Endobronchial Treatment of Lung Carcinoma
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Endobronchial treatment of tumors is not a new modality. Chevalier L. Jackson noted the treatment of benign bronchial tumors by forceps removal, implantation of radon seeds, and electrocoagulation. Specifically, he cited the efficacy of electrocautery because it does not precipitate hemorrhage. Grillo prefers the use of a rigid bronchoscope to "core out" tissue and establish a patent airway. In his hands, the use of a rigid bronchoscope to morcellate the tumor has been successful, and bleeding has been minimal.

Nishiyama et al noted a 5-year survival using local resection via a flexible bronchoscope. However, although there have been occasional prolonged survivors using endobronchial resection, with or without radiotherapy, these reports are relatively rare. The intent of any modality of transbronchoscopic surgery is to achieve palliation by establishing a patent airway, albeit temporarily.

CRYOSURGERY

Cryosurgery has been defined by Neel as "that branch of cryobiology and surgery which deals with the therapeutic application of cold at profoundly low temperatures (those below 0°C) for the purpose of destroying tissues in selected target sites." The utilization of a low-temperature probe induces coagulation necrosis, which is generally limited to the immediate area of the probe application and ice ball.

Cooper and Lee were the first to devise a closed cryogenic system using liquid nitrogen. The basic design of their probe has been little changed since then. Liquid nitrogen is fed into a cannula that has an inner tube, an outer tube, and a specifically designed tip. Except for the tip, the cannula is insulated. Liquid nitrogen is fed under pressure and delivered to the tip, where it expands and then escapes through the outer tube. Profound cooling occurs at the tip due to the Joule-Thomson effect (rapid expansion of a gas). Intracellular and extracellular ice crystal formation injures cells and reduces their survival, disrupts cell membranes, and has profound effects on blood supply. Those interested in cryobiology are referred to Neel's excellent review.

In animal experiments, the Mayo Clinic group noted complete necrosis of the mucosa and thrombosis of the vessels, but preservation of the basic bronchial architecture. There was a surrounding area of coagulation necrosis in the lung itself, which subsequently healed by fibrosis. The bronchi healed without stricture. They later applied the technique to 8 patients with endobronchial tumors.

In a more recent study, Homasson et al utilized a cryoprobes through a rigid bronchoscope in 27 patients. The cryoprobe itself was flexible and could reach into the right upper lobe bronchus. Electrical impedance was concurrently measured. It was found that extracellular crystallization of tumors and of normal tissue occurs at about 500 kΩ.

For malignant tumors, they achieved airway palliation in 13 of 21 patients. They also easily ablated 5 small granulomas without complications. Many of their patient group had received prior radiotherapy and/or chemotherapy. They recommend flexible fiberoscopy 4 to 6 days after cryotherapy to aspirate tissue slough. Treatment failures were technical (i.e., the probe was too short to reach the tumor in a few cases). A longer probe has not been developed.

Indications for the procedure seem to be the same as those for utilization of the laser. However, since it takes several days for the tissue to slough, immediate palliation of airway obstruction is not obtained.

ELECTROSURGERY

Endoscopic electrosurgery has been used safely for many years. Its principal use has been for removing colon polyps and as an adjunct in biopsy of various other colon lesions. More recently, it has achieved widespread use in the fulguration of various bleeding lesions in the upper gastrointestinal tract.

Hooper and Jackson cited 8 cases previously reported in the literature and added 4 of their own. The methodology was rather straightforward and involved passing a probe through the aspiration channel of the bronchoscope. They found cautery sectioning most easily accomplished with a polypoid lesion attached to a stalk. The alternative approach is vaporization using the closed wire snare as a cautery probe. In 1 patient, they had an endobronchial fire. In 3 patients, significant airway palliation was achieved. Diagnosis was elusive in the fourth case, in which a large piece of tissue was sectioned.

More recently, these authors extended their experience to 32 procedures on 18 patients, 13 of whom had a diagnosis of malignancy. Use of the electrocautery snare provided a diagnosis of malignancy in 2 of the latter patients, and successful airway palliation was achieved in the remaining 11 patients. Currently, they have combined endobronchial electrosurgery and the YAG laser in achieving airway patency. Their only 2 complications were the airway fire and an episode of bleeding, which subsided spontaneously.

