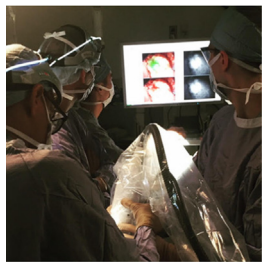
Novel Methods of Intraoperative Localization and Margin Assessment of Pulmonary Nodules

Jane Keating, MD, and Sunil Singhal, MD

Lung cancer screening has lead to frequent diagnosis of solitary pulmonary nodules, many of which require surgical biopsy for diagnosis and intervention. Subcentimeter and central nodules are particularly difficult to visualize or palpate during surgery, thus nodule localization can be a difficult problem for the thoracic surgeon. Although minimally invasive techniques including transthoracic computed tomography and bronchoscopic-guided biopsy may establish a diagnosis, these methods do not help locate nodules during surgery and can lead to inadequate tissue sampling. Therefore, surgical biopsy is often required for diagnosis and management of solitary pulmonary nodules. Additionally, after an excision, intraoperative margin assessment is important to prevent local recurrence. This is important for bronchial margins following lobectomy or parenchymal margins following sublobar resection. First, we examine methods of preoperative lesion marking, including wire placement, dye marking, ultrasound, fluoroscopy, and molecular imaging. Second, we describe the current state of the art in intraoperative margin assessment techniques.

Semin Thoracic Surg 28:127–136

Keywords: lung cancer, intraoperative, localization, margin



Surgeon and assistant holding an Artemis™ near-infrared intraoperative imaging device over an open thoracotomy incision depicting an area of fluorescence corresponding to pulmonary adenocarcinoma.

Central Message

Intraoperative localization of lung nodules and tumor margin assessment provides a challenging and increasingly important problem for thoracic surgeons. Novel techniques are reviewed here.

INTRODUCTION

Lung cancer occurs in 1.8 million patients and is responsible for 1.6 million deaths yearly worldwide.[1] It is the leading cause of cancer death in both men and women in the United States and accounts for more deaths than colon, prostate, and breast cancer combined.[2] Despite advances in therapy, the 5-year survival rate is approximately 16% for all individuals diagnosed with lung cancer.[3]

Evidence suggests that lung cancer screening is beneficial for several reasons, including the significant prevalence of the disease (0.5%-2.2%), and clinical outcome is directly related to stage at diagnosis (more than 60% 5-year survival for stage I disease when compared with less than 5% survival for stage IV disease).[4,5] Low-dose helical computed tomography (CT) for lung cancer screening is the modality of choice for lung cancer screening for high-risk populations. The National Lung Screening Trial that consisted of annual low-dose helical CT screening in patients aged 55-74 with a 30 pack-year history of smoking, demonstrated a decrease in lung cancer and all-cause mortality.[6]

Department of Surgery, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania

Address reprint requests to Sunil Singhal, MD, Department of Surgery, University of Pennsylvania School of Medicine, 6 White Building, 3400 Spruce St, Philadelphia, PA 19104. E-mail: sunil.singhal@uphs.upenn.edu

With the advent of lung cancer screening, diagnosis, and management of solitary pulmonary nodules (SPNs) have become an increasing clinical problem, with prevalence of SPNs as high as 50% in lung cancer screening studies of high-risk smokers.[7] Although there is considerable variation in management among clinicians, there is general consensus that patients with a high probability of malignancy such as solid and subsolid SPNs with evidence of growth on serial imaging or patients with solid SPNs >8 mm should have the lesion biopsied or surgically excised for diagnosis.[8]

For patients deemed appropriate surgical candidates, a diagnostic wedge resection by video-assisted thoracoscopic surgery (VATS) is the preferred method when a nonsurgical biopsy is unavailable, not practical, or nondiagnostic. In addition, many patients may not want the anxiety of a false-negative nonsurgical biopsy and would opt for VATS as a first choice for diagnosis. SPNs are typically located by visual inspection and palpation during VATS; however, for particularly small and deep lesions, SPN localization can be challenging.[9] Currently, several localization methods exist to increase the diagnostic yield during thoracoscopy, such as percutaneous wire placement, injection of dye, intraoperative imaging with ultrasound, fluoroscopy, or molecular imaging devices.

