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Mini Review

Role of Interventional Pulmonology in Lung Cancer Care

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Abstract

The mortality from lung cancer has decreased, however it is still the leading cause of cancer-related death in the United States. The decline in lung cancer mortality is due to the collaborative effort by different teams involved in care of these patients. Interventional Pulmonology has a pivotal role in multidisciplinary lung cancer care, with significant impact on quality of care. The related advancement in this specialty includes treatment of major airway obstruction, biopsy of small lung nodule in early stage lung cancer, mediastinal staging with Endobronchial Ultrasound, diagnosis and treatment of malignant pleural effusion and pleural based tumors, and management of comorbidities and pulmonary complications related to cancer or secondary to its treatment. In this review we present the application of major pulmonary procedures and how their evolution have changed the management and prognosis of this deadly disease.

Keywords: *Pulmonary; Interventional Pulmonary; Lung Cancer; Lung Nodule; Pleural Effusion*

Abbreviations

EBUS: Endobronchial Ultrasound; Radial Endobronchial Ultrasound; Electromagnetic Navigation Bronchoscopy; Non-Small Cell Lung Cancer; Interventional Pulmonary; Central Airway Obstruction; Transbronchial Needle Aspiration; Video Assisted Thoracoscopic Surgery

Introduction

Lung cancer represented 13.3% of all new cancer cases in the United States in 2012, yet it is the leading cause of cancer-related death in the western world for both men and women [1]. Fortunately, the mortality from lung cancer has begun to decline, in part due to the decreased prevalence of tobacco use, in addition to advances in lung cancer care. Lung cancer treatment requires a collaborative effort by a multidisciplinary team. The multidisciplinary team includes thoracic surgery, medical oncology, radiation oncology, thoracic radiology, nuclear medicine, palliative care and pulmonary subspecialties. The pivotal role of the pulmonologist in prevention, early diagnosis, and management of lung cancer has been widely recognized [2]. The growing discipline of Interventional Pulmonology (IP) has found its place in lung cancer care through advances in technology and procedural technique. The interventionalists' contribution to the advancement in lung cancer care includes treatment of major airway obstruction, biopsy of small lung nodules in early stage lung cancer, mediastinal staging with endobronchial ultrasound (EBUS), diagnosis and treatment of malignant pleural effusion, the evaluation of pleural based malignancy, interventions in massive hemoptysis and management of treatment-related side effects, such as post radiation or post immunotherapy pulmonary complications. In this article, we review different aspects of this relatively new specialty; the ways in which IP can help improve the care of this patient population; and outline pertinent cases from the IP division at our institution.

Central Airway Obstruction (CAO)

Obstruction of the central airways, including the trachea and mainstem bronchi, can be a significant cause of morbidity and mortality. Bronchogenic carcinoma is the leading cause of CAO, though the exact incidence and prevalence of central airway obstruction is unknown. Approximately 20 - 30% of patients with lung cancer will develop complications due to central airway obstruction including atelectasis, recurrent obstructive pneumonia, dyspnea and respiratory failure. In addition, 30 - 40% of lung cancer deaths can be attributed to such obstructing complications of the central airways [3].

When CAO is suspected by history and physical examination, further evaluation is required. Chest imaging including conventional chest radiograph and computed tomography (CT) are important tools in the evaluation of suspected CAO. Comparison to any prior imaging and careful review of the CT allows for the characterization of the obstruction (intraluminal lesion vs extrinsic compression); whether the airway distal to the obstruction is patent and potentially amenable to bronchoscopic dilation or endobronchial stenting; as well as the duration of the airway occlusion [3]. Usually any airway collapse of greater than 4 - 6 weeks is excluded for intervention. Other considerations before any plan for therapeutic bronchoscopy include: Can the patient tolerate therapeutic bronchoscopy? Are patient's symptoms explained by airway obstruction? What is the degree and location of airway obstruction? Is there any other comorbidity which can explain dyspnea? (examples: COPD, CHF, Pleural Effusion, Pulmonary Embolism) What is baseline performance status, and the overall prognosis of the patient? What are patient's preferences and expectations?

