Chapter 1
Minimally Invasive Diagnostic and Therapeutic Management of Lung Cancer

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Abstract

Minimally invasive procedures allow for the diagnosis and treatment of lung cancer while reducing length of hospitalization and complications and palliating symptoms. The procedures described in this chapter are key components of a thoracic oncology program.

Introduction

Rapid advancements are being made in minimally invasive diagnostic and therapeutic procedures for lung cancer patients. This chapter provides an overview of advanced tools in interventional pulmonology that are currently available as well as their indications, limitations, and risks.

Advanced Diagnostic Techniques

Endobronchial Ultrasound

Linear or Convex probe endobronchial ultrasound transbronchial needle aspiration (EBUS-TBNA) has become the premier modality for minimally invasive sampling of mediastinal and hilar lymph nodes and masses. EBUS (Olympus BF-UC160F-0L8, Olympus FV-UC180F, or Pentax EB-170BK) allows real-time visualization of transbronchial nodal aspiration [1] whereby the needle can be seen within the target lesion (Figure 1). It uses a 21- or 22-G cytology needle [2,3]. It is acclaimed for its high sensitivity and specificity, ability to simultaneously...
diagnose and stage lung cancer even reaching hilar regions that mediastinoscopy cannot. It is cost effective compared with mediastinoscopy while maintaining a very low risk of complications [4,5,6]. Yields range from 85% to 96% which can be influenced by nodal size, type of cancer and bronchoscopist experience [1-3,5,7]. EBUS has been shown to have equivalent sensitivity and specificity to mediastinoscopy for lung cancer staging [4,6]. In the current era of personalized medicine for NSCLS, it is important to note that EBUS-TBNA had demonstrated high yields for detecting driver mutations such as EGFR (epidermal growth factor receptor, 90-98%) and ALK (anaplastic lymphoma kinase, 91-100%) [8-9]. Importantly, most of the studies involving EBUS-TBNA were performed at high volume centers, with experienced bronchoscopist and dedicated lung pathologists so there are likely to be local variations in yield.

Endoscopic ultrasound (EUS) offers additional nodal station beyond that reached by mediastinoscopy and EBUS. It can access American Thoracic Society stations 4 L, 5, 6, 7, 8, and 9 with yields as high as 98% [10] and a combined EUS/EBUS approach established definitive nodal staging in 96% of cases [11]. Figure 2 shows the lymph nodes accessible to EBUS, mediastinoscopy and EUS.

Radial EBUS (Olympus® UM-BS20-26R, 2.5mm diameter and Olympus UM-S20-20R, 1.4mm diameter) is a specialized ultrasound probe that fits down the channel of a bronchoscope. It enables visualization of lymph nodes or peripheral lesions. As the probe must be removed for sampling to occur, it is not real-time. Yields in lymph node sampling with this modality are 85% [13]. Yields with the ultrathin probe for peripheral lesions range from 77% to 86% [14,15]. It can also be used in conjunction with navigational bronchoscopy (see below).

**Figure 1:** Endobronchial ultrasound view of a lymph node (LN) with a transbronchial needle seen within the lymph node.

**Navigational Bronchoscopy**

Electromagnetic navigation bronchoscopy (ENB) enables bronchoscopists to sample peripheral lesions and lymph nodes, place gold fiducial markers to aid in stereotactic radiation, or perform pleural dye marking for surgic-
cal resection of tumors. A dedicated computed tomography (CT) scan with thin cuts and high overlap is analyzed by the computer software enabling 3-dimensional (3D) reconstruction (Super Dimension; Medtronic/Covidien or Lung Point; Veran). Using the 3D reconstruction of the patient’s airway tree the bronchoscopist can map a course to the target lesion (Figure 3).

Figure 2: Diagram of different nodes and which can be accessed by different diagnostic modalities. Mediastinoscopy=Green, EBUS=Green and Blue, EUS=Purple. A, Azygous vein, PA, Pulmonary artery, EO, Esophagus. Adapted from Yasufuku et al. Chest 2006 [12].

Figure 3: Navigational bronchoscopy three-dimensional airway tree created from reconstructed computed tomography scan. The green sphere represents the targeted lesion.

