Photodynamic Diagnosis and Therapy as Alternative to the Management of Early Stage Lung Cancer

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There has been a dramatic expansion in the role of the bronchoscope as a therapeutic instrument, "Interventional Bronchology", not only for advance bronchogenic carcinoma but also for early cancer. There is now considerable interest in the potential of PDT for treating early bronchial carcinoma. Similarly laser light can be used to detect tumors by fluorescence at an early, and therefore more treatable stage, when they may elude routine bronchoscopy. The total number of early stage lung cancer cases was 107 consisting of 126 lesions, and complete remission was obtained in 85 cases (107 lesions) out of 103 cases (126 lesions, 84.9%) and partial remission in 19 lesions. Eighty patients (98 lesions) were disease free from 2 to 200 months, however, 5 patients died with lung cancer. The survival curve was calculated by the Kaplan and Meier method. The overall survival rate is 68.3%. PDD is another aspect of photodynamic reaction. The effectiveness of a new excimer laser endoscopic imaging fluorescence analyzer system using the photosensitizer for the detection of tumors was evaluated. Autofluorescence (650±10 nm, green fluorescence) from normal sites, red fluorescence (670 nm) of chlorine e6 in areas of cancer and the red fluorescence/green fluorescence ratio (R/G ratio) as the color image can be detected respectively. The greatest chlorine e6 fluorescence from the lesion was obtained at 3 hour after injection and the fluorescence disappeared at 24 hours. The greatest difference in the fluorescence of chlorine e6 and the R/G ratio in areas of tumor and in normal areas were observed at 5 hours after administration. At this period, chlorine e6 fluorescence from normal sites was negligible. These data suggest that fluorescence photodiagnosis may effective in the detection of cancers.

Key words: Photodynamic therapy, Photodynamic diagnosis, Early stage lung cancer

Introduction
Photodynamic therapy (PDT) is a new cancer treatment modality that selectively destroys cancer cells by an interaction between absorbed light and a retained photosensitizer. The effectiveness of PDT in the treatment of malignant tumors was established by Dougherty et al. for the treatment of skin metastatic lesions of breast carcinoma in 1973, since then increasing attention has been paid to this new diagnostic and therapeutic modality. The authors began investigation of these techniques in 1978 and demonstrated their effectiveness in both diagnosis and treatment in canine lung cancer models and applied these methods in clinical cases in 1980. Since then, 460 cases, including 270 lung cancer patients were treated with PDT in our institution. There were more than 30 cases of 5-year survival, including the first such case in the world treated by PDT alone.

In this paper, our experience of PDT especially

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early stage lung cancer as well as the photodynamic diagnosis for the early detection will be discussed.

Photodynamic diagnosis (PDD) - fluorescence diagnosis for lung cancer

Early stage lung cancer is now considered to have high curability by surgical treatment. In order to reduce the increasing mortality from lung cancer, it is necessary to detect early stage cases. The government of Japan has attempted to contribute to this endeavor by increasing lung cancer survays as part of the general medical care for the elderly. In these surveys, sputum cytology examinations are included and this is indeed effective in the detection of early stage central type lung cancer. Once roentgenographically occult lung cancer is detected by sputum cytology, the foci must be localized by bronchoscopy. However, it is sometimes difficult to locate lesions in patients with carcinoma in situ by conventional white light bronchoscopy alone, even with careful inspection and with multiple blind brushings and biopsies that takes over an hour. After the pioneering work of Profio et al.\textsuperscript{51}, Kato et al. began to use image fluorescence bronchoscopy, employing a tumor-specific photoactive drug as the most sensitive and accurate procedure for the detection of central type early stage lung cancer. In our institution, we have examined the possibility of photodiagnosis since 1978\textsuperscript{6}3, however, the development of photodynamic diagnosis (PDD) systems were hampered by problems including skin photosensitization and lower tumor selectivity of the photosensitizer employed, Photofrin, and also autofluorescence interference.

A block diagram of this system is shown in Fig. 1. The excimer laser (XeCl) uses a gas mixture containing 0.9% Xe, 0.1% HCl and 99% helium at 2 atm. pressure in order to generate its high-energy beam. The optimal performance of this laser at 308 nm is 30mJ/pulse at one-half peak power for 10.9 nanoseconds. The XeCl excimer laser (308nm) was coupled to a pump system containing saturated diphenyl sulphan dye in dioxane which converts the beam to 405nm, which is the wavelength used for diagnostic purposes. The radiation from excimer-dye lasers is focused onto 400-\(\mu\)m fused silica fibers (Fuji Photo Optical Co. Tokyo, Japan), the tips of which are fitted with microlenses for homogeneity of light distribution throughout the treatment field. The circular area of illumination is 2 cm\textsuperscript{2}. The endoscope system is equipped with 3 channels which contain the fiberoptics for field visualization (Xe lamp), the excimer-dye laser, and the fluorescence detector which can function simultaneously in this system. A chopper functions to alternate the delivery of white light and laser light, based on a system originally developed at the Mayo Clinic\textsuperscript{53}. Light from the detector is also processed by a separate path in order to transmit the endoscopic image, which is displayed on the same monitor. The

![Diagram of the excimer laser fluorescence image analyzer system.](image-url)
fluorescence, from which the violet excitation light has been totally filtered is detected by the optics of the bronchoscope. The image of the bronchoscope is amplified by means of an image intensifier consisting of a multichannel-plate, a fluorescent screen and a CCD device. The amplified image is digitized and can be visualized on a TV screen. Both red fluorescent image (664nm) of chlorin e6 and autofluorescence (550±10 nm, green fluorescence) are amplified separately and then treated with data analyzer. Finally the relative red fluorescence intensity of chlorin e6 is divided by the green auto-fluorescence intensity to correct for apparent intensity changes due to different distances from the bronchoscope. Thus, the red and green fluorescence images and R/G ratio as well as the white light image can be shown on the monitor respectively.