Bronchoscopy (flexible or rigid) is always necessary in the evaluation of CAO. Bronchoscopy allows for direct visualization of the extent of obstruction as well as tissue diagnosis when needed. Interventions are myriad including mechanical tumor debridement including the use of microdebrider, Electrocautery, Laser, Cryotherapy ablation, Argon Plasma Coagulation (APC), Brachytherapy, Photodynamic therapy, sequential balloon dilation and stent placement. Importantly, patients with advanced non-small cell lung cancer (NSCLC) with CAO which is treated with bronchoscopic debridement and/or stenting along with radiation and chemotherapy have similar survival outcomes compared to patients with advanced NSCLC without CAO treated with radiation and chemotherapy [4]. Patients with advanced NSCLC and CAO without local treatment are often unable to receive life prolonging radiation or chemotherapy due to respiratory complications such as lung collapse, post-obstructive pneumonia or poor functional status. This highlights the important therapeutic role the interventional pulmonologist has in the outcomes of lung cancer patients with CAO [3].

Case Example

A 56-year-old female was diagnosed with non-small cell lung cancer with metastasis to brain a few weeks before presentation. She had good functional status and was planning to receive tailored treatment including chemotherapy and radiation. Her status quickly complicated with respiratory failure. She was hospitalized, and imaging showed growth of the tumor in the right main stem and bronchus intermedius causing collapse of the entire right lung. She became too unstable and could not get any systemic or local treatment, and was about to be referred to hospice care. She underwent a therapeutic bronchoscopy with de-bulking of the tumor from inside of her airways and placement of an airway stent with immediate relief from respiratory symptoms. The top row in figure 1 shows the representative images of the endobronchial tumor with collapse of the right lung and shift of the heart to the right side. The bottom row are the images after the intervention which showed re-expansion of her right lung and a stent placement. She was able to walk about 10 blocks a few days after her procedure, do her normal daily activities and started her systemic chemotherapy and radiation.

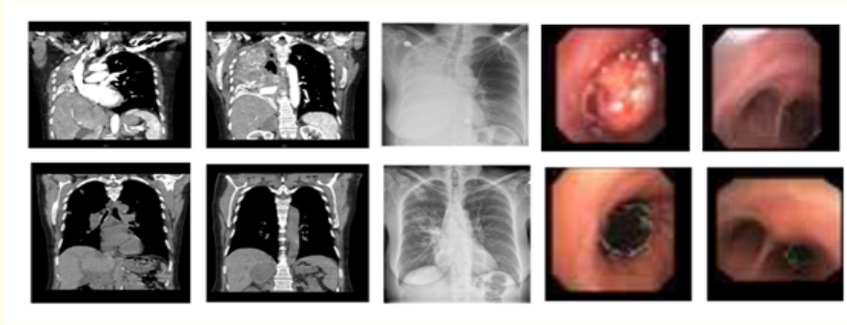

Figure 1: *Non-small cell lung cancer with endoluminal growth before (top row) and after (bottom row) therapeutic bronchoscopy in right main stem and bronchus intermedius and stent placement in bronchus intermedius.*

Small Pulmonary Nodules

Peripheral lung nodules present a significant challenge for the clinician. With the rise in CT screening for high risk patients, based on data from the National Lung Screening Trial [5] there continues to be a growing need for more accurate and less invasive sampling of peripheral lesions. In this cohort, > 25% of patients undergoing low-dose screening CT chest had findings concerning for lung malignancy. Patients will obviously benefit if they are able to avoid surgical biopsy, usually performed by video assisted thoracoscopic surgery (VATS) with wedge resection or lobectomy, especially in those that ultimately have benign nodules. Traditional bronchoscopy has shown a diagnostic yield of less than 20% in peripheral lung nodules of less than 2 cm in width. Transthoracic needle aspiration has shown good yields

but at a risk of pneumothorax of up to 25% as well as other complications [6,7]. Advancements in bronchoscopy technology including electromagnetic navigation bronchoscopy (EMN), virtual bronchoscopy and radial EBUS improve the diagnostic yield for small peripheral nodules.