During the procedure, the patient is placed on an electromagnetic location board on the surface of the endoscopy bed or fluoroscopy table. A sensor probe (locatable guide or LG) is inserted within an extended working channel (EWC) through the operating channel of a therapeutic bronchoscope. The locatable board and the LG are connected to the computer tower. The software senses the LG in relationship to the patient’s reconstructed airway
and guides the broncoscopist to the predetermined target. The LG is then retracted and biopsies are performed through the EWC with forceps, brushes, or needles [16,17]. The use of fluoroscopy or peripheral radial probe EBUS can provide additional confirmation of lesion proximity [17]. Yields for ENB range from 63% to 80% [16-18]. Combining ENB with radial probe EBUS, achieved 88% yield in one study [19]. Molecular genetic yields for EGFR driver mutations have been reported at 93% [20]. Figure 4 shows a fluoroscopic view of ENB in process and the corresponding radial probe imaging with the lesion visible in real time.

**Figure 4:** Navigational bronchoscopy with a) Fluoroscopic visualization of the bronchoscope and biopsy tool through the external working channel after navigation to a right middle lobe lesion, and b) Radial probe visualization of the lesion after navigation.

In addition to its role as a diagnostic tool, ENB can be used to aid therapeutic procedures. Gold fiducial markers can be placed through the EWC and into or adjacent to tumors to facilitate stereotactic body radiosurgery [21,22]. Pleural dye marking can also be performed through the EWC to aid cardiothoracic surgeons in surgical resection of tumors [23]. The risks of EMN are similar to those incurred with standard bronchoscopy except for a slightly higher pneumothorax rate (2% to 8%) [16-19], which is still an advantage over transthoracic fine needle aspiration with a pneumothorax rate as high as 23-44% [16].

**Tumor Debulking**

Lung cancers are known to cause airway obstruction either from extrinsic compression from large masses or endoluminal tumor growth or a combination of both. Endobronchial tumors can cause dyspnea, hemoptysis, cough, and post-obstructive pneumonia. Proximal endobronchial tumors either 2cm from the main carina or within the trachea may render patients inoperable. Tumor destruction can relieve life-threatening obstruction until chemotherapy and/or radiation therapy is initiated. In cases were the patient has exhausted other treatment modalities, tumor destruction can offer symptom relief to improve dyspnea and cough and resolve hemoptysis. Modalities for tumor debulking (Table 1) involve destruction though coagulation (argon plasma coagulation or APC), vaporization (laser therapy), and mechanical debulking (rigid scope debulking, microdebrider). Often coagulation or vaporization to reduce potential bleeding is performed followed by tumor debulking. This technique provides immediate relief of airway obstruction [24]. Tumor debulking may be followed by stenting if the integrity of
the airway wall is compromised (see the Stents section for further discussion). Figure 5 shows an airway tumor before and after tumor debulking.

Table 1: Modalities to Treat Endobronchial Tumors [24,25,29].

<table>
<thead>
<tr>
<th>Modality</th>
<th>Description</th>
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<tbody>
<tr>
<td>Laser</td>
<td>Light amplification is used to vaporize tissue</td>
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<tr>
<td>Argon plasma</td>
<td>Argon plasma is sparked to coagulate tissue</td>
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<tr>
<td>Cryotherapy</td>
<td>Tissue is frozen with nitrous oxide causing apoptosis</td>
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<tr>
<td>Photodynamic therapy</td>
<td>Tissue sensitization followed by UV light tumor destruction</td>
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<tr>
<td>Brachytherapy</td>
<td>Endoluminal radiation therapy</td>
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UV, ultraviolet

Figure 5: Bronchoscopic images of an endobronchial tumor in the left mainstem a) before debulking, and b) after debulking where the left upper and lower lobes can be visualized.

Laser Therapy

The Nd:YAG laser (neodymium-yttrium-aluminum-garnet light amplification by stimulated emission of radiation) therapy vaporizes and coagulates tissue by both contact and noncontact probes. It penetrates 3 to 4mm with a wavelength of 1064 nm to destroy tissue. Caution is exercised when treating lesions involving the posterior airway wall due to risk of perforation [25]. Inspired oxygen levels (FiO2) must be maintained at or <40% to avoid airway fire. Further mechanical tumor debulking can be performed after laser vaporization. Several studies have described high success rates with relief of hemoptysis, high rate or recanalization and control of obstructive complications using laser therapy [26,27]. Contraindications to laser therapy include high oxygen requirements, bronchoesophageal fistula, and coagulopathy. Procedural risks include airway fire, bleeding, perforation and fistula formation [24].

