Newer procedures using the fiberoptic bronchoscope in the diagnosis of lung cancer[1]

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The overall survival rate from lung cancer is barely over 10%, and in the last 25 years there has been no major therapeutic advancement. Chemotherapy has extended the survival among patients with small cell carcinoma by a few months, while resectional lung surgery remains the only curative procedure for other types. Making the diagnosis at the first suspicion of the disease, while it is still in a limited stage or resectable, is currently the only hope to improve the outcome of bronchogenic carcinoma. Fiberoptic bronchoscopy is a high-yield and noninvasive means of diagnosing this condition. The present article is a review of newer tests being developed to increase the utility of fiberoptic bronchoscopy in diagnosing and staging of bronchogenic carcinoma.

Index terms: Bronchoscopy • Lung neoplasms

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Bronchoscopy, an examination of the endobronchial tree, is not a new procedure. The first bronchoscopy was performed as early as 1897 by Killian[1] to locate a foreign body. Over the years, besides technical modifications, the role of bronchoscopy has also significantly changed. At Groninge Clinic in Holland in 1939, 53 bronchoscopies were performed, 29 of them to locate a foreign body. At the same clinic in 1950, out of 629 bronchoscopies, only 14 were to locate a foreign body.[2] Thus the role of bronchoscopy was no longer limited to removal of the foreign body. A few years following World War II, when the effects of "popular fashion smoking" were becoming evident, the real importance of bronchoscopy became apparent, especially in making the diagnosis of lung cancer. However,

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Table 1. Newer diagnostic procedures using the fiberoptic bronchoscope

Newer instruments:
7-mm brush
Flexible biopsy scraper
Transbronchial aspiration needle (TBNA)
Bronchoscope through bronchoscope
Endobronchial scintillation detector
Newer uses:
Bronchoalveolar lavage (BAL)
Thoracoscopy*
Lung mapping*
Photochemical laser techniques

* Rare uses

during that era the procedure of bronchoscopy was somewhat invasive, as it was performed through a rigid tube, with or without general anesthesia.

Invention of the fiberoptic bronchoscope in the late sixties by Shigeto Ikeda, a pulmonary oncologist at the National Cancer Center Hospital in Tokyo, instantaneously changed the image of the subspecialty of pulmonary medicine. Our practice no longer remains limited to chronic obstructive pulmonary disease (COPD), infections, and pneumoconiosis. The diagnosis of bronchogenic carcinoma no longer requires patients to cough up sputum through the rigid bronchoscope or to undergo nonspecific bronchography. In elderly, critically ill patients or patients on a respirator, bronchoscopy is no longer contraindicated. Bronchial washings, brushings, and endobronchial and transbronchial biopsies via a flexible scope have become routine tests in making the diagnosis of lung carcinoma in a relatively noninvasive fashion.

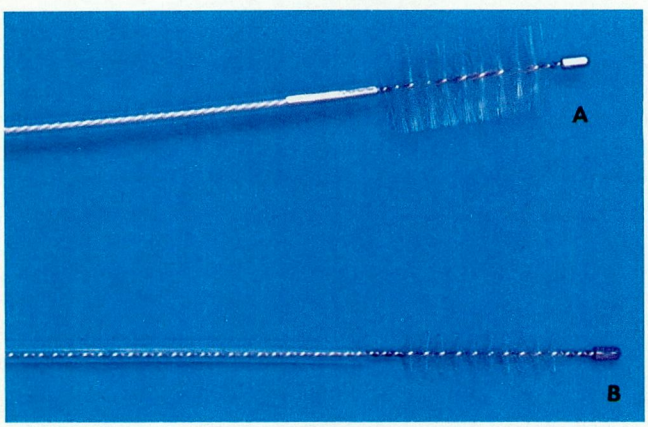

Fig. 1. 7-mm brush (**A**) vs. conventional brush (**B**).

This, however, has not changed the overall survival from bronchogenic carcinoma. Even though the fiberoptic bronchoscope helps to localize and sample the lesion much more easily and safely than the rigid scope, five-year survival is still around 10%. We all agree that the patients who achieve this five-year survival are the ones who have resectable disease at the time of diagnosis. Hence the promise still lies in making a diagnosis as soon as the disease is suspected, especially when the screening programs for bronchogenic carcinoma have proven to be impractical.[3] Capabilities of the flexible bronchoscope are being explored so that diagnosis can be made at the first suspicion of lung carcinoma. *Table 1* is a classification of areas in which new diagnostic techniques are being developed.

