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Several endoscopic or bronchoscopic interventions that are less invasive and better tolerated than traditional therapy may be applicable to treat early-stage lung cancer.

Endoscopic Treatment of Early-Stage Lung Cancer

Francis D. Sheski, MD, and Praveen N. Mathur, MBBS

Background: Disease-free survival after surgical resection of lung carcinoma *in situ* has been reported as over 90%. After resection of stage IA non-small cell lung cancer, survival at 5 years is approximately 60% to 70%. If endoscopic or bronchoscopic treatments of early-stage lung cancer can provide similar disease-free survival with less perioperative mortality, morbidity, and cost, then they may be alternative front-line therapies.

Methods: The authors review early-stage lung cancer detection by fluorescence bronchoscopy and the potential treatment of this disease by endoscopic techniques (photodynamic therapy, brachytherapy, Nd:YAG laser, electrocautery, and cryotherapy).

Results: Several reports have noted improved outcomes using endoscopic therapies for early-stage lung cancer, but insufficient data preclude firm conclusions regarding the role of fluorescence bronchoscopy, endobronchial brachytherapy, or electrocautery in early-stage lung cancer. Other than resection, photodynamic therapy may represent the best approach at this time. The principal indication for laser bronchoscopy is palliation of central airway obstruction.

Conclusions: The identification of early-stage lung cancer provides no advantage if we have little to offer the patient short of traditional therapy. The value of newer treatment techniques and methods requires verification.

From the Division of Pulmonary, Allergy, Critical Care, and Occupational Medicine at the Indiana University School of Medicine, Indianapolis, Ind.

Address reprint requests to Praveen N. Mathur, MBBS, Department of Medicine, Indiana University School of Medicine, 1001 West 10th Street, OPW 425, Indianapolis, IN 46202.

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Introduction

Determining the optimal treatment regimen for lung cancer depends on several factors, including cell type (small cell lung cancer [SCLC] vs non-small cell lung cancer [NSCLC]), stage, and patient performance status. Curative treatment is the main goal; however, most lung cancer patients present with advanced-stage

disease, where cure will occur in only a few. For SCLC, chemotherapy is front-line therapy. For stage I or II NSCLC, surgical resection is standard therapy, if the patient can tolerate surgery. Treatment of stage III or IV patients may involve one or more modalities (surgery, chemotherapy, and radiation). This article describes several endoscopic (or bronchoscopic) interventions available to treat early-stage NSCLC, with the intent of cure.

We define early-stage NSCLC as usually lung carcinoma in situ (CIS) — Tis N0 M0, stage 0 in the International System for Staging Lung Cancer, or microinvasive carcinoma.¹ The Armed Forces Institute of Pathology definition of CIS includes malignant cellular changes in the full thickness of the mucosa but an intact basement membrane (Fig 1).² CIS is usually squamous cell carcinoma. Microinvasive carcinoma is described as a few millimeters of bronchial invasion but not involving the muscle or cartilage. Perhaps this is truly stage IA. Whether stage IA NSCLC (but probably not IB) should be included in the early-stage definition is debatable.

The rationale for treating CIS is based on the assumption that it will progress to invasive carcinoma and thus treatment at this stage will yield a higher cure rate. The time frame for this progression may span 2 to 10 years, but whether all CIS will progress is unknown.³ Several investigators have reported that individuals with sputum atypia or dysplasia may develop lung cancer at a rate of 4% to 83% over a period of 5 to 10 years, depending on the severity of the cellular change.⁴ Thus, it may be reasonable to treat dysplasia as well, especially if these changes do not normalize after quit-

ting smoking. Since the endoscopic treatments penetrate the airway wall to a limited and unpredictable degree, the extent of cancer invasion will limit the effectiveness of these modalities. Cortese and Edell⁵ reported a 7.7% incidence of N1 (nodal) involvement when invasion up to the full thickness of the bronchial wall (5 mm) occurred. Nodal disease is not treatable by current endoscopic modalities.

Even if optimal treatments were available for cellular dysplasia, CIS, or microinvasive carcinoma, a major obstacle is early detection. Patients with these disease stages are usually asymptomatic and radiographically quiescent. Screening patients with sputum cytology continues to generate debate. Regarding radiographically occult lung cancer, Woolner and colleagues⁶ reported a CIS incidence of approximately 34%, while Nagamoto et al⁷ reported approximately 13%. CIS has been reported to occur concomitantly with a more advanced lung cancer in about 15% of cases.⁸ Dysplasia or CIS often produces no visible mucosal abnormalities on conventional bronchoscopy. These findings are often subtle, such as erythema or thickened or granular mucosa. The inability of conventional bronchoscopy to consistently detect early-stage lung cancer has led to the development of fluorescence bronchoscopy in an effort to improve early detection.

