious complication of air embolism is also reported in this procedure (11). The exact frequency of air embolism related to this procedure remains unknown. However, the frequency of air embolism in CT-guided trans-thoracic needle biopsy of lung lesions is reported to be 0.061% (6/9,783) (12), and this value can serve as a reference when performing a trans-thoracic localization of a nodule. Trans-bronchial approaches are expected to reduce the risk of air embolism as compared with trans-thoracic approaches, and it might in part explain why recent studies more frequently favor trans-bronchial approaches.

Marino *et al.* reported their results of localization with methylene blue using electromagnetic navigation bronchoscopy in a retrospective manner (13). Their study included lung nodules <10 mm and nodules ≤20 mm that were also located ≥10 mm from the pleural surface, and marking was successful in 70 of 72 nodules (97.2%). Recent trends for using trans-bronchial approaches are based on advances in multi-detector CT and software that allow three-dimensional visualization of images and generation of virtual bronchoscopic images. Electromagnetic navigation bronchoscopy utilizes virtual bronchoscopy and computer guidance to identify the route to the nodule through the bronchus and to guide small catheters accurately in the periphery of the lung. Combination of these techniques has enabled accurate preoperative localization of markers to identify small pulmonary nodules during VATS procedures.

The prevalence of CT screening for lung cancer has increased the number of small pulmonary nodules identified at the periphery, and solid evidence for preoperative localization is required when considering that the technique is utilized widely in clinical practice. Sato *et al.* conducted a multi-institutional prospective study of the trans-bronchial localization technique using virtual bronchoscopy and dye markers, with 1,781 markings in 500 patients who underwent VATS, and concluded that the technique was safe and reproducible among multiple centers (14).

In conclusion, surgeons should be encouraged to make use of preoperative localization techniques and VATS procedures guided by markers.

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