Newer instruments

7-mm brush

This brush differs from the conventional brush in several features. Obviously its diameter is larger and it is unsheathed (*Fig. 1*). Secondly, its bristles are Teflon-coated. Promoters of this brush claim that it provides a superior yield compared with any other available brushes and that it is less traumatic. To study this we used this brush at random but in conjunction with a regular brush (3 mm, American Endoscopy) in 20 patients with suspected endobronchial abnormalities. In all 13 patients with bronchogenic carcinoma, the diagnosis was established using both brushes, while in the seven remaining, cytologic findings on bronchial brushings were true negative with both brushes. According to our cytologist, cell return was somewhat higher with the larger brush, but diagnostic yield was not. No unusual bleeding occurred with either of the brushes. Adequate cells were obtained by a single pass, which saved some time, but there was a minor disadvantage. Because of the larger diameter of the brush, after obtaining the specimen, it could not be pulled back through the channel of the scope, and the pair (scope and brush) had to be pulled out together. That means that the brushing should be done last to avoid reinsertion of the bronchoscope, and that the brush blocks the view of the scope during its withdrawal, making the final look at upper airway structures difficult.

We conclude from our experience that the 7-mm brush is not a major breakthrough. Even though cell return is higher, the diagnostic yield

is not. It is cheaper by a few cents and less time-consuming but has its own drawbacks.

Flexible biopsy scraper

The flexible transbronchial biopsy scraper is not much different from what Zavala[4] described many years ago. Kato et al,[5] from Japan, reintroduced this instrument with minor but important modifications. The newer scraper now bares a smooth tip, and along with its sharp blade, the entire instrument is housed within a polyethylene sheath. The instrument is introduced via the channel of the bronchoscope and is pushed out of the sheath at the target site. Its blade is then extended, and the lesion is scraped and specimen is obtained for histological examination. Investigators[5] used the instrument in 20 cases and made accurate diagnoses in 11 patients with peripheral lung lesions. They claim that the major advantages of this instrument are that the smooth tip reduces the chances of pneumothorax, and the side direction of the scraper causes minimal bleeding. This instrument could have great significance in the diagnosis of peripheral extrabronchial Type III lesions (vide infra). For widespread acceptance, however, it needs further study.

Transbronchial aspiration needle

The most important development in the field of bronchology is the flexible transbronchial aspiration needle. The greatest advantage of this instrument is that it allows one to sample the tissue beyond the confines of the tracheobronchial tree.

The actual idea of needle aspiration originated from the rigid needle, used for sclerosing of the esophageal varix. Following its initial application through the rigid scope,[6] Ko Pen Wang introduced its flexible version in the United States.[7] A 22-gauge 13-mm-long beveled needle, which is attached to the flexible plastic tubing, is passed through the channel of the bronchoscope, keeping it retracted within the tubing and its tip protected within the metal spring located at the distal end. This is necessary to prevent damage to the channel of the bronchoscope. At the target site, the catheter is pushed out of the scope and then the needle through the catheter. Along with its metal stylet, which provides the stiffness, the needle is thrust through the wall of the bronchus or the trachea between the cartilaginous rings into the extrabronchial abnormality, and the stylet is withdrawn. With the help of a 60-mL plastic syringe containing 2–3 mL of normal saline, suction is applied to obtain tissue. The needle is then withdrawn, and the collected material is flushed out for cytological examination. Two to three passes are made at the same target with the same needle.

Table 2. Indications for transbronchial needle aspiration

Major:
Staging
Extrinsic compression and submucosal disease
Peripheral nodules
Minor:
Necrotic tumor
Hemorrhagic tumor
Carcinoid
Lymphoma
Small cell carcinoma (response)

Several different companies have come out with their own versions of this needle, such as the fixed vs retractable needle, with or without the stylet, plastic vs metal needles, 22-gauge vs 20-gauge, 10 mm vs 13 mm length, etc. We have used several of these versions and in our opinion Millrose-Wang needles are superior overall. *Table 2* lists the up-to-date indications for which transbronchial needle aspiration (TBNA) is performed.

Staging: For the purpose of staging, specimens are obtained from the carina (posterior right) and ipsilateral paratracheal areas (below the aortic arch, in cases of left-sided lesions). Two to three passes are made at each site with separate needles.

Table 3 shows results from major studies on staging of lung carcinoma using flexible needles. Shure and Fedullo[8] used a 20-gauge 1-cm needle

Table 3. Transbronchial needle aspiration for staging

	No. Pts.	N2 (%)	X-ray	E% +/−
Wang et al[9]	39	31 (79%)	39	70/34
Harrow et al[10]	66	26 (80%)	14 (12)*	62/32
Shure and Fedullo[8]	110	16		38/9

N2 (%) = number and % of true-positive examinations using a flexible needle.
X-ray = number of patients having radiographic evidence of N2 disease.
E% = diagnostic yield in %, when extrinsic compression is present (+) or absent (−).
* No radiographic evidence of N2 disease.