Gerasin and Shafirovsky similarly used a diathermic snare inserted into the fiberoptic bronchoscope in 14 patients. They concluded that the use of the snare was more effective than electrodestruction alone.

CARBON DIOXIDE LASER

A tremendous worldwide experience has been gathered since 1973, when laser technology was first adapted for use in the tracheobronchial tree. Extensive reviews of the biophysics of lasers have appeared in the literature and will not be repeated here.

The CO₂ laser was the first laser to be commercially introduced. The difficulties with the CO₂ laser are inherent in its wavelength. Hemorrhage was noted to be a problem since only blood vessels 0.5 mm or less in diameter could be coagulated. Direct pressure with the rigid bronchoscope or with sponges and the instillation of topical epinephrine

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Endobronchial Treatment of Lung Carcinoma (Jacobson, LoCicero)
were frequently necessary to control the hemorrhage. The CO₂ laser also has other technical disadvantages. It can be delivered only through a straight-line system which requires an awkward articulation arm system. Also for this reason, it has generally not been possible to use the CO₂ laser in upper lobe lesions and peripheral bronchi. Shapsay and Simpson⁵ used this modality on 34 patients with malignant airway disease (59 operations). They achieved airway palliation in 30 patients. Poor results were accounted for by distal airway obstruction and extrinsic tracheobronchial compression. In this group, they had nine complications and one postoperative mortality.

McElvein and Zorn⁶ used the CO₂ laser to treat 89 patients from 1979 to 1983. Of this group, 51 patients had malignant lesions. Forty-six of these patients achieved an immediate good result from relief of airway obstruction, and 5 had an immediate poor result. The authors concluded that if there is an intraluminal extension of a carcinoma in a main-stem bronchus, the intraluminal portion can be eradicated with the laser. However, in the case of extrinsic compression with internal narrowing, use of the laser would result in bronchial wall destruction and subsequent cicatrization. This point cannot be overemphasized. Laser treatment of benign strictures and extrinsic compression only cause a more serious and aggressive obstruction. Shapsay and Beamis⁷,⁸ have extensively reviewed the methodology and usefulness of the CO₂ laser.

**Neodymium-YAG Laser**

Since the initial reports about the use of the YAG laser transmitted through optical fibers, this method of transbronchial resection has achieved unprecedented enthusiasm and acceptance.

Aside from the ease of delivery via a flexible fiber, other advantages of the YAG laser are its excellent vaporization capability, poor absorption by hemoglobin, tissue penetration of 5 to 10 mm from the focal point, high energy output, and the ease with which coagulative necrosis is obtained.⁹,¹⁰

In an early study of 89 patients, Unger¹¹ achieved excellent results in 49%, fair results in 30%, and unsatisfactory airway palliation in 21%. He noted that endobronchial resection in central airways is most logical in terms of physiologically improving the V/Q ratio. In only rare cases does it pay to do the more hazardous resection of peripheral bronchi. An indication for a more peripheral resection might be obstruction of a distal bronchus with abscess or pneumonia behind it. Most European centers prefer its use via the rigid bronchoscope, although in the United States the flexible instrument is preferred.

Brutinel et al¹² reported on 176 laser treatments on 116 patients. There were 3 deaths from hemorrhage in the first 59 patients and 7 other instances of massive hemorrhage. When they reduced the power settings from 89 W to a mean of 40 W, there were no further instances of hemorrhage. It is also helpful to reduce exposure times to less than 3 s per application. Overall results (1 or 2 treatments) resulted in improved airway caliber in 83%. The success rate was higher in the trachea, main-stem bronchi, and bronchi intermedius. Overall initial results were equally good whether primary or metastatic lung carcinoma was being treated. In the treated group, 40% of the patients were dead at 7 months and 72% at 1 year. Treatment was most successful with lesions measuring 4 cm or less in length, with a distal bronchus free of tumor, and with distal functioning lung tissue.

