CLINICAL INVESTIGATIONS

Hematoporphyrin Derivative and Laser Photoradiation in the Treatment of Lung Cancer*

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Photoradiation therapy (PRT) was performed in 13 lung cancer cases and in one case of severely atypical squamous metaplasia following administration of hematoporphyrin derivative (HpD). The HpD is activated by visible red light (630 nm, 90 to 400 mW) from an argon dye laser. The cytocidal effects were due to the activation of the HpD, since 400 mW of power has in itself no effect on normal epithelium, even with long-term exposure. HpD is retained longer by malignant tissue than by normal tissue. Therefore, the lesions were irradiated with the red laser beam, delivered by a quartz fiber inserted through the instrumentation channel of the fiberoptic bronchoscope, 48 hours or more after intravenous injection of 2.5 to 4.0 mg/kg of HpD. A total of 14 cases received PRT. In one, two small, smooth-surfaced, squamous cell carcinoma tumors in the right B2b of a 74-year-old man who had refused surgery disappeared three days after HpD-photoradiation, and the patient remained disease-free 16 months after the treatment. In 12 cases of centrally located lung cancer local effects were obtained in all. However, there was no significant improvement in survival, attributable to the fact that all were advanced-stage cases. One patient with severely atypical squamous metaplasia requested treatment, and complete disappearance of metaplastic atypia was obtained.

Although the results of therapy for advanced lung cancer have improved slightly with advances in multidisciplinary treatment, they are still poor compared with the results of early-stage cases

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(more than 80 percent five-year survival in resected cases). Recently increasing lung cancer incidence is recognized internationally, and more cases of early-stage lung cancer are being detected with improvements in survey and diagnostic techniques, including fiberoptic bronchoscopy. However, some early-stage cases, inoperable due to age, poor pulmonary function, etc, are generally treated with conventional modalities such as radiation, chemotherapy, or intrabronchial arterial infusion. The advantages of a therapeutic method to curatively treat these lung cancer cases are clear. For advanced lung cancer cases, especially squamous cell carcinoma in larger bronchi, radiotherapy is the most common therapeutic approach, and it is important to develop preradiation therapeutic methods to prevent or to decrease the side effects of radiation.

Recently photoradiation therapy (PRT) for malignant tumors was introduced by Dougherty and colleagues.[1,2] In this method, which is based on the activation of photosensitive material by light, several potentially useful photosensitizers with tumor-specific characteristics may be used, especially certain porphyrins, which have been the most extensively investigated. In particular hematoporphyrin has a proved affinity for malignant tumors[3] and undergoes a photodynamic reaction on light exposure. In 1960 Lipson and Baldes[4] reported a derivative of hematoporphyrin (HpD), which he obtained by an acetic acid sulfuric acid preparation of hematoporphyrin. This material has been shown to be more specific for malignant tissue than pure hematoporphyrin in terms of both quantity judged by fluorescence and length of time of retention. It has also been shown that when

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HpD is excited by 405-nm wavelength violet light, it emits red light, with peaks at 630 and 690 nm, and has cytocidal effects on activation by red light.[6] Dougherty et al[7] reported on therapeutic applications of HpD and PRT in animal experiments and clinically in metastatic skin lesions from breast cancer.[2]

We have succeeded in inducing central-type lung cancer in dogs and using this animal model to perform studies on the diagnostic and therapeutic applications of HpD and laser PRT.[8] Based on the successful results of these experimental studies, we employed this method in human lung cancer cases via the fiberoptic bronchoscope.

Materials and Methods

Selection of Patients

Of the 14 cases, one was a patient with early-stage lung cancer, detected in a mass survey, who adamantly refused surgery, and another had severely atypical squamous metaplasia and strongly requested treatment. The remaining 12 were chosen at random from admitted lung cancer cases. Eleven were men and three were women. Age distribution was 38 to 74 years, with an average of 60.3 years. According to histologic type, five were well-differentiated squamous cell carcinoma, one was poorly differentiated squamous cell carcinoma, three were large cell carcinoma, two adenocarcinoma, and two were small cell carcinoma. Clinically two were in stage 1 (one early stage), eight in stage 3, and three in stage 4. In addition, one 61-year-old woman with severely atypical squamous metaplasia requested PRT. Preoperative photoradiation was performed in seven lung cancer cases. Five were resected curatively, and the remaining two were probe thoracotomy cases. Three stage 4 cases were treated with chemotherapy, radiation, and immunotherapy prior to PRT, and two cases were treated with chemotherapy or radiation after PRT. The early-stage case and the severely atypical squamous metaplasia case were treated by PRT alone.