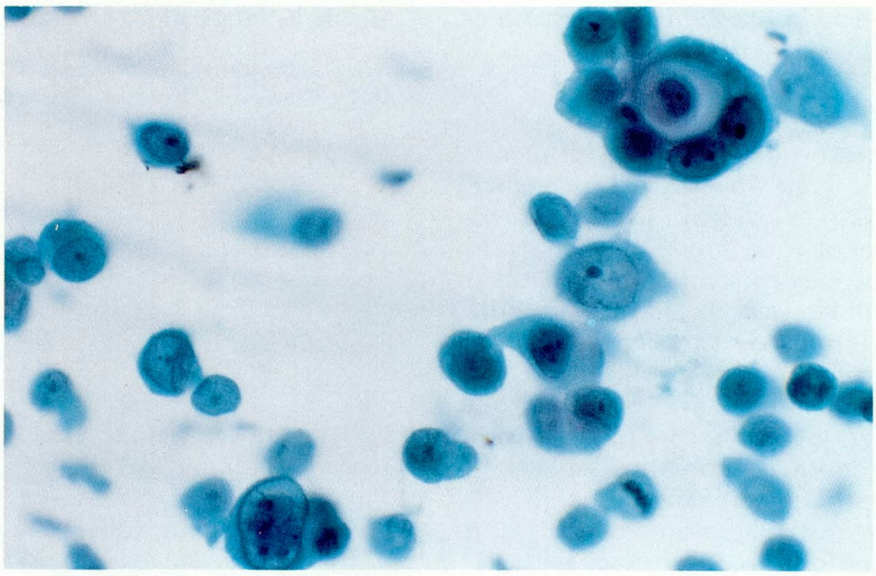

Fig. 2. Note large number of malignant cells seen on the specimen obtained by transbronchial needle aspiration.

made by Olympus and made only a single pass at the carina, while Wang et al[9] and Harrow et al[10] used a 22-gauge 13-mm needle and made two to three passes at the carina and paratracheal areas.

These studies demonstrate that if radiographic evidence of N2 disease is present or if endobronchial compression or carinal blunting is seen on bronchoscopic examination, diagnostic yield is much higher. Also under these circumstances results can be interpreted with confidence. In contrast, in the absence of such findings, interpretation is much more difficult. Even Wang et al,[9] who introduced this needle, caution that:

> Whether positive TBNA identifies potentially curable patients who have intranodal micrometastases, however, is unknown. Recent data suggest that subset of N_2 patients might benefit from surgical treatment. Thus, the decision regarding the risks and benefits of surgical approach for potential cure remains highly individualized and demands continued careful evaluation.

False-positive results could also occur if the lesion is located close to the paratracheal area but without nodal involvement[11] or if the respiratory tract is contaminated by malignant cells.[12]

The lesson from the above studies is that information obtained by TBNA is useful only if radiographic or endobronchial evidence of N2 disease is present. In their absence these TBNA results should be interpreted with extreme caution. False-positive, as well as false-negative, results can occur. To prevent false-positive results due to contamination, needle aspiration should be performed prior to any other endobronchial procedures, avoiding suctioning of and insertion through tracheobronchial secretions, and when necessary after flushing the channel of the scope with normal saline. Negative pressure should also be released after withdrawing the needle from the airway wall. Diagnosis should not be based on one or two abnormal cells present amid the respiratory epithelial cells. True-positive specimens usually have a large number of atypical cells and lymphocytes from the involved lymph nodes; however, presence of the latter is not mandatory (*Fig. 2*). If repeat bronchoscopy, after obtaining a CT scan of the chest for all cases, is done solely for the purpose of staging by TBNA, this procedure may not be more cost-effective than mediastinoscopy done just before thoracotomy, using single anesthesia.

TBNA in extrinsic compression and submucosal disease: Although the diagnostic yield of routine procedures performed through the fiberoptic bronchoscope is quite high for endoscopically visible tumor processes,[4] lesions producing only submucosal or extrinsic compression pose a significant difficulty in making the diagnosis. TBNA may have some role in overcoming this obstacle. In a study performed by Shure and Fedullo,[13] 22 out of 31 such patients had positive results on TBNA (71%), while endobronchial biopsy (EBx) yielded positive results in 17 (55%) cases. A com-

bination of TBNA-EBx and washing/brushing cytologic study enabled diagnoses in 30 out of 31 patients (97%). Of all the endobronchial procedures, TBNA was the only means of making a diagnosis in 10 patients (29%).