Prior to the development of bronchoscopic interventions for early-stage disease, surgical resection was the only treatment. Nagamoto et al⁷ reported on resection in 19 lung CIS cases — 18 lobectomies and 1 wedge resection. When followed over 4 to 113 months, 15

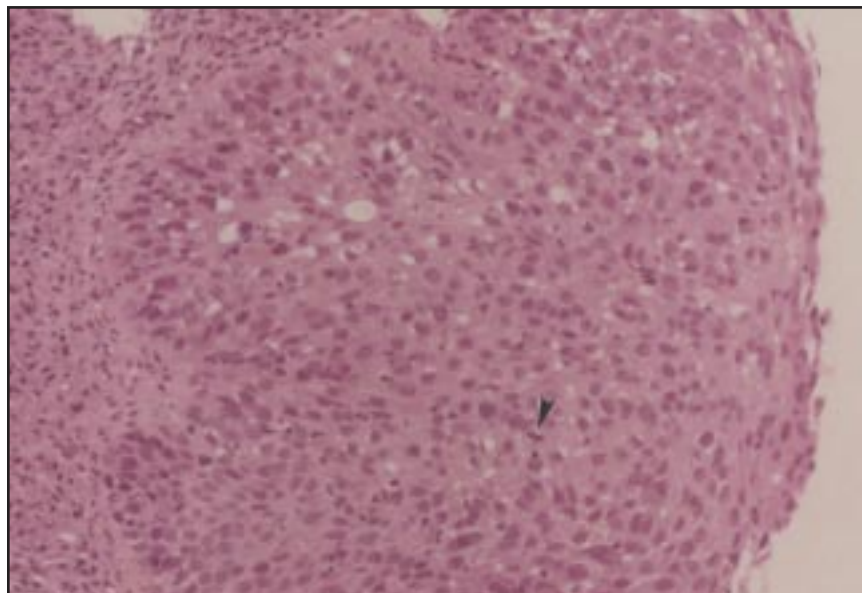


Fig 1. — Sections show a portion of bronchus. The respiratory epithelium has been replaced by squamous epithelium. The epithelium fails to mature. This is characterized by cytologic atypia extending from the intact basement membrane to the surface. Mitotic figures are present near the surface (arrow). There is chronic inflammation in the stroma below the epithelium.

patients were alive and disease-free, 2 died of unrelated causes, 1 died of an unknown cause, and 1 developed a more invasive lung cancer. Similarly, Ishida and colleagues⁹ reported that only 1 of 11 lung CIS resections developed a more advanced lung cancer, with follow-up ranging from 7 to 152 months; 2 patients died of unrelated causes and 1 died of pulmonary fibrosis. Woolner et al¹⁰ noted only 3 of 28 patients who underwent resection for lung CIS or microinvasive disease developed lung cancer. Perhaps the fact that no controlled trials comparing resection to any of the various bronchoscopic modalities have been reported means that using disease-free survival after resection as the standard to which the bronchoscopic data are compared is a suboptimal comparison at best.

Fluorescence Bronchoscopy

Fluorescence bronchoscopy is based on the fact that normal tissue fluoresces differently than abnormal tissue when exposed to an appropriate wavelength of light and that this difference can be detected. In early investigations, a patient was injected with a photosensitizer such as hematoporphyrin derivative (HpD) or dihematoporphyrin ether/ester (DHE), which preferentially concentrates in malignant tissue and causes it to appear red when excited by violet light.^{11,12} At bronchoscopy, the airway was illuminated with a violet light and a special system analyzed the emitted light. Palcic and colleagues,¹³ working with Xillix Technologies Corp in Vancouver, BC, later developed autofluorescence bronchoscopy, which does not require the photosensitizer. The Lung Imaging Fluorescence Endoscope (LIFE) involves the use of a flexible bronchoscopy, a helium-cadmium laser (442 nm wavelength), two image-intensified charge-coupled device cameras with green and red band-pass filters, a computer with an imaging board, and a color monitor. The emitted light is processed and displayed in real time, allowing biopsy under direct visualization. Abnormal tissue is displayed as brown or brown-red (Fig 2). Stepp et al¹⁴ worked in collaboration with Karl Storz of Germany on a system with the optical filters built into the bronchoscope. The use of inhaled 5-amino-levulinic acid to enhance fluorescence with this system is under study.¹⁵

In an early comparison of the LIFE unit with conventional bronchoscopy, Lam and associates¹⁶ performed biopsies on 53 patients with known or suspected carcinoma and on 41 volunteers not known to have cancer. They reported 72.5% sensitivity and 94% specificity in detecting moderate to severe dysplasia and CIS with the LIFE system compared with 48.4% sensitivity and the same specificity while using conventional bronchoscopy. A subsequent multicenter trial¹⁷ was conducted to determine if autofluorescence bronchoscopy as an adjunct improved the ability to localize intraepithelial neoplasia (defined as moderate/severe dysplasia or CIS) over routine bronchoscopy. The investigators examined 173 patients with known or suspected lung cancer with conventional white-light bronchoscopy followed by auto-

fluorescence bronchoscopy. Of the 142 biopsies that were moderate dysplasia or worse, routine bronchoscopy identified 35 (25%), while adding autofluorescence bronchoscopy detected 95 (67%). Forty-seven were considered to be false-negative findings. Of the moderate/severe dysplasia and CIS lesions, 9 (8.8%) were found on routine bronchoscopy while 57 (55.5%) were found after adding autofluorescence examination. Autofluorescence also increased the identification of invasive carcinoma compared with routine inspection (26 [65%] of 40 without autofluorescence, 38 [95%] with autofluorescence). However, to determine the utility of the LIFE system for detecting lung metaplasia or dysplasia, Kurie and colleagues¹⁸ reported their findings involving 53 patients, 39 of whom underwent both conventional and LIFE bronchoscopy. They reported a similar detection rate (24%) on biopsy between abnormal and normal areas by autofluorescence and no improvement in detection over those who had only conventional bronchoscopy. No carcinomatous changes were found. The LIFE system may be adequate to detect severe tissue abnormalities, which were not prevalent in this population.

