Bronchoscopic Localization and Treatment of Occult Lung Cancer

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The flexible fiberoptic bronchoscope is currently the standard tool for localization of radiographically occult carcinomas of the tracheobronchial tree. It allows direct inspection of proximal airways and can establish the location of most occult lung cancers. A small percentage of patients present with bronchoscopically as well as radiographically occult carcinoma, particularly challenging because definitive localization is required before a therapeutic plan can be outlined. Selective cytologic brushing of each lobar segment, taking random biopsy specimens, has been used to assist in localization of these early cancers. Recently, fluorescent compounds have been used to assist in localizing early lung cancers and in the treatment of radiographically occult carcinoma. We review the current methods of bronchoscopic localization and treatment of radiographically occult lung cancer. (Chest 1989; 96:919-24)

HpD = hematoporphyrin derivative; DHE = dihematoporphyrin ether

Lung cancer is currently the leading cause of cancer-related death in the United States. The overall therapeutic results have changed very little in the past decade in the face of an increasing incidence of this disease throughout the world. Most patients are found to have advanced disease at the time of diagnosis, and treatment of this population is disappointing, often only palliative. Several studies, however, have demonstrated that early detection, localization, and aggressive treatment of intrabronchial or preinvasive stages of lung cancer results in five-year survival rates of 70 to 80 percent.1

The chest roentgenogram and sputum cytology tests are currently the only simple means available for detection of early asymptomatic lung cancer. In one study, 75 percent of patients with normal chest roentgenograms and abnormal sputum cytology tests had squamous cell cancer that was either in situ or early invasive.1 Detection at such an early stage should provide the best opportunity for long-term survival.

Localization of lung cancer at its earliest stage can generally be accomplished by direct visualization of the tracheobronchial tree using the flexible fiberoptic bronchoscope. Prior to the introduction of the flexible bronchoscope by Ikeda et al2 in 1969, access to the tracheobronchial tree was limited to the proximal large airways. The flexible bronchoscope provides an avenue for inspection of peripheral airways including those of the upper lobes. Central carcinoma of the tracheobronchial tree can generally be localized after a single inspection with the flexible bronchoscope. Localization of the earliest cancer can sometimes be difficult because the tumors may not produce gross mucosal abnormalities. Such bronchoscopically occult carcinomas may require repeated examinations over many months before localization is accomplished.

Fluorescent compounds, such as hematoporphyrin derivative (HpD) and dihematoporphyrin ether (DHE) have been shown to act as cancer tags.3 These compounds are retained in malignant tissue at higher concentrations than normal tissue and emit a characteristic salmon-red fluorescence when exposed to light of the proper wavelength.4 The fluorescent property of these compounds has been applied to the tracheobronchial tree as an aid in early localization of squamous cell carcinoma.5

Therapeutic options for early squamous cell carcinoma have traditionally been limited to surgical resection. The introduction of phototherapy using HpD or DHE has provided a new therapeutic alternative to surgery. This form of therapy may be particularly helpful because patients with bronchogenic carcinoma are at risk for the development of a subsequent primary lung cancer. Therapy that potentially preserves lung parenchyma would be of benefit in the long-term management of these patients. The following is a brief discussion on the role of phototherapy using HpD or DHE in the bronchoscopic localization and treatment of occult lung cancer.

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BRONCHOSCOPIC LOCALIZATION

Roentgenologically occult lung cancer is detected by an abnormal sputum cytology test. When a test result is suspicious or positive, confirmation by two additional three-day pooled collections of sputum is desirable. Once a roentgenologically occult cancer is strongly suspected, localization becomes the next challenge. Oral, pharyngeal, and laryngeal sources for neoplastic cells must be excluded by a thorough examination. Finding a tumor in one of these sites, however, should not preclude a search elsewhere, because approximately 7 percent of these patients have simultaneous cancers.1

After a thorough inspection of the upper airway, flexible bronchoscopy is required for localization of bronchogenic cancer. Over one-half of the roentgenologically occult cancers will be grossly visible at the first bronchoscopic inspection. The cancers range in appearance from obvious endobronchial masses to subtle mucosal irregularities. Topical anesthesia is generally adequate for recognition and biopsy-obtained confirmation of these obvious carcinomas.

A more detailed and careful endoscopic examination using general anesthesia is necessary in the remaining patients in whom the cancer is not obviously visible. This examination allows the endoscopist time to inspect the mucosal surfaces for signs of early cancer, such as thickening, irregularity, erythema, or pallor. Ideally, all patients should discontinue smoking and have bronchitis treated with antibiotics and bronchodilators prior to inspection. This may facilitate recognition of subtle mucosal changes.

The larynx and subglottic trachea should be carefully visualized before intubation, since an endotracheal tube may obscure a small tumor in the upper trachea. Thorough inspection of the tracheobronchial tree is completed before any sampling begins. Multiple sheathed cytology brushes, preferably with bristles from 3 to 5 mm in diameter, are used for sampling each segmental and subsegmental bronchus. Care should be taken to avoid withdrawing the brushes through the working channel of the bronchoscope. The working channel should be washed between each brushing (to avoid contamination). After brushings are collected, multiple biopsy specimens from various sites are obtained. A cytotechnologist is present throughout the examination to prepare the bronchial brushing slides and to make certain that all specimens are accurately labeled. Localization of a cancer is confirmed if biopsy material is positive for carcinoma. If only brushings are positive, the possibility of contamination from other sites must be considered. Localization is confirmed if, at subsequent bronchoscopic examination, ie, one to two weeks later, a brush from the same region is again positive for carcinoma.