At the Cleveland Clinic Foundation, we performed TBNA in 50 patients having extrinsic compression as a sole endobronchial finding. The procedure was performed under fluoroscopic guidance and without prior CT scanning of the chest. Decision for needle aspiration was made during the initial bronchoscopy when the only endobronchial abnormality was found to be an extrinsic compression. Needle aspiration was performed prior to any other endobronchial procedure. Thirty-five of these patients were eventually proven to have bronchogenic carcinoma, 20 (57%) by fiberoptic bronchoscopy. In four patients, the diagnosis was solely based on TBNA, increasing the diagnostic yield of fiberoptic bronchoscopy by 25%. There were no false positives and no complications.[14]

Thus, in selected patients, TBNA increases diagnostic yield without adding to cost or risks to the patient.

TBNA in the diagnosis of peripheral lung nodules: According to anatomical relationship with adjacent bronchus, pulmonary nodules can be divided into Types I, II, III, and IV[15] (*Fig. 3*). Because of such a relationship, it is likely that brushings, washings, and bronchial biopsies may not provide a diagnosis in Type III and IV lesions, where TBNA could be more helpful.

Wang et al[16] performed TBNA in 23 patients having peripheral pulmonary nodules, and in this small study they found that regardless of location, size, and cell type, TBNA was the sole diagnostic procedure in 35% of cases. In a similar study performed by Shure and Fedullo[17] on 42 patients, TBNA increased the diagnostic yield from 30% to 70%. Diagnostic yield was higher in patients whose lesions were larger than 2 cm. The major difference was due to better sampling of Types III and IV tumor by TBNA.

Minor indications: While dealing with hemorrhagic endobronchial lesions, such as carcinoid, if endobronchial bleeding is likely with routine endobronchial biopsy, TBNA can be safely performed to obtain the tissue for diagnosis. Similarly, an endobronchial biopsy specimen obtained from the surface of a necrotic airway lesion may fail to establish an accurate diagnosis. TBNA in such cases may aid in obtaining identifiable tumor tissue from the core of the lesion. On occasion, the procedure has been found useful in making the diagnosis of lymphoma and studying the response of small cell carcinoma to chemotherapy. There are reports supporting the above indications.[7,10]

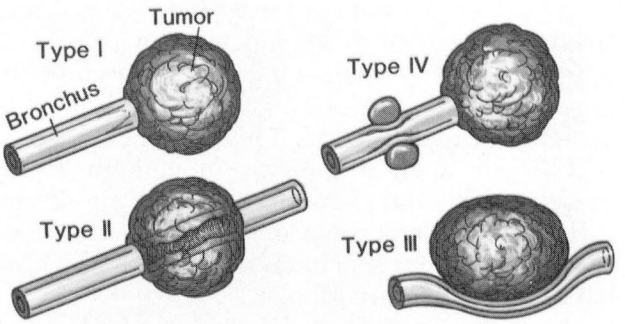

Fig. 3. Types of peripheral lung neoplasms:
I. Bronchus ending in the tumor mass.
II. Bronchus passing through the tumor mass and having endobronchial involvement.
III. Extrinsic compression of the bronchus by tumor mass without endobronchial involvement.
IV. Obstruction of the bronchus due to submucosal process or enlarged lymph nodes proximally.

In summary, these preliminary data suggest that TBNA increases the yield of fiberoptic bronchoscopy in the diagnosis and staging of bronchogenic carcinoma in selected patients. The usefulness of this information, however, remains highly individualized.

18-Gauge flexible transbronchial needle

Cytological examination of any tissue material, such as that obtained by TBNA using a 22-gauge needle, requires a highly sophisticated laboratory and highly qualified personnel. On occasion, false-positive results can also occur. To overcome this drawback, Wang[18] has developed an 18-gauge flexible transbronchial needle. This needle can provide a core of extrabronchial tissue for histopathological examination. The safety of an 18-gauge needle for such use has been previously established by its use through the rigid scope.[19,20]

A 15-mm-long 18-gauge flat-tipped needle with an inward-tapering cutting edge is attached to a 120-cm-long plastic catheter. A 20-gauge 5-mm-long beveled retractable needle, attached to the guide wire, is housed within the 18-gauge needle. The 20-gauge needle is withdrawn within the 18-gauge needle during the insertion through the channel of the bronchoscope. Prior

to the puncturing of the target site, the 20-gauge needle is projected beyond the tip of the 18-gauge needle and locked in place. Then insertion is performed in the usual fashion at carinal, paratracheal, or hilar areas. The 20-gauge needle is withdrawn; with a jabbing movement of the larger needle and suction applied by the 20-mL syringe attached at the proximal end of the plastic catheter, a tissue specimen is obtained for histopathological examination.