HpD

The hematoporphyrin derivative (HpD) was provided by Dr. T. J. Dougherty and his associates at Roswell Park Memorial Institute, who prepared it[1,2] by a modification of Lipson's method.[4] The pH of the preparation was 7.2 to 7.4, and the solution was kept frozen and in the dark until use.

Light Source

An argon laser-dye laser system (Spectra-Physics) was used as a red light source. It consisted of an argon laser (model 171-08, 15 W power and 457.9 to 514.9 nm wavelength) and a dye laser (model 375-03, 630 to 640 nm wavelength using rhodamine B dye without the tuning wedge).

A quartz fiber (Quartz Products Co, 400 μ) was coupled to the dye laser using a fiber holder assembly (Spectra-Physics). The maximum intensity available through the quartz fiber was approximately 1,600 mW. The beam was transmitted via the quartz fiber inserted through the instrumentation channel of a fiberoptic bronchoscope (Olympus BF-B3, BF-B2, BF-B4, or BF-1T).

Procedure

Photoradiation was performed once or more for 10 to 40 minutes 48 hours or more after intravenous (IV) injection of 2.5 to 4.0 mg/kg of HpD. The power output was 90 to 400 mW from the fiber tip. After inserting the fiberoptic bronchoscope, the tip of the quartz fiber was placed approximately 1.0 to 2.0 cm from the lesion, giving a spot size of 4-8.5 mm. Irradiation lasted for 10 to 40 minutes. The fiber was moved so as to cover the entire lesion during the procedure. The distance naturally varied with respiration.

Evaluation of Therapeutic Effects

The tumor response to PRT was evaluated histologically, cytologically, by fiberoptic bronchoscope, and roentgenologically. In surgically resected or autopsied cases the treated lesions were examined histologically and macroscopically. Tumor response was classified into four grades: complete remission, significant remission, slight remission, and no remission. Complete remission indicates no evident tumor on chest x-ray film, endoscopically, cytologically, and histologically. Significant remission means that 60 percent or more of the original tumor volume disappeared roentgenologically or endoscopically, and slight remission means that less than 60 percent disappeared roentgenologically or endoscopically.

Results

Photoradiation was performed in 14 patients. Table 1 shows the details of the individual cases. The 74-year-old man with early-stage lung cancer (case 3) was a heavy smoker who complained of sputum and cough. He underwent chest x-ray and sputum cytologic examinations. Results of sputum cytology studies showed well-differentiated squamous cell carcinoma, but no abnormality was seen on his chest x-ray film. Fiberoptic bronchoscopy revealed two tiny tumors in the right B2b bronchus (Fig 1, left). Both tumors measured approximately 2 mm in diameter as observed endoscopically. Brushing cytology and biopsy of the lesion revealed well-differentiated squamous cell carcinoma.

Since this patient adamantly refused surgery, he was given the option of undergoing HpD administration and laser PRT. PRT was performed 72, 96, and 120 hours after a single IV injection of 2.5 mg/kg of HpD. PRT was performed for 20 minutes in each session with 200 mW total power output from the fiber tip. A large amount of white-grayish gelatinous substance occupied the B2 bronchus on the day following each PRT session. Submucosal hemorrhage and tumor necrosis were observed on the third day after the first PRT session. The tumor was recognized to have disappeared at five days