Rarely, the sequence described above fails to con-

![FIGURE 1. Squamous cell carcinoma of the left upper lobe spur before and after hematoporphyrin derivative phototherapy.](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21602/)

firm localization sufficiently to determine therapeutic options. Problems in localization of the cancer are most often encountered when the cancer is either in situ or early invasive squamous cell carcinoma. It may take several months with repeated bronchoscopic examinations before localization is accomplished.

To facilitate localization, many chemicals have been evaluated as potential tumor markers including eosin, berberine sulfate, fluorescein, tetracycline, acridine orange, hematoporphyrin, and HpD. HpD and more recently DHE have received the most attention as compounds that are preferentially concentrated by malignant cells.8 Both compounds absorb light from the ultraviolet to the visible red region of the spectrum. The greatest absorption occurs around 405 nm. HpD and DHE are excited to a singlet state when exposed to radiation in this region. Spontaneous decay results in the production of a characteristic red fluorescence whose wavelength is approximately 630 to 690 nm. Detection of the fluorescent light has been used to aid in the localization of some early carcinomas.

HpD and DHE are given IV at a dose of 2.5 mg/kg, 48 to 72 h prior to bronchoscopy. Inspection of the tracheobronchial tree for occult cancer is then undertaken. HpD fluorescence (of small superficial carcinomas of the tracheobronchial tree) is not consistently and reliably seen with conventional flexible bronoscopes. The reasons for this include the small tumor, small quantity of chemical concentrated in the tumor, low fluorescence yield, and optical losses in the fiberoptic bundles. Special instrumentation developed to overcome the technical problems of fluorescence detection has resulted in the development of several detection systems. Each system relies on amplification of a fluorescent signal, which is then displayed as either an audio signal or visual image. The overall experience using these detection systems demonstrated that these compounds may be helpful in localization of tumors that are both roentgenogenically and endoscopically occult. Fluorescence detection is, however, not specific for carcinoma. Areas of cellular atypia ranging from moderate to marked degrees have also been sites of low level fluorescence. Therefore, the endoscopist must rely on diagnostic biopsy material to confirm the presence of a cancer.
Bronchoscopic Treatment of Occult Lung Cancer

Traditional management of early lung cancer has been surgical resection of the involved region. Unfortunately, this results in the loss of functional pulmonary parenchyma. Studies have also shown that patients found to have squamous cell carcinoma are at risk to develop a second primary cancer at an annual rate of 5 percent per year. A method of treatment that is safe and that preserves functional lung parenchyma, therefore, is desirable.

HpD and DHE produce not only fluorescence when exposed to the light of the proper wavelength, but also photodynamic reactions that result in cellular death through production of toxic radicals including singlet oxygen and hydroxyl ion. Experimental studies have shown that the photodynamic effect of these compounds may be useful in the treatment of small superficial cancer.

HpD was first used in the treatment of lung cancer in 1980. Subsequently, more than 150 patients with malignancies of the tracheobronchial tree have been treated with photodynamic therapy. A recent report demonstrated at least a 50 percent complete response rate in tumors that measured less than 3 cm² in surface area. Patients were classified as having a complete response if, on follow-up evaluation, no tumor was visible on a chest roentgenogram, and if bronchoscopic biopsy, brushing, and cytology studies revealed no evidence of tumor (Fig 1). Similar results have also been reported from the Tokyo Medical College, where complete response was observed in 20 of 30 patients treated with HpD phototherapy. Each group of investigators followed up patients with repeated bronchoscopy examinations at three- to six-month intervals. We reported 11 cancers with no local recurrence after follow-up periods that ranged from 3 to 53 months. Kato et al [19] recently reported a patient who had survived more than five years after initial therapy. HpD phototherapy, therefore, offers a potential alternative to surgical resection in properly selected patients with in situ and early invasive squamous cell carcinoma.

Management of malignancy of the tracheobronchial tree continues to present a formidable challenge. Data clearly indicate that early detection, localization, and treatment provide the best opportunity for long-term survival. Once detected, most cancers are readily localized by standard bronchoscopic evaluation. Localization of the earliest cancers may require repeated bronchoscopic evaluations and prolonged evaluation. Fluorescent compounds such as HpD or DHE, when used as tumor tags, may facilitate this process. More importantly, phototherapy with either HpD or DHE appears to be a viable alternative to surgical resection. Patients with primary lung cancer are not only at increased risk of developing subsequent primaries, but also may be at relatively higher risk for surgery, because most have coexisting COPD and ischemic heart disease. In properly selected patients, HpD or DHE phototherapy appears to be a reasonable alternative. Further controlled studies are necessary to compare these two treatment modalities.

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