Using this technique, Wang[18] successfully obtained tissue in 21 out of 25 patients studied (84%). Diagnosis was established in 18 (72%), while false-negative results occurred in four. There were no complications. Distally placed, a 20-gauge needle works as a safety mechanism, preventing puncture of intrathoracic vessels by a wide-bore needle. However, the degree of bleeding encountered during the aspiration is related more to intramural vessels than intrathoracic vessels and is independent of the size of needle used.[18]

This preliminary study establishes the efficacy and safety of the 18-gauge needle in obtaining tissue from mediastinal or hilar areas; however, its potential in maximizing the diagnostic yield or minimizing the need for mediastinoscopy has yet to be proven.

Bronchoscope through bronchoscope

The Olympus Company has recently developed a new fiberoptic bronchoscope that is 1.8 mm in its outer diameter and 100 cm long.[21] It can be passed through a conventional 2.6-mm channel fiberscope to the peripheral airways. This scope has no control devices and obviously has no lumen. Specimen retrieval is not yet possible with this system, and its role is strictly limited to visualization and photographic documentation. Pictures of bronchioles of less than 1 mm have been successfully taken with this scope. Transbronchial biopsy of suspicious areas can be performed following examination by this scope. This scope is likely to gain popularity when diagnosis by laser photodynamic techniques is widely accepted (vide infra).

Endobronchial scintillation detector

We are all familiar with the role of gallium scanning in the detection of mediastinal and hilar involvement from lung carcinoma.[22] Factors limiting the detection of small primary tumors by this method are low tumor-to-background ratio and a poor resolution by the gamma camera in picking up a small "hot" lesion from a "warm" background. In addition, the tumor process cannot be differentiated from inflammation. Investigators[23] have developed a new imaging technique in which, following intravenous administration of 1 mCi (37 MBq) of Co-57-labeled bleomycin (a tumor-cell-specific radiotracer), a small crystal of thallium-activated sodium iodide (NaI) is inserted through the channel of the bronchoscope and the suspicious areas of the tracheobronchial tree are scanned. A nuclear count is gathered and the tumor site is localized. Diagnosis is confirmed by the usual biopsy procedures.

The first study of its kind using this technique[23] obviously lacked specificity and sensitivity; however, with possible technical advancements and by finding a more tumor-specific radiotracer, it holds great promise in the early diagnosis of submucosal and extrinsic disease.

Newer uses

Bronchoalveolar lavage

Bronchoalveolar lavage (BAL) has proven its value in diagnosis, prognosis, and treatment of selected nonmalignant lung diseases. There is now enough evidence to indicate that BAL can play a significant role in the diagnosis of lung cancer.

Following wedging the tip of the bronchoscope in the bronchial subsegment of the involved lung area, normal saline is instilled in 20–30-mL aliquots and aspirated back. About 100 mL of total return is collected, cells are separated by cytocentrifugation, and cytological examination is performed.

Using this method, Springmeyer et al[24] diagnosed bronchoalveolar-cell carcinoma in a patient with a bleeding disorder in whom results from both bronchial washings and brushings were negative. Immunoperoxidase staining on BAL cell return helped Costabel et al[25] diagnose lymphoma involving the lungs in four out of seven patients studied. In the remaining patients, BAL supported the diagnosis of drug-induced pneumonitis (two patients) and hypersensitivity pneumonitis (one patient). Fedullo and Ettensohn,[26] besides diagnosing lymphangitic spread of adenocarcinoma from BAL, were impressed by associated marked lymphocytosis (67%).

Olsen and Gangemi[27] took one step further and tried to study cellular and humoral immunity markers in BAL fluid. No specific clues were

found; however, BAL carcinoembryonic antigen (CEA) levels were higher in smokers and in patients with bronchogenic cancer, and BAL IgA levels were elevated not only in lung cancer patients, but also in the involved lung compared with the contralateral uninvolved lung.

BAL is a safe and inexpensive procedure. Also there is no need for fluoroscopic guidance. It should be considered in patients with peripheral infiltrative lesions and contraindication for transbronchial biopsy. Its role in immunological diagnosis of lung cancer, however, remains a subject of major research.

Thoracoscopy

Undiagnosed pleural effusion is a common diagnostic challenge. With routine biological, bacterial, cytological, and histological examinations of the pleural fluid and closed pleural biopsy, the diagnosis will be established in about 70% of cases.[28–30] In the remaining patients, the disease process either will remain undiagnosed or will require open pleural biopsy.

Usefulness of thoracoscopy in such cases, as well as in patients with peripheral or diffuse lung disease, has been previously established.[31–38] These studies were performed mainly through the rigid systems, and as with other rigid endoscopes, examination was somewhat invasive and on occasion required two separate incisions to obtain the tissue specimen safely.[38]

The same procedure can now be performed with the help of a fiberoptic bronchoscope. Gwin et al[39] studied a total of nine patients with pleural diseases, bronchopleural fistula, and peripheral lung lesion. The procedure was performed mainly using local anesthesia, with the patient in the lateral position, by introducing a sterile fiberoptic scope through a 1–2-cm incision in the chest wall. A suction channel of the bronchoscope helped to control the degree of pneumothorax as well as to obtain the tissue specimen. There were no major complications, and a diagnosis was established in each case. Senno et al[40] and Miller and Hatcher[41] reported similar results from their studies. There were minor differences in their techniques.