Table 1—*Photoradiation Therapy (PRT) with HpD Argon Dye Laser**

Case No.	Histologic Findings	Stage	Location	HpD, mg/kg	Frequency of PRT	Endoscopic Gross Findings		Operation	Response
						3 Days	2 Wk		
1	Adenocarcinoma	4	Trachea	2.5	1	Pale, WGS	Scar		Complete
			Trachea		1	White, necrosis, WGS	Scar		Complete
			Right main bronchus		1	Necrosis, WGS	Scar		Partial
			Carina		4	Necrosis, WGS, petechiae	Scar		Partial (significant)
			Left main bronchus		2	White, necrosis, WGS	Scar		Partial (significant)
			Right upper lobe bronchus (obstruction)		1	Petechiae, WGS	Scar		Partial (significant) (opening of the bronchus)
2	Large cell carcinoma	3	Right upper lobe bronchus (obstruction)	2.5	6	Necrosis, WGS	Necrosis	Before PRT (probe)	Partial (significant) (opening of the bronchus)
3	Squamous cell carcinoma	Early stage	Right B2b (2×2 mm)†	2.5	3	Necrosis, WGS, edema, petechiae	. . .		Complete
4	Squamous cell carcinoma	1	Right B9 (1×1 cm)†	2.5	1	Necrosis, petechiae	. . .	1 wk after PRT	Partial (significant)
5	Squamous cell carcinoma	3	Middle lobe bronchus	2.5	2	Necrosis, edema, WGS	Necrosis, decrease of tumor	1 wk after PRT	Partial
6	Large cell carcinoma	3	Right main bronchus (extra-bronchial tumor)	4.0	1	Necrosis, WGS	Petechiae, edema, WGS	Before PRT (probe)	Partial (significant)
7	Small cell carcinoma	4	Right trunc. intermediate (middle and B6)	4.0	1	Edema, WGS, petechiae	Scar		Partial
8	Large cell carcinoma	4	Right middle lobe bronchus	3.0	1	Petechiae, WGS	Scar		Partial (endoscopically complete)
9	Squamous cell carcinoma (low diff.)	3	Right upper lobe bronchus	2.5	2	Necrosis, WGS	Scar	2 wk after PRT	Partial
10	Squamous cell carcinoma	3	Left lower lobe bronchus	2.5	2	Necrosis, WGS, petechiae opening of the bronchus	Necrosis, petechiae	1 mo after PRT	Partial (significant) (opening of the bronchus)
11	Small cell carcinoma	3	Left upper lobe bronchus	2.5	1	Necrosis, WGS, petechiae	Necrosis		Partial (opening of the bronchus)
12	Adenocarcinoma	3	Left upper lobe bronchus	2.5	1	Necrosis, WGS	Necrosis		Partial
13	Squamous cell carcinoma	3	Right upper lobe bronchus	2.5	1	Necrosis, WGS	Scar (decrease of tumor)	1 mo after PRT	Partial
			Right main bronchus	2.5	1	Petechiae, WGS	Scar		Complete
14	Severe squamous metaplasia		Right upper lobe bronchus	2.0	1	Edema, petechiae	Normal		Complete

*Abbreviations: HpD, hematoporphyrin derivative; WGS, white gelatinous substance.
†Tumor size.