Cavaliere and colleagues¹³ reported on 1,396 applications in 1,000 patients—almost all with a rigid bronchoscope. In their group, 593 patients had bronchogenic carcinoma. An unexpected benefit in 8 cases was that after laser resection the tumors were found to be surgically resectable since they were more distal than had originally been thought. In another 10 patients, less extensive surgery than had been planned became possible. Cavaliere et al also found that results depended more on location and microscopic appearance than on histologic type. Good immediate results were obtained in 94% of cases. Cumulative survival percentages were similar to those in other series, with 50% of patients alive at 6 months and 26% at 1 year.

The current treatment of bronchial adenomas remains problematic. Cavaliere et al¹⁴ feel that deeply infiltrating carcinoids recur rapidly and behave like bronchial adenomas. Others that are polypoid behave in a benign manner. Adenoid cystic tumors are often wide based and tend to recur. These authors' main complications were hypoxemia and related cardiovascular disorders, as well as hemorrhage. The mortality rate was 0.35%.

Unger et al¹⁵ reported on 446 procedures in 175 patients, 81% of which were performed with the flexible scope and topical anesthesia. In this group, 147 patients had far advanced intraluminal carcinoma no longer amenable to surgical resection. About half had an excellent response. Multiple applications were frequently required. Another 50 patients (28%) had improvement with partial reestablishment of the lumen. Treatment failures occurred in 15 of the 175 patients. One death occurred 6 days after the procedure and was not directly attributable to it.

In a series of 1,503 procedures on 839 patients, Dumon and colleagues¹⁶ encountered 6 fatalities. Major causes of death during or after the procedure were hypoxemia and perforation. Hemorrhage was rarely massive but was dangerous because of the resultant hypoxemia. Hypoxemia also arose from obstruction by secretions and debris.

The principles of safety that Dumon and colleagues have set forth in the use of the rigid bronchoscope include low laser power levels (below 50 W), short pulses (under 3 s), and an FIO₂ of less than 0.5. They advise mechanical removal of necrotic tumor debris and, needless to say, close coordination between the bronchoscopist and the anesthesiologist.

**Endobronchial Interstitial Brachytherapy**

Henschke¹⁷ described interstitial therapy of unresectable or residual lung cancer using permanently implantable sources over 30 years ago. Hilaris and Martin¹⁸ reported their 20-year experience in 1979, showing that local control appeared improved with this technique over surgery alone. In that report and in another published later that same year,¹⁹ they described endobronchial implantation of ionizing radiation sources for the management of endobronchial lesions. Further developments in this field include the use of flexible bronchoscopy and the placement of a flexible sheath that is subsequently loaded with radiation sources.²⁰,²¹ New machines for delivery and retrieval of radiation sources

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**CHEST / 100 / 3 / SEPTEMBER, 1991**
have shortened therapy from days to hours. Complications include respiratory compromise and posttreatment erosion of the pulmonary artery. Reports of this technique remain sporadic and anecdotal. Establishment of this procedure as a standard form of therapy for endobronchial tumors awaits control trials.

Laser Resection Combined with Radiotherapy

A number of investigators have combined laser recanalization with either external beam radiation or brachytherapy. Shray and colleagues reported on 65 patients who underwent 1 or more implantations with an intraluminal afterloading catheter. Iridium 192 was used for low-dose-rate irradiation. Five of the patients were approached with curative intent, and the remainder for palliation. In the palliative group, 59 of 60 had received previous external irradiation. A response rate of 54% was achieved in patients who received laser treatments prior to radiotherapy; the rate was 75% when no laser had been required. Of those treated with curative intent, 4 of 5 were disease free at a median of 16 months. Fistulas with major vessels or involvement of the esophagus occurred in 11 patients.

Shray et al feel that external beam irradiation provides palliation similar to that obtained with brachytherapy. Patients most suitable for further external beam radiation rather than brachytherapy are those with bulky extraluminal and/or extrinsic lesions. Based on their retrospective experience with laser alone, Shray et al feel that they have prolonged the duration of airway palliation by 2 to 3 times.

Macha and colleagues also used iridium 192 as high-dose endobronchial therapy. Nineteen of their 56 patients had previously undergone external irradiation, and in 20 the tumor was canalized before implantation using the YAG laser. In 44 (79%) there was a lessening of the dyspnea, and in 46 (82%) there was radiologic evidence of tumor regression. Radiographic evidence of reexpansion distal to a previous obstruction was noted in 22 of 25 (88%). Pulmonary function parameters similarly improved. After the procedure, there were no deaths and only 2 episodes of hemoptysis.