We performed PDD in 13 cases of lung cancer. All lesions were squamous cell carcinoma in situ. The dose of chlorin e6 was 1.0mg/kg body weight. Examinations were performed 72 hours after administration of chlorin e6. Red fluorescence and/or R/G ratio fluorescence were recognized in all bronchoscopically positive CIS cases. Strikingly enough, 3 cases of bronchoscopically negative CIS cases were recognized as positive with R/G Fluorescence Bronchoscopy. When testing histologically proven “normal” lesions, false-positive results were obtained in 50% of the total 26 “normal” lesions. However, when utilizing R/G ratio fluorescence the false-positive decreased significantly to 30%. In each case, red fluorescence at 670 nm of chlorin e6 from the tumor was detected at corresponding site, which on the contrary, green fluorescence was detected from the normal area not but tumor site. R/G ratio fluorescence was obtained as a red color image from the cancerous area more distinctly.

The advantages of this system are as follows: analysis of the fluorescence wavelength, observation of fluorescence under normal endoscopy illumination conditions, signal imaging of the cancer by the image processor and the simplicity of the procedure. However, there are still some problems for this system. Improvements widening the angle of divergence of the laser beam and standardization of fluorescence measurement are necessary. The false positive ratio was 30%, due to slight chlorin e6 fluorescence and autofluorescence from the normal bronchial mucosa. New photosensitizers for PDD also should be developed, with emission peak at longer wavelength and minimal phototoxicity. HAT-D01, meta-phenylene spacer-bearing chlorine hetero-dimers is a promising photosensitizer which has spectral peak at 670 nm that has no interference from autofluorescence from normal tissue. With further technological advance, improvement of photosensitizers, and monitoring sophistication, PDD could be applied to definitive diagnosis to early stage cancer.

PDT for early stage lung cancer

The total number of cases was 107 consisting of 126 lesions with an age distribution ranging from 36 to 85 years old. There were 106 males and 1 female. Histologically, all the cases were squamous cell carcinoma except one case of adenocarcinoma. All patients were required to have histopathologically and cytologically proven superficial cancer of the lung. Each patient had a bidimensionally measurable lesion. Informed consent was obtained from all patients or their relatives. Reasons why PDT was conducted in the enrolled patients were refusal of surgery, inoperability because of poor organic functions, serious concomitant disease, advanced age or possibility of cure by this modality.

Procedure

Bronchoscopical PDT is performed with topical anesthesia approximately 48 hours after the intravenous injection of 2.0mg/kg body weight of Photofrin. After injection of Photofrin, the patients are instructed to avoid direct sunlight for at least two weeks. A frequently used system for PDT is the argon pumped dye laser. Each system emits a 630 nm wavelength beam which has deepest tissue penetration among the wavelengths exciting Photofrin. In Japan, excimer dye lasers have been using since 1985. The laser beam is transmitted via a quartz fiber (400mm) inserted through the instrumentation channel of a fiberoptic bronchoscope. The fiber tip, at a distance of 1-2 cm and perpendicular to the target, yields a circular
area of illumination of 4-8 mm. The power output at the fiber tip was adjusted to 200 mW/cm² in case using the argon dye laser. Using the excimer dye laser, the frequency was 30 Hz and the energy was adjusted to 4 mJ/pulse. For surface irradiation of early stage lung cancer, giving energy densities of 200 Joules per cm² in cases of the argon dye laser use and 100 Joules per cm² in case of using the excimer dye laser was recommended. After the PDT procedure, bronchial toilet was performed every 2 or 3 days for 1 week.

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The therapeutic effectiveness of PDT was analyzed according to both the longitudinal tumor size and the visibility of the distal tumor margin. The univariate analysis was based on 2 x 2 tables and differences were tested by the χ² test. Of the 69 cancer lesions that had a longitudinal tumor extent of 1 cm or less, 65 (94.2%) obtained a CR after initial PDT, however of the 26 carcinomas that had a longitudinal tumor extent of greater than 1 cm, 14 (53.8%) showed CR after PDT. The survival curve was calculated by the Kaplan and Meier method. The overall survival rate is 68.3%.

Photodynamic therapy, a relatively new modality used in the treatment of cancer, has gained considerable acceptance in the past decade. A wide variety of malignancies have been treated by this method and according to the literature, over 3000 patients worldwide have been treated with photodynamic therapy. The estimate of the number of institutions and investigators worldwide is about 90 and 180 respectively. In Japan, PDT with Photofrin and excimer dye laser obtained government approval in October 1994 and finally obtained national insurance reimbursement status in April 1996.

PDT holds great future potential in the curative treatment of early stage cancer, palliative treatment of advanced cancer for local improvement of lesions, combination therapy with surgery and with ionizing radiation and chemotherapy. More stable, definitive and more successful results will be obtained if new dyes which distribute more equally in the tumor tissue and deeper tissue penetration by longer wavelength beams are used.

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