In our institution, we favor radial EBUS with a small caliber bronchoscope. The small caliber bronchoscope has a limited working channel but allows for closer access to more distal subsegments of the lung. The radial EBUS mini-probe has a 1.4 mm outer diameter 20-MHz ultrasound probe which is passed through the working channel of the bronchoscope. Radial EBUS delivers a circumferential ultrasound image of the nodule which is also correlated with fluoroscopic location of the bronchoscope. The nodule in radial ultrasound image may be concentric (probe within the nodule) or eccentric (probe adjacent to the nodule) depending on the location of the nodule in relation to the bronchi. Following radial EBUS confirmation of nodule location, the radial EBUS is removed and a biopsy tool (either transbronchial needle, forceps or brush) is applied for sampling of the lesion [7,8]. Guide sheath technique has also been described when using larger sized bronchoscopes [9]. Chen., *et al.* reported successful localization of 446 of 467 (96%) nodules using radial EBUS only, with overall diagnostic yield 69% and a low pneumothorax rate of 2.8%. Only 4% of nodules (21 of 467) could not be visualized in this study, showing that radial EBUS alone can locate the vast majority of nodules. Importantly, when concentric views of the nodule were obtained, biopsy yields were much higher compared to those when only eccentric views could be obtained (84% versus 48%, p = 0.0008) [8].

Using the AQuIRE (ACCP Quality Improvement Registry, Evaluation, and Education) registry data a multicenter study of consecutive patients who underwent transbronchial biopsy (TBBx) for evaluation of peripheral lesions in 15 centers from 2009 to 2013 revealed controversial outcomes and significant practice pattern differences across the nation; highlighting the current challenges in establishing diagnosis of small peripheral lung lesions [10]. Ultimately, the decision to pursue sampling of peripheral lung nodules by any of the available techniques or in combination depends on local expertise and training with each technology.

Case Example

A 56-year-old male past smoker with past medical history of squamous cell carcinoma of the left hypopharynx status post excision, chemotherapy and radiation presented for evaluation of CT chest and positron emission tomography(PET)/CT imaging showed growing nodules in both lungs and mediastinal lymphadenopathy, all showing fluorodeoxyglucose (FDG) avidity giving concern for metastatic disease from his prior carcinoma. Bronchoscopy using both linear and radial EBUS was performed (Figure 2). The samples were negative for any malignancy. TBNA of the right lung nodule showed atypical and reactive bronchial cells with granular debris and inflammatory cells. The culture and microbiology testing showed mycobacterium avium complex (MAC). The patient was referred to an infectious disease specialist and was started on antibiotics including treatment for MAC. Follow up imaging studies showed decrease in size and number of the nodules. This case highlights the importance of advanced peripheral lung lesion sampling and the ways IP can help in the care of complex oncology patients.

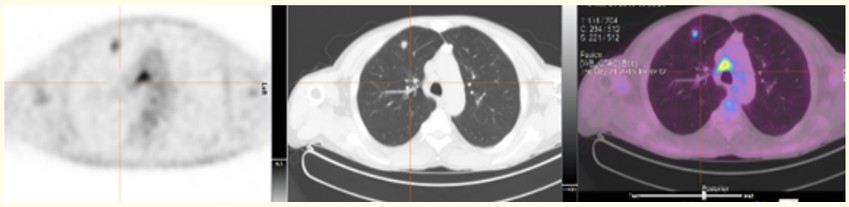

Figure 2: *This representative positron emission tomography(PET)/CT imaging shows fluorodeoxyglucose (FDG) avid lesions: a paratracheal lymph node and a small peripheral right upper lobe lung nodule. Biopsy of the small lung nodule with radial EBUS guide showed Mycobacterium Avium Complex infection, and the needle aspirate of the paratracheal lymph node with linear EBUS was negative for malignancy*