Argon Plasma Coagulation

Argon plasma coagulation uses the release of an argon gas jet (plasma) that is sparked to cause tissue coagulation. Argon flow can be adjusted from 0.3 to 2L/min and is sparked by an applied power of 10 to 80 Watts. APC is a superficial modality compared with Nd:YAG laser therapy which may be preferable if blood vessels are in close proximity. Also, APC can maneuver around airway bends suggesting an advantage in treating branching airway segments compared with laser therapy which is a linear de-
livery system. Morice et al. [28] describe 57 patients with malignancy undergoing APC debulking and recanulization who had 100% resolution of their hemoptysis. They achieved 99% symptomatic improvement with no procedural complications. Similar to laser therapy, FiO2 must be maintained at <40% to avoid airway fire. Other rare risks include perforation, fistula formation, and gas emboli. As with laser, tumor debulking can occur following coagulation and necrosis [24].

Rigid Bronchoscopy

The rigid bronchoscope is a hollow, stainless steel cylinder. Diameters for rigid barrels range from 9 to 14 mm and the bronchoscopist can choose the shorter tracheal barrel or longer bronchial barrel. One end is beveled for tumor debulking and the other contains connection ports for jet ventilation. This open ventilation system creates a lower risk of airway fire during APC or laser compared with the closed system of an endobronchial tube with flexible bronchoscopy, however it can increase the risk of barotrauma as minute ventilation cannot be accurately measured. Large forceps can be used for tumor debulking or the bevel of the rigid scope itself can be used to core out tumor. The rigid bronchoscope can accommodate large forceps, laser, argon plasma or cryoprobe. Simultaneously a large suction catheter can fit into a separate port to manage any associated bleeding. Risks of rigid bronchoscopy include dental trauma, damage to the oropharynx, laryngeal edema, posterior wall perforation, and pneumothorax. In addition, the anesthesiologist cannot obtain accurate end-tidal CO2 giving the additional risk of hypercarbia [29].

Therapeutic Modalities With Curative Intent

Early stage endobronchial lesions without nodal involvement (i.e., carcinoma in situ and microinvasive squamous cell cancer) are targets for curative bronchoscopic modalities. Cryotherapy, APC, brachytherapy, and photodynamic therapy (PDT) (Table 1) can all be used with curative intent in the appropriate setting [24,30].

Cryotherapy

Unlike argon plasma and laser, cryotherapy does not pose a threat when patients have high oxygen requirements. Cryotherapy uses nitrous oxide to freeze and crystallize cells to induce apoptosis. It can be performed through a flexible or rigid bronchoscope. For tumor destruction, a freeze-thaw-freeze-thaw-freeze-thaw cycle (30 to 60 seconds of each freeze and each thaw) is performed as the tumor surface is coated. The induced apoptosis results in necrotic tissue which will slough over the following week. Repeat bronchoscopy in 7 to 10 days can remove residual sloughing, necrotic tumor if needed. Cryotherapy can be used for curative intent in carcinoma in situ as well as palliation of tracheobronchial neoplasms [29,30]. Risks include fever, hemoptysis, fistulas and bronchospasm [31].
Photodynamic Therapy

Photodynamic therapy (PDT) provides slower tumor destruction with a low risk of perforation or bleeding. It can be used for symptomatic relief or curative intent. It is most effective for small lesions of <10 mm in length and can be performed in conjunction with debulking modalities, radiation and chemotherapy. If tumor debulking is also needed, this should occur before PDT to reduce necrotic debris from sloughing and causing obstruction [31,32].

PDT involves IV administration of a photosensitizer (most commonly Porfimer sodium [Photofrin; Sanofi Pharmaceuticals, New York, NY]) followed in two to three days by bronchoscopy and intraluminal ultraviolet light exposure at a wavelength of 630 nm. Tumor cells (as well as liver, spleen and skin) preferentially retain the photosensitizer. When exposed to UV light, it is excited and generates free radicals that destroy the tumor cells. Necrotic debris is removed in 24 to 48 hours via a repeat bronchoscopy. During this procedure, repeat laser exposure can be performed if there is residual tumor [31,32].

PDT effectiveness is reported as high as 85% [33]. It can cause transient liver dysfunction (1.9%), allergic reactions (7.7%) and other pulmonary complications (7.7%)—dyspnea, fever and obstructing pneumonitis. Due to the risk of sun burn following the photosensitizer, patients should avoid sun exposure for 4 to 6 weeks [32].