Although the gold standard for treatment of non–small cell lung carcinoma (NSCLC) includes lobectomy or pneumonectomy, occasionally a limited or sublobar resection is the preferred method of management for NSCLC. A sublobar resection consists

1043-0679/$-see front matter

http://dx.doi.org/10.1053/j.semtcvs.2016.01.006

of removing 1 or more anatomical segments (segmentectomy) or performing a nonanatomical wedge resection. Sublobar resection may be optimal for patients with limited pulmonary function, advanced age, and extensive comorbidities, and it should generally be limited to primary tumors ≤ 3 cm.[10]

During both lobar and sublobar resection of NSCLC, surgical margin assessment is important for both complete oncologic resection as well as for clinical staging and adjuvant treatment planning. Specifically, patients with microscopic tumor involvement of the resection margin (R1) have a markedly worse prognosis than those with negative microscopic margins (R0). Currently, there are limited methods of intraoperative margin assessment other than vigorous inspection using vision and palpation. Following sublobar resection, specimens may be evaluated by frozen section analysis, but this is time consuming and impractical.

The purpose of this article is to review the current and emerging methods of intraoperative tumor localization and margin assessment. First, we provide a brief overview of nonsurgical biopsy techniques. We then discuss preoperative tumor marking strategies that aid in intraoperative tumor localization. Next, we describe intraoperative imaging techniques useful for small tumor localization. Finally, we review the role of intraoperative margin assessment for NSCLC.

OVERVIEW OF PREOPERATIVE NONSURGICAL BIOPSY

Minimally invasive methods for SPN biopsy include both bronchoscopic and transthoracic techniques. When indicated, these procedures are generally preferred to more invasive surgery; however, they have imperfect sensitivity and lack therapeutic potential.

Bronchoscopic biopsy obtains diagnosis via instrumentation of the airway under conscious sedation. This method, including endobronchial ultrasound-guided transbronchial needle aspiration, is ideal for large, visible, or central lesions. Endobronchial ultrasound–guided techniques, including navigation-guided bronchoscopy, when available, are preferred to conventional bronchoscopic biopsy because of relatively higher diagnostic sensitivity (85% vs 73% for large, centrally located lesions).[11] Conversely, transthoracic needle biopsy or aspiration involves passing a needle percutaneously through the chest wall into a lung nodule, usually under CT guidance. This method is ideal for peripheral nodules; however, it is associated with a significant risk of pneumothorax (19%).[12] The risk of pneumothorax is highest in smokers, patients with underlying chronic obstructive pulmonary disease or emphysema, and older patients. Additionally, this method has a high false-negative rate (22%), so a negative result may have limited value. Biopsy is preferred to needle aspiration as it allows for histologic architecture for diagnosis unlike aspiration.[13]

The more invasive VATS provides an accurate modality for assessing primary tumors, mediastinal lymph node involvement, and pleural involvement. Although it requires general anesthesia and carries higher morbidity and mortality than minimally invasive techniques, it is often used when alternative procedures are unable to access the primary tumor or are nondiagnostic. Additionally, VATS provides an opportunity for therapeutic intervention at the time of diagnosis.

PREOPERATIVE INVASIVE LOCALIZATION TECHNIQUES

Overview

Preoperative techniques are occasionally used by thoracic surgeons to increase localization and diagnostic accuracy (Table). Inspection and palpation

Table. Wire-Guided and Ink-Guided Techniques for Preoperative Pulmonary Nodule Marking and Intraopertive Imaging Techniques for Pulmonary Nodule Localization

Preoperative marking techniques		
Wire guided	Microcoil	Powell et al[17], Mayo et al[19]
	Hook wire	Miyoshi et al[21], Dendo et al[22], Gonfiotti et al[23]
	Spiral wire	Eichfeld et al
Ink guided	Methylene blue	Lenglinger et al, McConnell et al
	Lioplo	Watanabe et al, Nomori et al
	Technichian 99	Chella et al
Intraoperative imaging techniques		
Ultrasound		Kondo et al, Piolanti et al, Santambrogio et al
Fluoroscopy		Nomori et al
Computed tomography		Gill et al
Molecular imaging		Okusanya et al, Keating et al

These techniques may be used in conjunction with preoperative marking with radiopaque wires or dye or both.