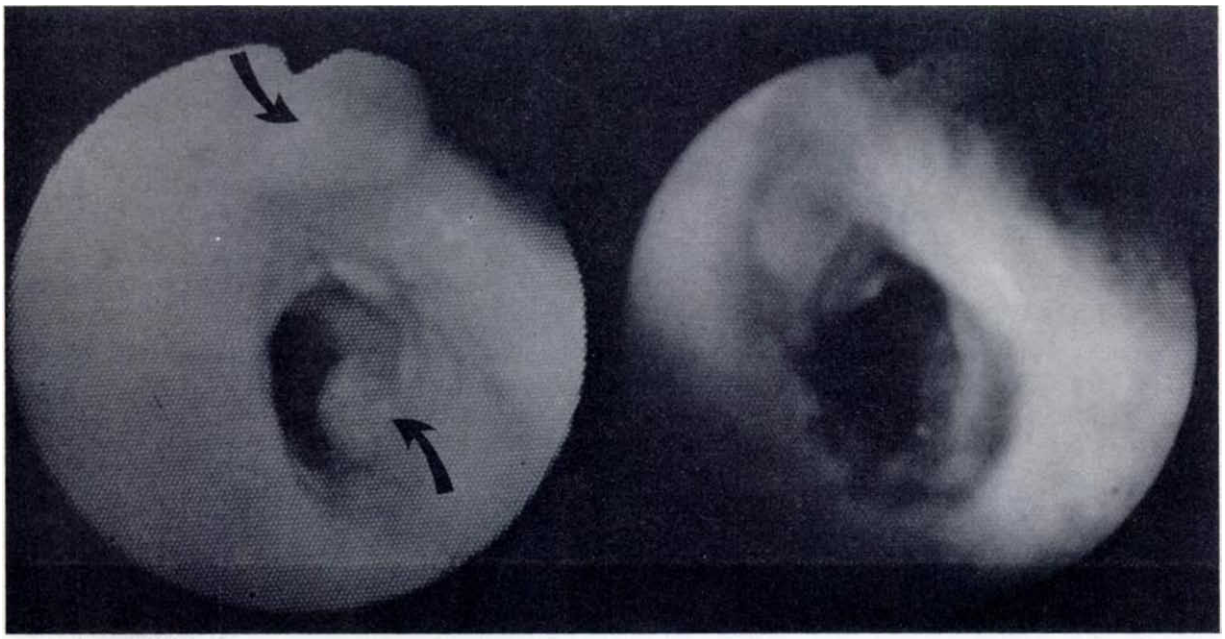

FIGURE 1 *(left)*, Case 3. Fiberoptic bronchoscopy showed two tiny tumors at bifurcation of right B2b bronchus *(arrows)*. *Right*, Case 3. No abnormality seen 11 months after photoradiation therapy (PRT). Complete response obtained.

after the third PRT session. There is no evidence of recurrence, and no tumor cells could be recognized by brushing cytology 16 months after PRT (Fig 1, right). The patient remains disease-free.

The case with severely atypical squamous metaplasia (case 14) was a 61-year-old woman in whom an infiltrative shadow was detected in her right upper lung field. She was a heavy smoker. Although her sputum cytology showed no abnormalities, fiberoptic bronchoscopy was performed. The gross findings showed slight redness and thickening of the right upper lobe bronchus. Brushing cytology results were strongly suspicious of squamous cell carcinoma, but biopsy revealed severely atypical squamous metaplasia. On her request PRT was performed, 72 hours after injection of 2.5 mg/kg of HpD, for 20 minutes with 200 mW power at the fiber tip. Thereafter no abnormal findings were observed bronchoscopically or cytologically.

In the other cases, which were all advanced, 18 foci in 12 patients were treated. None of the 12

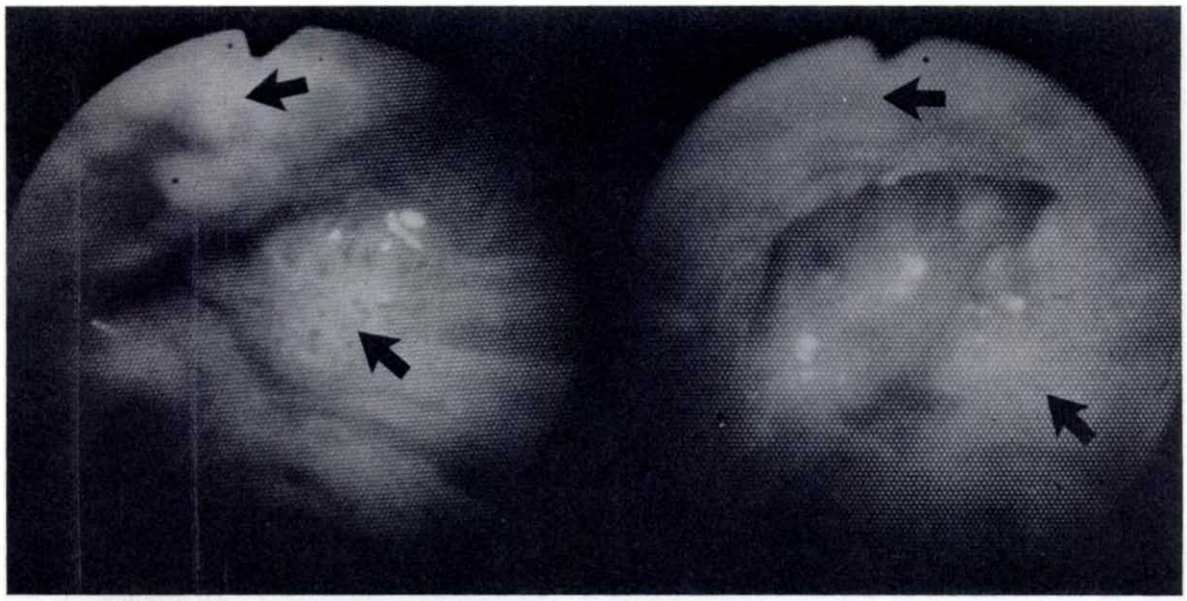

FIGURE 2 *(left)*, Case 13. Remarkable decrease of tumor size and area of invasion 19 days after treatment. *Right*, Case 13. 54-year-old man. Obstruction of right upper lobe bronchus with invasion in main bronchus.