The role of autofluorescence bronchoscopy has yet to be clearly defined. False-positive findings, which may be caused by airway trauma or inflammation, may be less of a concern than false-negative findings. The patient population best served by this technique has yet to be determined. Are these heavy smokers with or without airflow obstruction? Are their markers in the collected sputum? Will health care systems cover the associated costs? The initial data are intriguing, but several issues are yet to be resolved.

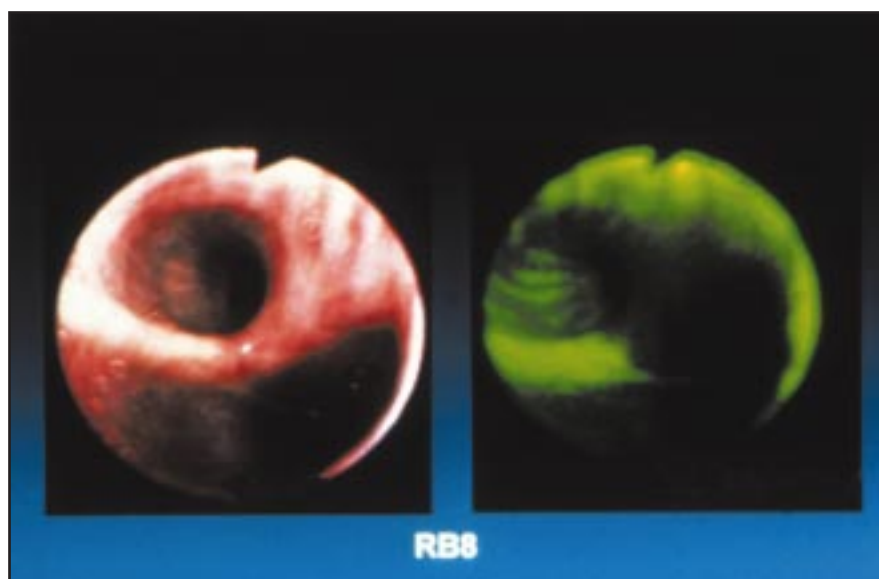


Fig 2. — The right lower lobe with carcinoma in situ seen with white light and autofluorescence bronchoscopy. Abnormal tissue is displayed as brown or brown-red. Courtesy of Michael Unger, MD, FACP, FCCP, of the Fox Chase Cancer Center, Philadelphia, Pa.

Photodynamic Therapy

In the 1960s and 1970s, several investigators reported using photodynamic therapy (PDT) to treat cutaneous manifestations of metastatic breast cancer. Dougherty¹⁹ developed PDT and its scientific basis using a rodent model. In 1982, Hayata et al²⁰ published the first report of PDT to treat a patient with early-stage lung cancer. The patient died of an unrelated cause 4 years later and was disease-free at that time. Since then, many investigations have used PDT to treat various stages of NSCLC and other cancers with endobronchial metastases.

Photodynamic therapy involves the preferential retention of a photosensitizer by malignant or premalignant tissue, followed by the use of light to excite the sensitizer such that it interacts with oxygen to generate cytotoxins, and then the preferential destruction of abnormal tissue. The use of photochemical reactions to affect biologic systems dates back to 1900. The biologic mechanism involves the transfer of energy from the excited photosensitizer to oxygen, producing singlet oxygen, which then causes cell damage by oxidation. Also, vascular congestion and red-cell extravasation shortly after light exposure have been demonstrated in the tissue.^{19,21} These may contribute to cell death by eliminating the tumor blood supply and possibly by producing local inflammatory mediators. Cytotoxicity and tissue slough occur over a few days. At the time of treatment, the mucosa seldom shows any changes following light exposure. Since light is necessary to excite the photosensitizer, the depth of light penetration through the tissue is an important factor in the effectiveness of PDT. The actual depth is unpredictable but is suspected to be no more than 1 cm and probably less than 0.5 cm. This factor may limit the use of PDT to local, more superficial disease.

HpD (2 to 5 mg/kg) and DHE (2 mg/kg) are the most common photosensitizers currently in use. Administering parentally to the patient approximately 48 hours before light exposure allows normal tissue washout to occur, thus leaving the tumor with the retained chemical. Tumor may retain the photosensitizer for 5 to 7 days, allowing a second treatment a few days after the initial treatment. Usually 2 days after receiving the photosensitizer, the patient undergoes bronchoscopy for light exposure. A quartz fiber inserted through the working channel of the bronchoscope illuminates the involved airway with a red light (630 nm) from argon, excimer, or a potassium titanyl phosphate (KTP) laser. This wavelength allows optimal tissue penetration and photosensitizer activation. At the tip of the fiber is usually a cylindrical diffuser that varies in length from 0.5 to 2.5 cm from which the light

is emitted in 360 degrees. The diffuser is placed into or next to the tumor. Light dosages have ranged from 20 to 600 J/cm², and power at the tip has ranged from 20 to 800 mW, although settings of 200 to 400 J/cm² and 200 to 300 mW, respectively, are usually sufficient for endobronchial treatment.²¹ Exposure times range from 5 to 30 minutes. Optimum settings have not been determined. Depending on the amount of tissue destruction, "clean-up" bronchoscopy may be required in the ensuing days to remove slough that can cause airway obstruction and respiratory distress. Since any residual tumor will still retain usable photosensitizer, a repeat treatment may be performed a couple of days from the initial one. Successfully treated mucosa usually appears normal in 4 to 6 weeks. The number of treatments a patient can undergo is unknown.