Mediastinal Staging of Non-Small Cell Lung Cancer

When NSCLC is either identified or suspected, staging of the disease is of critical importance, as staging will determine both management and prognosis. In patients with distant metastasis, palliative treatment will be the goal. In patients with disease confined to the chest, mediastinal lymph node involvement (and thus mediastinal staging) will help to determine the most appropriate treatment strategy. Patients with stage IA, IB, IIA and IIB disease often benefit from surgical resection of their tumor; while those with stage IIIA and IIIB disease rarely benefit from surgical resection [11]. There are many modalities used in the evaluation and staging of suspected NSCLC including CT scan, positron emission tomography (PET), radiology guided sampling, bronchoscopy with transbronchial needle aspiration (TBNA) and mediastinoscopy. In the past, CT scan, PET-CT and mediastinoscopy have been the major modalities for mediastinal staging but this staging strategy can result in incorrect staging in 25% of operable tumors. In addition, the need for multiple procedures in order to reach an accurate diagnosis and stage can lead to delayed treatment [12].

American College of Chest Physicians (ACCP) Evidence-Based Clinical Practice Guidelines published the sensitivity and specificity of CT scanning 55% and 81%, PET scanning 77% and 86%, and sensitivity of EBUS, endoscopic ultrasound (EUS) and EBUS/EUS combined 89%, 89%, and 91% respectively for identifying mediastinal lymph node metastasis [11]. In most situations, EBUS-TBNA can simultane-

ously confirm the diagnosis and the stage of the malignancy in one procedure, thus reducing time to diagnosis and treatment; in some studies, by half. In this way, EBUS-TBNA has been shown to more accurately stage unresectable tumors and avoid unnecessary thoracotomies [11,12]. Currently, the ACCP recommends EBUS-TBNA (sometimes used with EUS-TBNA) as the initial test of choice in suspected or confirmed patients with discrete mediastinal lymph node enlargement (without distant metastasis) with or without PET uptake. If negative, these needle techniques should be followed by surgical biopsy [11].

During mediastinal staging with EBUS-TBNA, a 7.5-MHz convex (sometimes called linear EBUS) ultrasound probe integrated into the distal tip of the bronchoscope delivers ultrasound waves in a linear fashion over about a 55-degree area. This technique allows for real time sampling of the TBNA sample through the working channel of the bronchoscope. The procedure can be performed under either moderate sedation or general anesthesia [13].

Importantly, the cytologic samples obtained by EBUS-TBNA supply adequate tissue specimens for molecular analysis of common targeted therapies used in the treatment of adenocarcinoma such as epidermal growth factor receptor (EGFR) somatic mutation or anaplastic lymphoma kinase (ALK) mutation. In the age of growing customized treatment and immunotherapy in patients with lung cancer, EBUS-TBNA will continue to play a vital role in the treatment planning for these patients [14].

Management of Malignant Pleural Effusion

Malignant pleural effusion is one of the most frequent causes of pleural effusion. Pleural involvement may be seen in up to 50% of patients with metastatic disease. Lung cancer, breast and ovarian cancer and lymphoma account for the majority of malignant pleural effusions. Lung cancer makes 30% of cases. Patients with malignant pleural effusion by definition have advanced disease and generally show median survival of 3 to 12 months [16]. Malignant pleural effusions are exudative effusions with evidence of malignant cells within the fluid by cytologic analysis [16-18].

Thoracic ultrasound has shown growing acceptance in the evaluation of pleural effusions due to its ability to quickly assess small pleural effusions in addition to identify processes that can radiographically mimic effusion such as consolidation. Importantly, thoracic ultrasound can detect pleural thickening or nodularity that may help point to the etiology of the pleural effusion [16-18].

The interventional pulmonologist can have an impactful role in the diagnosis and management of these complex patients. Medical thoracoscopy (sometimes called pleuroscopy), medical pleurodesis and placement of indwelling pleural catheters are all procedures undertaken by the interventional pulmonologist in the case of confirmed or suspected malignant pleural effusion [16-18]. Pleural fluid cytology has a mean sensitivity of about 72% when at least two pleural fluid specimens are collected. The diagnostic yield for closed pleural biopsy ranges from 38% to 47% and from 75% to 88% for image-guided closed biopsy. Thoracoscopic biopsy of the pleura carries the highest diagnostic yield, 95% to 97% [6].