Pleuroscopy appears to be of particular value in patients with pleural effusion from malignant pleural implants. As the subspecialty of pulmonary medicine becomes more technically oriented and as DRGs become more common, this technique is likely to receive more consideration before performing open pleural biopsy in view of its simplicity, low morbidity, and high diagnostic yield.

Lung mapping

In rare cases of occult lung cancer, lung mapping may have some diagnostic value. Patients with sputum cytology findings positive for lung cancer but with normal chest radiographs, ear, nose, and throat evaluations, and fiberoptic bronchoscopy findings, usually are found through a lung cancer screening program or when they seek medical attention for hemoptysis.

In these patients, fiberoptic bronchoscopy is repeated using general anesthesia, and brushings and washings from each subsegment of both lungs are obtained and examined separately. The usual number of cytological specimens varies from 30–45. If any of these specimens demonstrate tumor cells, then a month later the fiberoptic bronchoscopy is repeated and brushings and washings are obtained from only the subsegments from which the malignant cells were recovered during the previous bronchoscopy. If malignancy is confirmed, corresponding segmentectomy or lobectomy is performed. Martini and Melamed[42] studied 21 such patients referred from the Sloan-Kettering Lung Screening Project during 1973–1979 and were able to diagnose at least five patients by this method. These patients had either carcinoma in situ or Stage I disease. In the remaining patients who were eventually proven to have disease beyond the stage of occult lung cancer, diagnosis was established by routine endobronchial sampling.

With the failure of lung cancer screening projects and with increasing interest in diagnosis by photodynamic reaction, there is little prospect of this procedure gaining popularity.

Photodynamic techniques

So far all our efforts have been in the direction of diagnosing lung carcinoma when it becomes symptomatic. At this stage, however, only about 25% of the patients have resectable disease.[43] If this trend continues, obviously the future is not very bright. But efforts are being made to diagnose the disease when it is in situ or in the superficial stage. One way such tumor localization is done is by photodynamic technique using photosensitizers and laser light.

The chemicals hematoporphyrin D (HpD) or dihematoporphyrin ether (DHE), following intra-

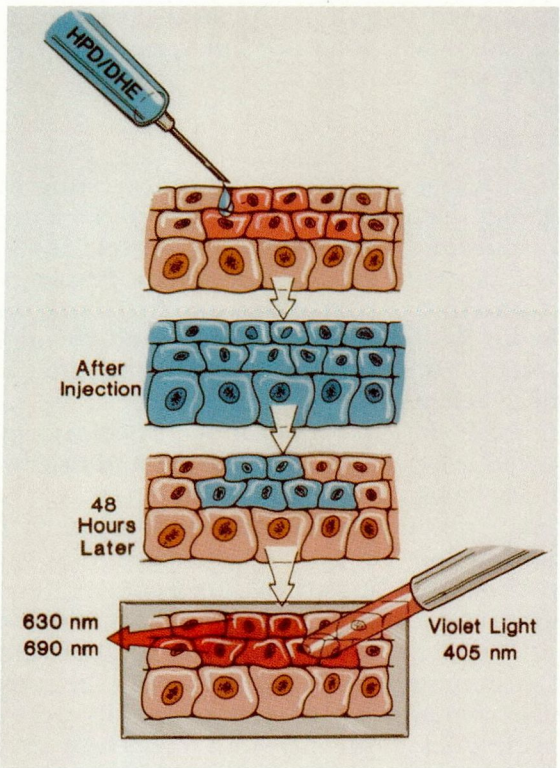

Fig. 4. Diagnosis of bronchogenic carcinoma by using laser photodynamics (see text).

venous administration, are distributed throughout the body. However, after 48 hours they are retained mainly by malignant tumor tissue. When such tumor tissue is exposed to light with a wavelength of 405 nm (violet), these chemicals fluoresce at 630 nm and 690 nm (red) (*Fig. 4*).[44] Visualization of this fluorescence allows localization of the tumor process. However, some type of wavelength detection device is required, since this red fluorescence is not easily detected. For this purpose, Hayata et al[45] used an image intensifier made by Profio. This attachment increases the signal gain by 30,000 times; thus the tumor site can be located and diagnosis confirmed by performing multiple biopsies at the site. Kato[46] studied 40 patients who had hemoptysis or positive sputum cytologic findings plus normal chest radiographs and was able to make a diagnosis in 33 patients. Three patients had severe metaplasia. False-negative results were found in patients with submucosal disease, or hemorrhage or sloughing covering the tumor site.