The most common side effect is skin sensitivity (sunburn) from the effect of sun or ultraviolet light with the photosensitizer. For 4 to 6 weeks after the injection, the patient follows a protocol to limit photosensitivity. Slough and secretions can cause respiratory distress or can lead to pneumonia. Hemoptysis, sometimes fatal, has been reported.²²

As already noted, PDT has also been used in advanced-stage lung and other metastatic cancers, primarily in a palliative role. No reports of PDT as a treatment for lung dysplasia appear in the literature. As an initial step in treating dysplasia, the patient should avoid any respiratory irritant or possible carcinogen; tobacco smoke is likely the most common agent. If the dysplasia persists, then PDT may be a legitimate option since dysplasia is an epithelial process that is within reach of PDT. Currently, the degree of dysplasia that should be treated and when to initiate treatment are unknown.

In 1984, Hayata and colleagues²³ reported the use of PDT in 13 patients with early-stage lung cancer and in 8 patients with stage I lung cancer. Patients either refused other treatment options or were not candidates. Whether these early-stage lung cancers were CIS or invasive was not described. Of the 13 patients with early-stage lung cancer, 8 underwent only PDT and were disease-free over a period of 13 to 41 months. The remaining 5 underwent surgery following PDT because it was believed that PDT incompletely treated the tumor. All were alive and disease-free over a period of 7 to 30 months. Results of treatment of stage I disease were less dramatic. In 1987, Edell and Cortese²⁴ reported using PDT to treat 40 lesions in 38 patients who failed or rejected other therapy or were not candidates for other therapy. Twenty-five lesions were occult cancers initially detected by sputum analysis. Fourteen of these cancers (in 13 patients) following

one or two PDT sessions were thought to be successfully treated. Over 3 to 53 months of follow-up, 3 patients had a recurrence (2 died of lung cancer), 4 died of a second cancer but with no evidence of recurrence, and 1 died of an unrelated cause. In the responders, the tumor surface area was believed to be less than 3 cm². Specific pathology (eg, CIS, invasion) on the biopsy was not reported. In 1990, Monnier et al²⁵ described treating 16 NSCLC patients with PDT — 4 with CIS, 10 with microinvasive carcinoma, and 2 with submucosal invasion. Two recurrences, 1 in both groups, occurred over 3 to 60 months of follow-up. Imamura²⁶ reported on 29 patients with 39 occult NSCLC. PDT alone was used in 25 lesions; in the remaining 14, PDT was followed by external beam radiation or surgery. McCaughan and Williams²⁷ described the use of PDT in the different stages of NSCLC, including 3 patients with CIS and 16 with clinical stage I disease. All 3 patients with CIS were alive and disease-free at 8, 74, and 121 months. Of the 16 patients with stage I disease, 11 were alive and disease-free with a median survival of 29 months, and 5 died (2 of lung cancer and 3 of unrelated causes). In a report by Cortese et al²⁸ in which PDT was used to treat 21 patients with 23 early-stage NSCLC, only 11 patients were disease-free after 12 months. Ten of the 21 patients eventually underwent surgery, including 2 of these 11, after each developed a new primary NSCLC. Nine patients avoided surgery, with a follow-up of 24 to 116 months. Of note, 3 patients who underwent surgery were found to have N1 disease. Whether the initial lesions were dysplasia, CIS, or invasive carcinoma was not reported.

In summary, PDT appears to be effective in cases where the lung cancer is relatively noninvasive, is limited in surface area, is not bulky, and can be accessed by the diffuser. Lung dysplasia, CIS, and perhaps microinvasive carcinoma meet these criteria. Since tissue penetration by the laser light is probably limited to less than 1-cm tumors, these stages can be affected. The power, energy, and exposure times varied among studies and probably affected results, although to what degree is difficult to assess. Whether PDT should precede or replace surgery as first-line therapy is yet to be determined. No comparative studies have been reported; the difficulty in conducting such a study has been addressed by Cortese and colleagues.²⁸ This point also applies to other alternative therapies. PDT is clearly an option in a non-operative candidate.

The above reports note the synchronous and metachronous nature of lung cancer and of aerodigestive tract cancers in general. Surgical options may be limited in these patients, and PDT may have a role. PDT is associated with few side effects, the most common being sunburn, which is avoidable.