Pleuroscopy is a procedure in which a small incision is made in the lateral chest wall through which an endoscope is passed. The procedure is done in an awake patient using moderate sedation and cardiopulmonary monitoring; often in an endoscopy suite (Figure 3). Indication for pleuroscopy is generally reserved for the evaluation and management of pleural effusion through inspection and biopsy of the parietal pleura; as opposed to VATS which allows for interventions including lung resection under general anesthesia in an operating room. Both rigid and semirigid thoracoscopes can be used during pleuroscopy with semirigid thoracoscopes having controls very similar to the flexible bronchoscope. The benefit to the patient, compared to more invasive VATS procedure, is smaller incision, lack of general anesthesia and faster recovery. Patients usually return home the same day after the procedure [16-18].

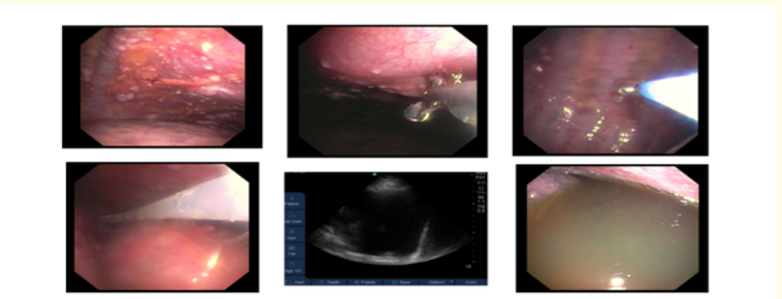

Figure 3: *Medical pleuroscopy with parietal pleural biopsy and tunneled pleural catheter placement. Top left image: View of the pleural space showing multiple nodules on the parietal pleura. Top center and right images: Forceps biopsy with direct visualization via pleuroscope. Bottom right image: View of the pleural space showing pleural fluid before complete drainage. Bottom center image: Ultrasound image of the pleural fluid before pleuroscopy. Bottom left image: View of the inserted pleural catheter at the end of the pleuroscopy.*

In addition to diagnostic use, pleuroscopy can be performed alongside two major therapeutic interventions for malignant pleural effusion; pleurodesis and indwelling catheter placement. Pleurodesis can be performed at the end of pleuroscopy after pleural fluid drainage and biopsy are undertaken. Talc poudrage or other chemical irritant is most often use during pleuroscopy causing pleuritis and obliteration of the pleural space. Mechanical methods of pleurodesis are better reserved for VATS given the technical aspects of the procedure [16-18].

Finally, placement of indwelling pleural catheters are also an option in the management of recurrent malignant pleural effusions, which can be placed either at the end of a pleuroscopy procedure or separately on an outpatient basis, especially in those with entrapped lung who would less likely benefit from pleurodesis. Indwelling pleural catheters allow for patients to return home and continue to drain pleural fluid intermittently. In addition, up to 45 - 70% of patients receiving an indwelling pleural catheter will have spontaneous pleurodesis. The decision to pursue pleurodesis versus indwelling pleural catheter depends on clinical factors as well as the technical experience of the provider [16].

Ultrasound Guided Biopsy of Pleural Based Tumors

When there is evidence of pleural thickening, pleural nodularity or masses, peripheral lung or chest wall masses on imaging, either CT or thoracic ultrasound, ultrasound guided pleural biopsy is another option for further investigation. Using a core needle or aspiration needle, samples can be obtained for histologic and immunohistochemical evaluation.

Benefits of ultrasound guided biopsy include real-time images, no radiation exposure, bedside availability, low cost, speed and ease of exam and doppler availability to check for vascular structures [15]. Image guided pleural biopsies can increase the sensitivity of pleural biopsy significantly, with CT guided biopsy more commonly described, while ultrasound guided pleural biopsy falls more under the purview of the interventional pulmonologist [16].

Using ultrasound guidance Halifax*., et al*. described a 94% (47 out of 50) success rate for adequate tissue sampling for histologic analysis of pleural tissue. In this series, results included both malignant and benign causes (including tuberculosis and sarcoidosis) of pleural effusion and pleural thickening [19]. Pleural biopsy, especially image guided, is another key tool in the interventional pulmonologist's armament for the diagnosis and management of pulmonary malignancies.