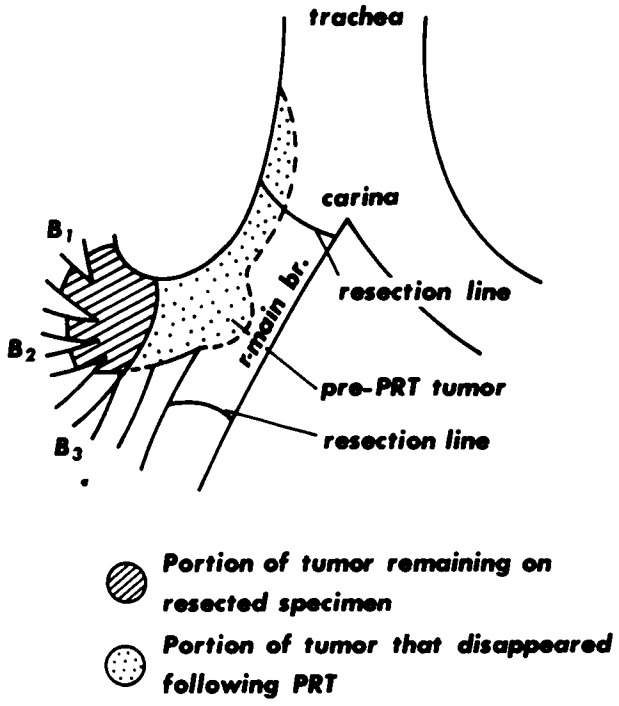

FIGURE 3, Case 13. Schematic representation of resected specimen.

patients was cured completely due to the extensiveness of the disease, but at least partial response was observed in 100 percent of cases. Complete response of the irradiated lesion was obtained in three of 18 lesions treated (16.7 percent). These were areas of tracheal invasion of adenocarcinoma (case 1) and squamous cell carcinoma situated in the right main bronchus (case 13, Fig 2). In case 13 the tracheal invasion treated by PRT disappeared, and the patient became able to undergo sleeve resection of the right upper lobe 30 days after PRT. Detailed examination of the resected specimen revealed no tumor cells in the area in the right main bronchus in which invasion had been recognized (Fig 3). Among the 18 foci significant remission was obtained in eight foci (40 percent). Opening of bronchi was obtained in four of eight patients with bronchi obstructed by tumor (50 percent; Fig 4; Table 2). The symptoms of dyspnea in these patients were alleviated.

Changes recognized in treated foci included loss of glossiness. They became pale or brown in color, with edema, petechiae, and necrosis and a large amount of grayish-white polypoid gelatinous material (Fig 5) on the necrotic tissues in all can-