Endobronchial Brachytherapy

The initial application of endobronchial brachytherapy (EB) required instillation of the radioactive source directly into the tumor. Henschke and colleagues²⁹ introduced modern afterloading techniques in the 1960s, but it took almost another 2 decades to describe the use of the plastic catheter with the flexible bronchoscope.³⁰ The use of iridium-192 (¹⁹²Ir) as the radioactive source occurred at approximately the same time. Initial delivery modes consisted of low- and intermediate-dose rate brachytherapy, but high-dose rate (HDR) brachytherapy, described in the 1980s, is now the usual mode. HDR brachytherapy involves delivering 3 to 10 Gy/fraction over minutes and repeating this fraction every 1 to 2 weeks for 2 to 4 sessions. EB has been used primarily to palliate symptoms such as hemoptysis, cough, and dyspnea that are caused by endobronchial malignancy. For patients with NSCLC, EB is frequently used in those who either are not candidates for or have failed other therapy, such as surgery or external beam radiation.

The goals of EB are to deliver therapeutic irradiation to the tumor and to minimize normal airway injury. The irradiation effect declines from the source in an inverse proportion to the radius of the airway lumen. Although this limits the area to be treated, it also reduces toxicity. A current approach involves using a flexible bronchoscopy to place a polyethylene catheter adjacent to and beyond the malignancy so the irradiation can be delivered close to the tumor. Thus, complete airway obstruction cannot be present. Under bronchoscopic and fluoroscopic guidance, a catheter with a guidewire is placed beyond the involved airway. The bronchoscope and guidewire are then removed, leaving the catheter in place. A radiopaque “dummy” insert with marker pellets is placed into the catheter. This is fastened externally to the patient after proper placement is confirmed fluoroscopically. Using radiographic and bronchoscopic visualization of the tumor load and location, the radiation oncologist determines the radiation dosing. The total dose and fractionation schedule varies from institution to institution, which complicates comparison of results.

Fig 3 shows the catheter with irradiation isobars. The dose is frequently described as 1 cm from the source. The procedure is conducted in a shielded room, and the radiation is delivered automatically by an afterloader to limit personnel exposure.

Two serious complications from EB are fatal hemoptysis and fistula formation. Fatal hemoptysis rates have been reported to be 0% to 42%.³¹ The explanation for this range may involve tumor infiltration of

the vessel wall, direct injury to the vasculature by irradiation and, with initially effective treatment, eventual further tumor growth with vessel involvement.³² Prior external beam radiation and involvement of the upper lobes near the pulmonary vessels may also be factors. Other later complications include radiation pneumonitis, bronchitis, and bronchial stenosis.

Studies of EB used with a curative intent in lung cancer usually include patients who were not candidates for surgery, those whose disease has recurred following surgery or external beam radiation, or those who had other therapy such as chemotherapy, laser, or cryotherapy. Few studies on EB are available that report the pathology as lung dysplasia, CIS, or microinvasive carcinoma. Most indicate that the tumor is limited endobronchially or is early-stage tumor. Sutedja and colleagues³³ described 2 patients with clinical stage I NSCLC treated with EB who were alive and tumor-free at 22 months and 54 months. Tredaniel et al³⁴ reported on 29 patients with localized endobronchial malignancy who underwent high-dose rate EB. Mean survival had not been reached after 23 months of follow-up. Four patients had recurrences, 1

patient died of pulmonary hemorrhage, and 2 died of respiratory compromise from severe bronchorrhea. In a review of 365 patients treated with EB, Macha and colleagues³² treated 19 patients for cure, but only 4 were without evidence of tumor. They also reported a 21% rate of fatal hemoptysis. In 1997, Perol et al³⁵ also treated 19 patients with EB for cure, 4 of whom had lung CIS. The follow-up period ranged from 7 to 49 months. Only 7 of the 19 patients were alive and disease-free, with a 1-year disease-free survival of 70%. Two patients died of hemoptysis. The details of the patients with CIS were not reported. Lastly, Nori et al³⁶ used EB with external beam radiation and reported no malignancy on biopsy in 10 of 32 patients, although when these biopsies were performed following treatment is unclear.

The role of EB in the treatment of lung dysplasia, CIS, or microinvasive carcinoma remains uncertain. Further study of patients with these pathologies is needed to define the role. However, the risks of EB — particularly fatal hemorrhage, fistula formation, bronchial stenosis, and radiation pneumonitis/bronchitis — may preclude these investigations as front-line