The tumor site can also be located by converting the fluorescent light signals into audio signals. Using this technique, Cortese et al[47] detected tumor sites in patients selected from the Mayo Clinic lung carcinoma screening project. At Roswell Park Memorial Institute efforts are being made to convert these light signals into electronic signals and display them on a computer screen.

This technology has great potential but also major obstacles. Very few patients present with carcinoma in situ or superficial lung tumors. Screening programs that could identify such patients have not been found to be cost effective. Photosensitization from HpD and DHE requires staying away from sunlight for as long as 30 days, making patient acceptance difficult. False-positive results do occur with metaplasia, and if multiple areas are detected in one patient, the chance for cure from conventional surgical treatment may be lost. False-negative results have also been reported. Above all, this procedure requires expensive equipment and expert technical assistance. Widespread acceptance of this technique depends on further research.

In this decade and probably the next, lung cancer will remain a deadly disease. Research in the direction of early diagnosis and means of cure is being done. However, equal effort toward prevention is also necessary.

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References

1. Killian G. Direct endoscopy of upper air passages and esophagus: its diagnostic and therapeutic value in search for and removal of foreign body. J Laryngol 1902; **18:**461–468.
2. Edens ETH. Bronchoscopy. Boehringer Ingelhem International Gmbh. Canada, 1982.
3. National Cancer Institute Lung Cancer Cooperative Study. Early lung cancer detection: summary and conclusions. Am Rev Respir Dis 1984; **130:**565–570.
4. Zavala DC. Diagnostic fiberoptic bronchoscopy: techniques and results of biopsy in 600 patients. Chest 1975; **68:**12–19.
5. Kato H, Goto H, Leke R, et al. A new, fully protected biopsy scraper for transbronchial lung biopsy. Communication to the editor. Chest 1985; **1:**143.
6. Wang KP, Marsh BR, Summer WR, Terry PB, Erozan YS, Baker RR. Transbronchial needle aspiration for diagnosis of lung cancer. Chest 1981; **80:**48–50.
7. Wang KP, Terry PB. Transbronchial needle aspiration in the diagnosis and staging of bronchogenic carcinoma. Am Rev Resp Dis 1983; **127:**344–347.
8. Shure D, Fedullo PF. The role of transcarinal needle aspiration in the staging of bronchogenic carcinoma. Chest 1984; **86:**693–696.