Seagren et al reported on 22 procedures in 20 patients, 4 of whom underwent laser debulking. All patients had undergone prior external thoracic irradiation and now had local recurrence. Remote afterloading with a small cobalt source was used. Seventeen patients had partial palliation of symptoms, and 8 had complete amelioration of symptoms. In 6, the palliation was durable. The median survival rate was 9 months from implantation (range, 4 to 29 months).

Photodynamic Therapy

Photoactivation of light-sensitive compounds to produce chemical reactions, a recognized phenomenon since 1900, has been applied to human cancers since 1966. To date, it is estimated that over 3,000 patients with various tumors have received photodynamic therapy (PDT).

Patients receive a purified derivative of the hemoglobin molecule (hematoporphyrin derivative). This drug circulates in all cells but clears faster from normal cells than from cancer cells. Photoactivation by light at 630 nm causes cell death, presumably by production of toxic oxygen metabolites.

All of the initial reports to date are encouraging. Investigators at the Mayo Clinic used this technique on patients with early lung cancers, including some patients with in situ carcinomas. They estimated that nearly 700 new early lung cancers would be suitable for local therapy each year in the United States. In 1987, Edel and Cortese reported the entire experience from the Mayo Clinic. Forty tumors were treated in 38 patients, and 50% of the tumors showed a complete response to PDT. The adverse effects were relatively infrequent and included photosensitivity reactions and temporary airway obstruction requiring pharmacologic intervention. Two patients required ventilator support.

Hayata reported on 100 patients treated with PDT in Tokyo. In 60%, the bronchial lumen was opened after PDT. Some patients in this series with early lung cancers were treated with PDT alone. Nine patients with early-stage cancer were treated with PDT followed by surgical resection. In this group, 6 patients had residual microscopic tumors. He postulated that the incomplete response was due to insufficient light penetration of the tumor.

McCaughan et al showed that patients could undergo frequent and repeated treatments. They treated a series of 18 patients with 30 treatments to 26 different areas of the lung. At 1 month, 96% experienced either complete or partial response. A total of 61 patients improved clinically. The mean survival was 8.3 months. They reported complications of first-degree photosensitivity, pneumonia, hemoptysis, and endobronchial obstruction.

In a series of 14 patients with advanced squamous carcinoma, Hugh-Jones and Gardner showed that adequate palliation could be achieved. All tumors responded to initial therapy. Sixty percent of the patients achieved 50% reduction of tumor, and 3 patients achieved complete clearing of the bronchus. One patient remained disease free after 2 years.

Clinical phase III trials are presently under way across North America. It is hoped that US Food and Drug Administration approval of this treatment will be forthcoming within the next 3 to 5 years.

COMMENT

Endobronchial obstruction is a common complication of advanced-stage lung cancer. A wide variety of modalities are available for palliation in such patients. Significant relief is often possible when these tumor obstructions are acute, and therapeutic relief is prompt. Even in cases where metastatic disease is present, local control allowing the patient adequate air exchange leads to months of productive life.

No one modality has clear advantage over another at this time. It is necessary that the surgeon treating such obstructions be facile with a variety of techniques. The treatment of each patient's obstruction must be individualized.

In general, external beam radiation is the best first-line treatment for local/regional disease. The best results with cryosurgery, electrosurgery, and laser resection are in patients who have acute obstruction with respiratory compromise. Ultimately, optimal treatment may be a combination of modalities, such as laser resection followed by interstitial brachytherapy or photodynamic therapy followed by external beam radiation. Ongoing trials will help to answer some of these questions over the next few years.
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Primary, Adjuvant, and Palliative Radiation Therapy

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(Ches 1991; 100:841-45)

The role of radiotherapy in the management of lung cancer is growing in magnitude and significance. Modern radiotherapy planning and delivery systems allow more precise delivery of higher doses of ionizing radiation to desired tumor volumes with preferential sparing of sensitive uninvolved tissues. This provides a hope of cure for the patient with non-resectable or inoperable nonmetastatic lung cancer, improves the thoracic control rate in node-

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**Table 1—Indications for Preoperative Radiation Therapy**

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