Endobronchial Brachytherapy

Brachytherapy for lung cancer can be for palliative or curative intent. Palliative intent usually follows debulking of tumor in a mainstem that cannot be resected due to its proximity to the main carina or due to the patient’s performance status. Curative intent usually follows postsurgical resection with positive margins. Brachytherapy involves bronchoscopically placing a catheter into the airway segment with infiltrative tumor (Figure 4). The catheter is secured in place (either taped to the nose if performed with moderate sedation or taped to the endotracheal tube if performed with general anesthesia). Radiation Oncology can then place radioactive seeds (Iridium-192) into the catheter and local radiation therapy is performed. It may take up to 3 weeks for the full effect for radiation-induced DNA alterations to result in apoptosis [31]. For this reason, obstructive tumors need to undergo debulking prior to consideration for brachytherapy.

Brachytherapy has been successful in up to 85% [31] of patients with improvements in dyspnea, cough, hemoptysis, and post-obstructive pneumonia [34]. Complications include bleeding, fistulas, arrhythmias, bronchospasm, radiation pneumonitis and stenosis. Fatal hemoptysis occurs at a rate of 0% to 32% and has been attributed to radiation damage of airway integrity and/or tumor ingrowth into adjacent vascular structures [31].
Airway Stents

Airway stents have been employed for use in lung cancer patients for many decades. They may be placed when endoluminal tumor compromises the structure of the airway wall especially following tumor debulking. Stents can be placed in the trachea, left mainstem, right mainstem, bronchus intermedius, and they come in varying lengths and diameters to accommodate these different locations. The bronchoscopist must have training in stent placement, type and size determination and clinical decision making to determine true benefit [25,29].

The main types of airway stents are silicone (Dumon; Novatech), polymer (Polyflex; Boston Scientific), metal stents (Ultraflex; Boston Scientific) and hybrid stents (Aero; Merit Medical Endotek). The Dumon stent is studded to help prevent migration and comes in straight, L-shaped and Y-shaped designs that can be cut to accommodate airway length. It requires placement and removal under rigid bronchoscopy with general anesthesia. The Polyflex stent is a polyester mesh covered in silicone. Silicone and polymer stents are prone to migration and may also cause granulation tissue accumulation or mucus obstruction. The Dynamic Y-stent is a silicone-steel hybrid that extends from the trachea to the mainstems and is designed for obstructions proximal to or involving the carina, especially tracheoesophageal fistulas [24,25,29].

Modern metal stents consist of self-expanding metal (nitinol) and are covered by a thin polymer membrane (Ultraflex [covered and uncovered designs]; Boston Scientific, and Aero; Merit Medical Systems). They can be placed with flexible bronchoscopy under moderate sedation or general anesthesia. Complications include mucus obstruction, stent migration or fracture and granulation tissue accumulation causing airway stenosis or occlusion [25]. Figure 6 shows an Aero stent deployed in a mainstem bronchus.

Multiple studies have published the utility of stent placement, especially following tumor destruction. They have achieved resolution of the obstruction, improvement in dyspnea and improvement in quality of life [35,36].

Pleural Disease

Malignant pleural effusions (MPEs) carry a poor prognosis and lung cancer is one of the types of MPE with a shorter anticipated survival (ranges 3 to 12 months). Other predictors of truncated survival with MPE are poor performance status and with low pleural fluid glucose and pH [37].

Pleuroscopy

Pleuroscopy allows for visualization of the pleural cavity using a semirigid endoscope (Olympus LFT-160) introduced inside the thoracic cavity through the intercostal space. The procedure can be performed under local or general anesthesia. The instrument has an outer diameter of 7 mm and a 2.8-mm working channel which can be used for introducing instruments to sample the parietal
pleura. Pleuroscopy is usually indicated for undiagnosed pleural effusion with yields for malignancy as high as 90% [38]. During the procedure, the pleura may be visualized and biopsies can be taken from suspicious areas. Complications include empyema, persistent pneumothorax, pleurocutaneous fistula, subcutaneous emphysema, hemorrhage, reexpansion pulmonary edema, and malignant invasion of scar [38-41]. After the procedure, a chest tube is placed to allow the lung to re-expand. In addition, pleuroscopy may be used therapeutically to perform pleurodesis for symptomatic, recurrent malignant effusions[41]. In a Cochrane Review, thorascopic talc pleurodesis was superior to chest tube-guided talc insufflation with relative risk of nonrecurrence of effusion being 1.68 (95% confidence interval, 1.35-2.10) [39].