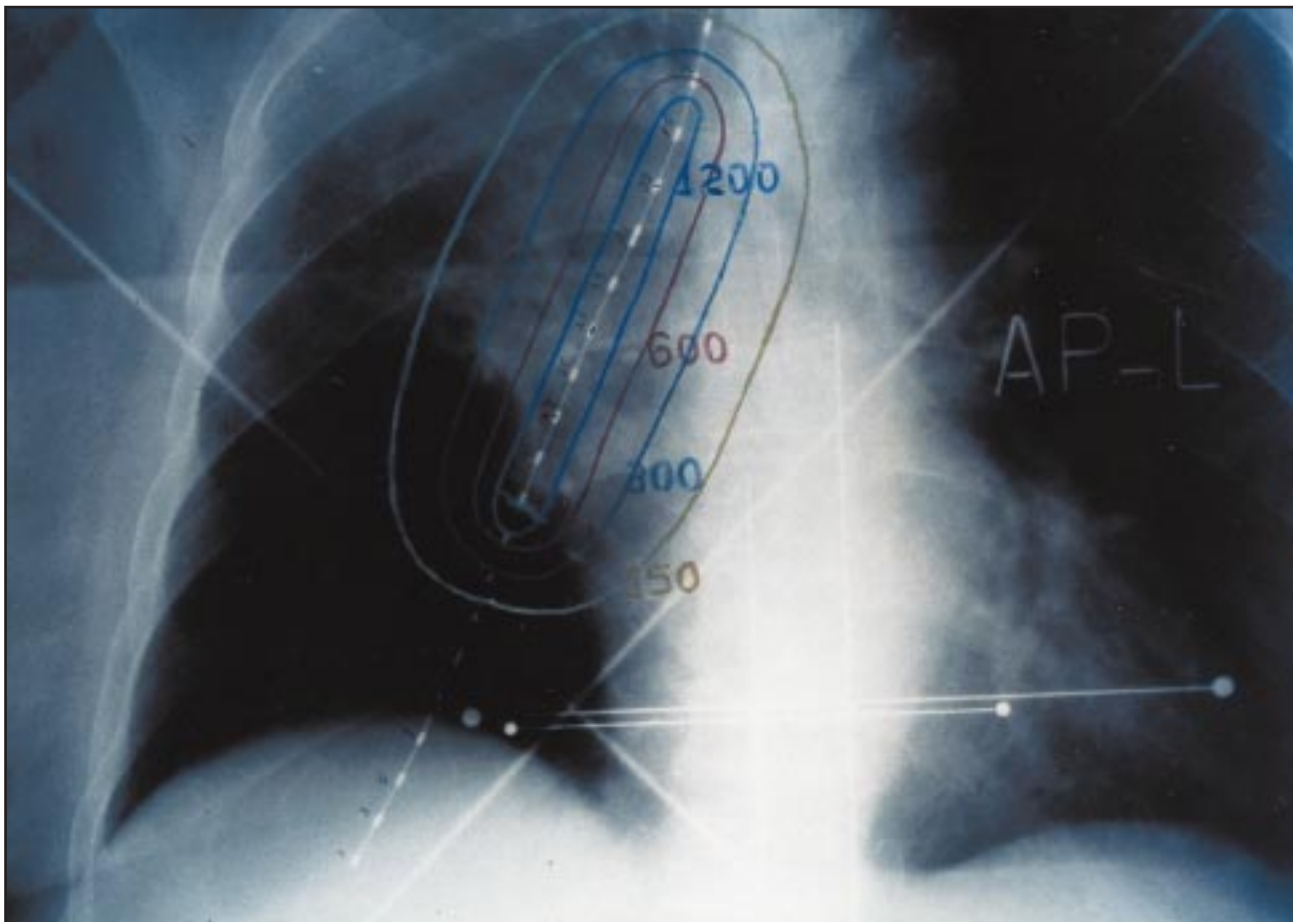


Fig 3. — Depicts the “beaded” brachycatheter and isobar irradiation field. From Sheski FD, Mathur PN. Cryotherapy, electrocautery, and brachytherapy. *Clin Chest Med.* 1999;20:123-138. Reprinted with permission.

therapy. Nonetheless, the above data in presumably more advanced lung malignancies suggest that EB could be curative in these less invasive states since the pathology should be well within the irradiation treatment field.

Laser Therapy

Light-amplified stimulated emission of radiation (LASER) has been used for several decades for airway disorders. The first treatment of an endobronchial malignancy is often accredited to Laforet and colleagues³⁷ who used laser to treat a tracheal lesion. Laser bronchoscopy with a neodymium yttrium aluminum garnet (Nd:YAG) laser delivers laser energy with a flexible quartz fiber. This laser is preferred for endobronchial disorders because it is compatible with either rigid or flexible bronchoscopy, provides deeper tissue penetration, has better hemostasis than CO₂ laser, and maintains good coagulation, cutting, and carbonization properties. Based on more than 20 years of experience with laser bronchoscopy, the primary indication for this technique is palliation of central airway obstruction by either primary or metastatic malignancies, although it has been used in other conditions as well.³⁸

Lasers use light energy that is transformed into heat as it reacts with tissue, allowing for tissue carbonization or cutting as well as for hemostasis. The ability of excited yttrium-garnet glass coated with neodymium to produce this quality light — a narrow band of wavelengths (monochromatic) that is minimally divergent (spatial coherence) and uniform in time and travel (temporal coherence) — has contributed to the success of this laser. The amount of energy delivered to the tissue is dependent on the power setting (watts), distance of the laser tip to the target, and duration of exposure. The depth of light penetration depends on the tissue and laser light properties and is affected by the power used during treatment. With the Nd:YAG laser, depth of tissue penetration may be up to 1 cm.

The Nd:YAG laser can be used with either rigid or flexible bronchoscopy. Adequate visualization of the target and adjacent structures is imperative for successful treatment with minimal complications. For most conditions, the tip of the laser should be within 1 cm of the target before firing the laser in half-second to 1-second pulses with the energy setting between 20 and 40 watts. Tissue can be vaporized (carbonized) or coagulated and then manually removed.

Unique complications include retinal damage (if exposed to the laser light) and endobronchial fire (ignition of the endotracheal tube or flexible bronchoscope

in a high inspired oxygen environment). Hemoptysis, fatal hemorrhage, airway perforation, pneumothorax, and systemic or cerebral air embolism have been reported.