9. Wang KP, Brower R, Haponik EF, Siegelman S. Flexible transbronchial needle aspiration for staging of bronchogenic carcinoma. Chest 1983; **84:**571–576.
10. Harrow EM, Oldenburg FH, Smith AM. Transbronchial needle aspiration in clinical practice. Thorax 1985; **40:**756–759.
11. Schenk DA, Chasen MH, McCarthy MJ, Duncan CA, Christian CA. Potential false positive mediastinal transbronchial needle aspiration in bronchogenic carcinoma. Chest 1984; **86:**649–650.
12. Cropp AJ, Dimario AF, Laukerani M. False positive transbronchial needle aspiration in bronchogenic carcinoma. Chest 1985; **5:**696–697.
13. Shure D, Fedullo PF. Transbronchial needle aspiration in the diagnosis of submucosal and peribronchial bronchogenic carcinoma. Chest 1985; **88:**49–51.
14. Tita JA, Livingston DO, Mehta AC, Sivak ED. Diagnostic utility of transbronchial needle aspiration in bronchogenic carcinoma presenting as extrinsic compression. (Abstract) Chest 1986; **89:**449S.
15. Tsuboi E, Ikeda S, Tajima M, et al. Transbronchial biopsy smear for diagnosis of peripheral pulmonary carcinomas. Cancer 1967; **20:**687–698.
16. Wang KP, Haponik EF, Britt EJ, Khouri N, Erozan Y. Transbronchial needle aspiration of peripheral pulmonary nodules. Chest 1984; **86:**819–823.
17. Shure D, Fedullo PF. Transbronchial needle aspiration of peripheral masses. Am Rev Resp Dis 1982; **128:**1090–1092.
18. Wang KP. Flexible transbronchial needle aspiration biopsy for histologic specimens. Chest 1985; **88:**860–863.
19. Wang KP, Britt EJ, Haponik EF, Fishman EK, Siegelman SS, Erozan YS. Rigid transbronchial needle aspiration biopsy for histological specimens. Ann Otol Rhinol Laryngol 1985; **94:**382–385.
20. Pauli G, Pelletier A, Bohner C, Roeslin N, Warter A, Roegel E. Transbronchial needle aspiration in the diagnosis of sarcoidosis. Chest 1984; **85:**482–484.
21. Tanaka M, Satoh M, Kawanami O, Aihara K. A new bronchofiberscope for the study of diseases of very peripheral airways. Chest 1984; **85:**590–594.
22. DeMeester TR, Golomb HM, Kirchner P, et al. The role of gallium 67 scanning in the clinical staging and preoperative evaluation of patients with carcinoma of the lung. Ann Thorac Surg 1979; **28:**451–464.
23. Woolfenden JM, Nevin WS, Bradford Barber HB, Donahue DJ. Lung cancer detection using a miniature sodium iodide detector and cobalt-57 bleomycin. Chest 1984; **85:**84–88.
24. Springmeyer SC, Hackman R, Carlson JJ, McClellan JE. Bronchioloalveolar cell carcinoma diagnosed by bronchoalveolar lavage. Chest 1983; **83:**278–279.
25. Costabel U, Bross KJ, Matthys H. Diagnosis by bronchoalveolar lavage of cause of pulmonary infiltration haematological malignancies. Br Med J 1985; **290:**1041.
26. Fedullo AJ, Ettensohn DB. Bronchoalveolar lavage in lymphangitic spread of adenocarcinoma to the lung. Chest 1985; **87:**129–131.
27. Olsen GN, Gangemi JD. Bronchoalveolar lavage and the immunology of primary lung cancer. Chest 1985; **87:**677–682.
28. Donohoe RF, Katz S, Matthews MJ. Pleural biopsy as an aid in the etiologic diagnosis of pleural effusion. Ann Intern Med 1958; **48:**344–362.
29. Mestitz P, Purves MJ, Polland AC. Pleural biopsy in the diagnosis of pleural effusion. Lancet 1958; **2:**1349–1353.
30. Hampson F, Karlish AJ. Needle biopsy of the pleura in the diagnosis of pleural effusion. Q J Med 1961; **119:**249–255.
31. Weissberg D, Kaufman M. Diagnostic and therapeutic pleuroscopy. Chest 1980; **78:**732–735.
32. Bloomberg AE. Thoracoscopy in diagnosis of pleural effusions. NY State J Med 1970; **70:**1974–1977.
33. Bergqvist S, Nordenstam H. Thoracoscopy and pleural biopsy in the diagnosis of pleurisy. Scand J Respir Dis 1966; **47:**64–74.
34. Hatch HB, DeCamp PT. Diagnostic thoracoscopy. Surg Clin North Am 1966; **46:**1405–1410.
35. Fleishman SJ, Lichter AI, Buchanan G, Sichel RJ. Investigation of idiopathic pleural effusions by thoracoscopy. Thorax 1956; **11:**324–327.
36. Boutin C, Cargnino P, Viallat JR. Thoracoscopy in the early diagnosis of malignant pleural effusions. Endoscopy 1980; **12:**155–160.
37. Boutin C, Viallat JR, Cargnino P, Farisse P. Thoracoscopy in malignant pleural effusions. Am Rev Respir Dis 1981; **124:**588–592.
38. Boutin C, Viallat JR, Cargnino P, Rey F. Thoracoscopic lung biopsy. Chest 1982; **82:**44–48.
39. Gwin E, Pierce G, Boggan M, Kerby G, Ruth W. Pleuroscopy and pleural biopsy with the flexible fiberoptic bronchoscope. Chest 1975; **67:**527–531.
40. Senno A, Moallem S, Quijano ER, et al. Thoracoscopy with the fiberoptic bronchoscope. J Thorac Cardiovasc Surg 1974; **67:**606–611.
41. Miller JI, Hatcher CR. Thoracoscopy: a useful tool in the diagnosis of thoracic disease. Ann Thorac Surg 1978; **26:**68–72.
42. Martini N, Melamed M. Occult carcinomas of the lung. Ann Thorac Surg 1980; **30:**215–223.
43. Shields TW. Surgical therapy for carcinoma of the lung. Clin Chest Med 1982; **3:**369–387.
44. Profio AE, Doiron DR, King EG. Laser fluorescence bronchoscope for localization of occult lung tumors. Med Phys 1979; **6:**523–525.
45. Hayata Y, Kato H, Konaka C, et al. Fiberoptic bronchoscopic laser photoradiation for tumor localization in lung cancer. Chest 1982; **82:***10–14.*
46. Kato H. Localization by stimulation of fluorescence. [In] Hayata Y, Dougherty TJ, eds. Laser and Hpd in Cancer. Igaku Shoin Ltd. Publications 1983, pp 39–56.
47. Cortese DA, Kinsey JH, Woolner LB, Payne WS, Sanderson DR, Fontana RS. Clinical application of a new endoscopic technique for the detection of in situ bronchial carcinoma. Mayo Clin Proc 1979; **54:**635–641.