**Tunneled Pleural Catheters**

Tunneled pleural catheters (TPCs) offer an alternative to surgical intervention in select patient cohorts. They can be placed for recurrent, symptomatic effusion in a) patients who need therapeutic relief until chemotherapy can be provided and hopefully help resolve the effusion, or b) patients who have had chemotherapy and the effusion persists and they cannot undergo talc pleurodesis due to trapped lung or poor performance status [42].

Two companies currently market the TPCs: Care Fusion (PleurX) and Bard Access Systems (Aspira). The fenestrated ends allow for drainage while the tunneled portion is designed to reduce risk of infection and dislodgement. The one-way valve at the distal end seals the catheter when not in use. The procedure can be performed as an out patient with local anesthesia and under ultrasound guidance [42].

Approximately 2 weeks after insertion, sutures are removed. Pleural catheters can be drained aggressively daily in hopes of autopleurodesis or sporadically based on patient symptoms. The choice should be based on patient preference. Aggressive daily drainage might be difficult depending upon the availability of caretakers and daily tape changes may cause local skin irritation. When the fluid is 50 mL or less for 3 consecutive drainages and chest x-ray (or ultrasound) confirms resolution of the pleural effusion, then the catheter can be removed [42].

TPCs are highly successful at symptomatic relief (96% on one systematic review, n=1370 patients) [43]. Spontaneous pleurodesis may occur after which the catheter can be removed. Pleurodesis rate are variable: 12% to 58% [44]. The presence of trapped lung and absence of malignant cells on cytology make auto-pleurodesis less likely [4-46]. A randomized trial of 147 patients with malignant pleural effusion compared TPCs to talc pleurodesis. TPCs were as effective as talc pleurodesis in relieving symptoms while eliminating the need for hospitalization (TPC length of stay 0 days vs 4 days for talc pleurodesis) [45]. In addition, TPCscan achieve significant quality of life improvement in patients with trapped lung [46].

More recently, a pilot study of 30 patients with MPE
performed medical thoracoscopy with concurrent TPC placement and talc poudrage. Successful pleurodesis occurred in 92% with a median hospital stay of just 1.8 days. All patients had symptomatic improvement. Complications occurred in 13% (2 fever, 1 TPC replacement needed, 1 empyema) [47]. This combined approach provides a high pleurodesis rate with rapid hospital discharge while eliminating the need for ongoing drainage and management of TPC. Further comparative studies are needed.

Infection can occur in the form of cellulitis or empyema (as high as 15%) [42]. The former can be treated with outpatient antibiotics where as the later may require inpatient monitoring. Empyema can be diagnosed through symptoms (fever and change in fluid appearance), laboratory values (leukocytosis) and imaging as well as culturing fluid from the catheter [48]. The most likely organism is staphylococcus aureus and initial antibiotics should cover this species according to local susceptibilities. If empyema occurs, the patient should be evaluated for possible pleurodesis as it is more likely in this setting (62% in one study) [48]. If this has occurred, the catheter should be removed near the end of the antibiotic course when the pleural space is likely sterile [48].

Other complications include tumor seeding, pneumothorax (1%), occluded catheters or loculated effusions (7%) and catheter fracture upon removal [42]. Tumor seeding along the catheter occurs around 2% of the time and can be treated with local radiation [49]. There has been one case report of bronchopleural fistula [50]. Occluded catheters may require simple flushing or intracatheter dwell of tPA (tissue plasminogen activator) where as intrapleural fibrinolytics may be tried for loculated effusions. This requires a one hour dwell of tPA and DNAase (dornase alpha) in the pleural space followed by drainage and overnight observation [42]. Further studies are needed to discern the most effective treatment for loculations in the setting of TPCs.

**Conclusion**

Interventional Pulmonology has become an integral component in the diagnosis, staging and management of lung cancer. Minimally invasive techniques can offer lower risk diagnostic approaches as well as palliative and even curative intent therapies for malignancies. Knowledge of the indications, technique and outcomes of these procedures can facilitate Oncologists, Radiation Oncologists, Thoracic Surgeons and Pulmonologists referral of patients for minimally invasive procedures.
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