Management of Massive Hemoptysis

Hemoptysis is frequently encountered by the pulmonologist. Massive hemoptysis, occurring in 5 - 15% of cases and can be life threatening. Bronchogenic carcinoma has been reported to be the cause of massive hemoptysis between 4 to 35% of the time. Bleeding is often from the high pressure bronchial artery system and less often from pulmonary vascular system. The volume of blood to define massive hemoptysis is controversial but is commonly agreed on either ≥ 500 mL of expectorated blood over a 24-hour period or bleeding at a rate ≥ 100 mL/hour. The ability of the patient to protect airway, the presence of abnormal gas exchange and hemodynamic instability have significant clinical impact.

Initial management of massive hemoptysis starts with first identifying which lung is bleeding, then immediately turn the patient with bleeding side down. Protection of the airway is the next step and at the same time ensuring adequate respiratory and cardiovascular function. A multidisciplinary team with different skills are necessary and need to be assembled rapidly in the case of massive hemoptysis. The multidisciplinary team includes: Anesthesia, Interventional Pulmonary, Interventional Radiology, Thoracic Surgery, Extracorporeal Membrane Oxygenation (ECMO) team and Blood bank.

Bronchoscopy is an important early modality which works as both a diagnostic and therapeutic tool. Rigid bronchoscopy is used less often than flexible bronchoscopy in the initial diagnostic evaluation of massive hemoptysis because of needs for operating room and general anesthesia and limited ability to visualize the airways as far distally as in flexible bronchoscopy. However rigid bronchoscopy has advantages of greater suctioning capacity, superior overall visualization, preserving ventilation and safeguarding airway patency. It also allows for many different interventions to be undertaken due to the large lumen of the rigid bronchoscope [20]. A wider variety of interventions are available via rigid bronchoscopy, which is beneficial if a lesion is amenable to immediate treatment.

Control of hemoptysis can be undertaken by: blood product infusion, balloon tamponade via bronchoscopy, iced cold saline lavage, topical medications, laser therapy, electrocautery, argon plasma coagulation, and endobronchial stent placement. Surgical options are usually limited to local diseases after the massive bleeding is temporarily controlled. Ultimately the above interventions can stabilize the patient but are not always effective in stopping bleeding, in these cases bronchial artery embolization is the definitive intervention for uncontrolled massive hemoptysis if the source of bleeding is not from the major airways [20-23]. Figure 4 is an endoscopic image of a massive airway bleeding due to invasion of a non-small cell cancer of the left upper lobe into left main stem bronchus. The bleeding was controlled with use of APC and electrocautery.

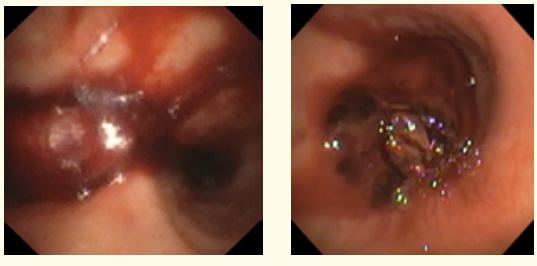

Figure 4: *(left) Massive airway bleeding from left main stem tumor.*
(right) Bleeding was controlled by use of argon plasma coagulation and electrocautery.

Conclusions

Interventional Pulmonology is a growing field within pulmonary medicine. Lung cancer continues to be a major cause of morbidity and mortality in the United States. Interventional pulmonologist plays a key role in the care of lung cancer patients. In this review, some of the diagnostic and therapeutic modalities utilized by the interventional pulmonologist for the diagnosis and treatment of lung malignancy have been summarized. These include diagnosis and staging of lung cancer, treatment of central airway obstruction, management of the complications due to cancer treatment, as well as management of malignant pleural effusion and pleural based disease. Relevant patient cases have also been reviewed. Advances in technology and procedural technique will continue to grow and with increasing number of IP trained pulmonologist this specialty continues to expand its impact on lung cancer care.

Conflict of Interest

No conflict of interest to report.

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