Few reports are available on the use of Nd:YAG or CO₂ laser therapy for lung dysplasia, CIS, or microinvasive carcinoma. A case reported by Gerasin et al³⁹ described using Nd:YAG laser to treat a patient with presumably early-stage NSCLC in the contralateral lung after the patient underwent lobectomy for a more invasive cancer. Cavaliere et al⁴⁰ reported 19 patients with lung CIS who were treated with only Nd:YAG laser. The authors reported no recurrences, but follow-up information was not provided. The lack of data prevents any meaningful discussion of the role of laser in treating early-stage lung cancer.

Electrocautery

The use of electrocautery for tracheobronchial tumors was initially described in 1926, followed by several reports in the 1930s.^{41,42} Electrocautery uses high-frequency alternating current to produce heat, which destroys the tissue. As tissue temperature rises, cellular water evaporates and cellular constituents break down chemically, followed by cell/tissue vaporization. Depending on the power setting, this may result in coagulation, cutting, or vaporization. The degree of destruction depends on several factors: the power setting, the tissue's electrical properties, and the device-tissue contact time and surface area. Superficial coagulation occurs at lower power settings and direct device-tissue contact. Deeper coagulation and vaporization occur at the highest power settings, with a space between the device and tissue to allow electrical arc formation. Cutting uses settings between these two.

Insulated, flexible bronchoscopes and the electrocautery accessories are now available in the United States, so this procedure can be accomplished with either rigid or flexible bronchoscopy. A blunt tip probe and a wire snare are available for use with the flexible bronchoscope. These devices are monopolar, so the patient needs to be grounded to minimize risks of electrical shock or burn. A generator regulates the power (watts), so the operator can select the power and the mode (eg, cut, coagulate). The blunt probe may be applicable for flat lesions, while the snare may be appropriate for polypoid lesions. Reported complications include endobronchial fires, hemoptysis/hemorrhage, and aspiration pneumonia. Complications include electrical shocks and burns, pacemaker or automatic implantable cardioverter/defibrillator malfunction, pneumothorax, and perforation, stenosis, or mala-

cia or the airway, but they have not yet been described clinically.

Many of the published studies describe electrocautery as a palliative measure for endobronchial malignancy. A recent investigation by van Boxem et al⁴³ using electrocautery as primary treatment for radiographically occult NSCLC involved 13 patients with 15 lesions. Two cases were lung CIS and the others had a tumor surface area believed to be less than 1 cm² (stage I clinically). Follow-up ranged from 16 to 43 months. Three patients were unsuccessfully treated and underwent other therapy. Three patients died of unrelated causes at 4, 8, and 11 months, respectively, but they were believed to be tumor-free based on recent predeath evaluations. Overall, treatment for 10 of the 13 patients was considered to be successful, with 7 patients being alive and tumor-free with a median follow-up of 22 months. No complications were reported. Similar to previous discussions, insufficient data prevent any firm conclusions on the role of electrocautery as primary treatment for early-stage lung cancer. It appears this approach can be used to treat lung dysplasia or preinvasive or microinvasive carcinoma.

Cryotherapy

The use of endobronchial cryotherapy was reported initially in 1968. Since the 1980s, the majority of the work with bronchoscopic cryotherapy has been done in Europe,³¹ mostly as palliation for lung malignancy using either rigid or flexible bronchoscopy. In 1996, Mathur et al⁴⁴ published the initial report in the United States using

cryotherapy with flexible bronchoscopy. The 22 patients in the study were undergoing palliative treatment.

As opposed to electrocautery, cryotherapy uses cold to destroy tissues. When tissue temperature reaches between -15°C and -40°C or colder, intracellular dehydration occurs, intracellular and extracellular ice crystal form, intracellular pH and tonicity change, and primarily venous and capillary blood flow stagnates. These factors lead to cell/tissue death.⁴⁵ Efficient tissue destruction depends on rapid freeze-slow thaw repeating cycles, adequate surface area contact, and adequate freeze time.

Endobronchial tumor is cryosensitive. If successful, the treated airway mucosa appears normal in approximately 2 weeks. For use with the flexible bronchoscope, the cryoprobe must be flexible and able to pass through the working channel. The probe tip must contact the tissue for effective therapy. The probe should extend beyond the bronchoscope by several centimeters so the fiberoptics are not damaged. Nitrous oxide, a common cryogen, is used with this flexible probe. The tissue can be adequately frozen in approximately 30 to 45 seconds, while thawing occurs passively through body heat, usually in 30 to 60 seconds. Reapplication to the same spot or application to a new spot with some overlap in the freezing fields is the usual method (Fig 4A-B). Debulking of tumor often can be done at the same session. This limits the technique to patients not requiring urgent treatment. Over time, slough with subsequent expectoration removes debris. Another treatment may be needed in 2 to 3 weeks.

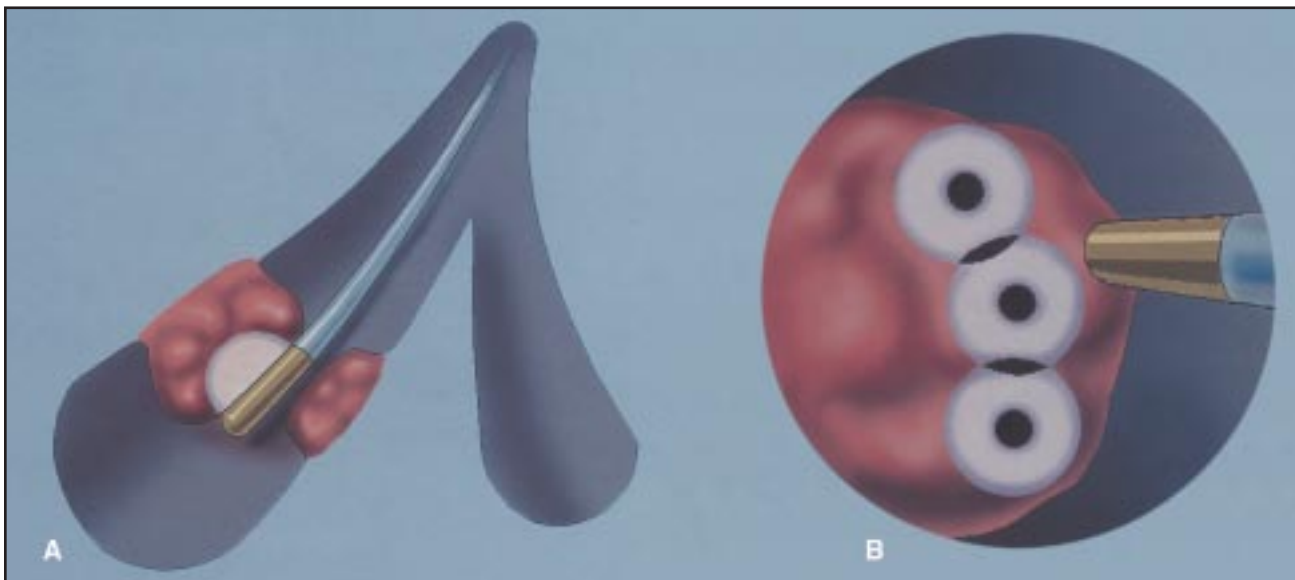


Fig 4A-B. — (A) Cryotherapy can be applied to tissue using either the probe tip or side. (B) Reapplication to the same area after thawing allows a deeper freeze and tissue destruction. From Sheski FD, Mathur PN. Cryotherapy, electrocautery, and brachytherapy. *Clin Chest Med.* 1999;20:123-138. Reprinted with permission.

Respiratory or cardiopulmonary arrest, fatal hemoptysis, and tracheoesophageal fistula have been reported. Other complications include pneumothorax, bronchospasm, atrial fibrillation, bradycardia, and aggravation of cold-agglutinin anemia.

In a recurring theme, with respect to endoscopic therapies for early-stage lung cancer, insufficient data prevent any conclusive comments on the role of cryotherapy in this form of lung disease. Ozenne and colleagues⁴⁵ described endobronchial cryotherapy in 15 patients with 20 lesions, either lung CIS or microinvasive carcinoma. Six patients had a second aerodigestive tract carcinoma. One patient failed therapy and had surgery. Six lesions recurred that required retreatment or an alternative treatment. Three patients died — 2 of a new invasive lung cancer and 1 of prostate cancer. Follow-up ranged from 10 to 36 months. Overall, 15 lesions, including 2 recurrences, were believed to have been controlled with cryotherapy alone. We treated 1 patient with lung CIS in his left lower lobe bronchus and at the take-off of the right upper lobe bronchus. Previously, he had a left upper lobectomy for stage I NSCLC. After 3 treatments, he had persistent CIS and subsequently underwent PDT with no evidence of recurrence 1 month after treatment.

Conclusions

Conducting an accurate comparison of studies on treatment for early-stage lung cancer requires a uniform definition of "early stage." Investigators should report the pathology and degree of cancer invasion. Whether lung dysplasia should be treated if it persists after smoking cessation is debatable. Evidence for eventual development of malignancy may support active treatment. More effective detection methods for early-stage lung cancer are needed.

The debate over screening with chest radiograph and sputum cytology has resurfaced. Improvements in fluorescence bronchoscopy continue. Study is ongoing to determine the high-risk population best served by screening, centering on tobacco smokers and those with chronic obstructive pulmonary disease. If an acceptable early detection algorithm becomes available, then the therapeutics will need to come to the fore. Another difficulty with early lung cancer is localizing its margins endoscopically so appropriate therapy can be undertaken. Compared with conventional bronchoscopy, fluorescence bronchoscopy seems superior in this aspect, yet its limitations make its wide-scale use impractical at this time.

If endoscopic treatment is to become the primary choice, it will need to be equivalent to or better than surgical resection in terms of disease-free survival. Cost and complications also are factors to consider. Randomized, controlled trials should be conducted between therapies, but this will be difficult to do. As long as the endoscopic modality penetrates the mucosa sufficiently to encompass and eradicate the tumor, it may be an alternative when other factors (cost, complications, and availability) are equal. Other than resection, PDT may represent the best approach at this time, given the relatively supportive data, its few serious side effects, and its ability to treat disease not easily seen on conventional bronchoscopy yet exposed to the photosensitizer and laser light.

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