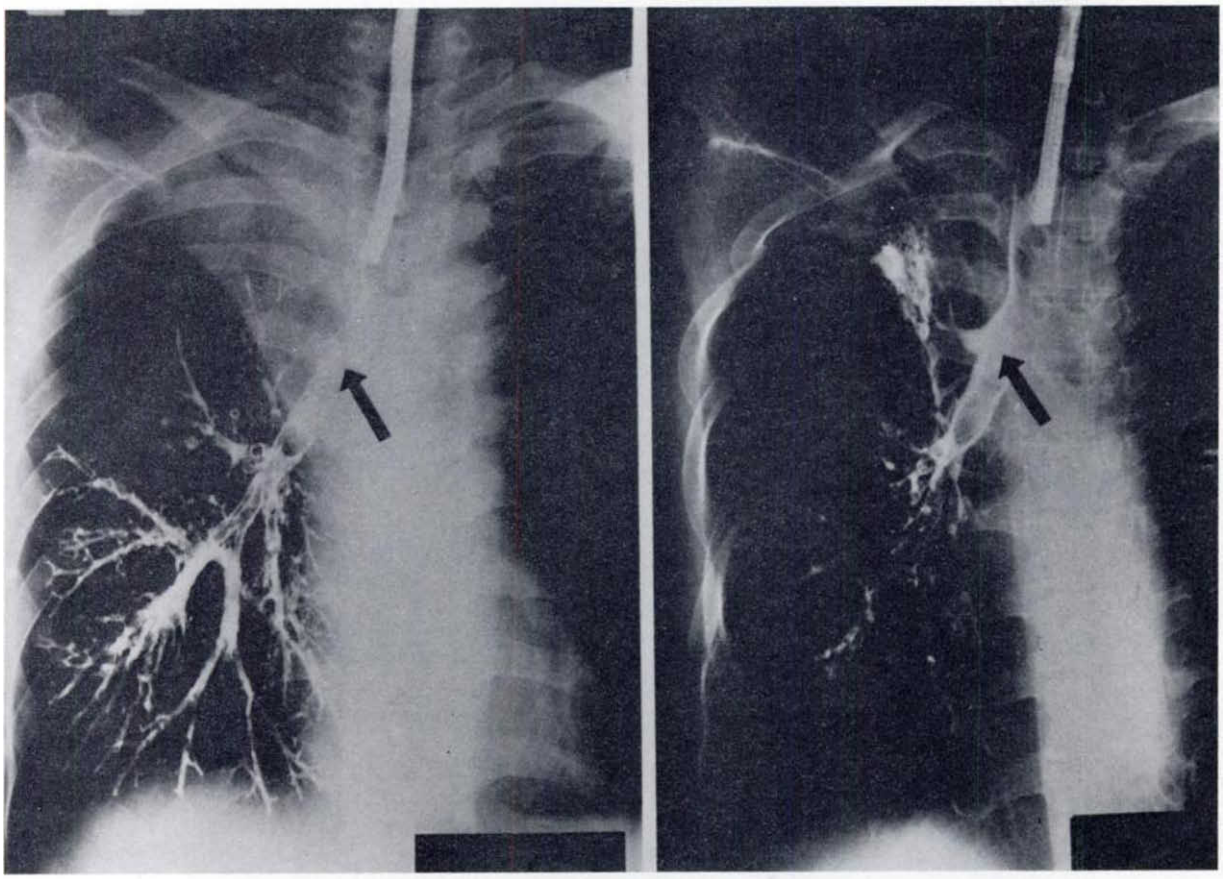

FIGURE 4 *(left)*, Case 2. Bronchographic findings confirm obstruction of right upper lobe bronchus. *Right*, Case 2. Bronchography performed one month after PRT, also showed opening of right upper lobe bronchus.

Table 2—*Results of Photoradiation Therapy in 19 Foci**

Condition	No. (%)
Complete remission	4 (21)
Significant remission	8 (42)
Slight remission	7 (37)
No remission	0 (0)

*Opening of bronchi obstructed by tumor was obtained in four of eight foci (50%).

cer cases. This substance also resembled highly viscous sputum, and was observed obstructing bronchi a few days after PRT. Fiberoptic bronchoscopy was performed every day for a few days after PRT to remove these secretions. This substance histologically consisted of degenerated tumor cells, serum protein, and inflammatory cells. In the case of severely atypical squamous metaplasia, although no significant changes were seen after PRT except slight edema, petechiae were observed three days after PRT.

In five of 14 advanced cases curative operations were performed following PRT, and the resected specimens were examined pathologically in detail. Although no complete responses were obtained, at least partial tumor remission was observed in all cases. Tumors exposed in the lumen of the bronchus were mostly degenerated but viable tumor cells remained in tumors extending extrabronchially (Fig 6).

The histologic changes reflected the degeneration of cancer cells, which was seen as nuclear destruction, consisting of karyolysis, karyorrhexis, pyknosis, and vacuolization, and cytoplasmic vacuolization. Submucosally, hemorrhage, edema, and infiltration of inflammatory cells such as leukocytes, eosinophilic leukocytes, lymphocytes, and histiocytes were recognized (Fig 7).

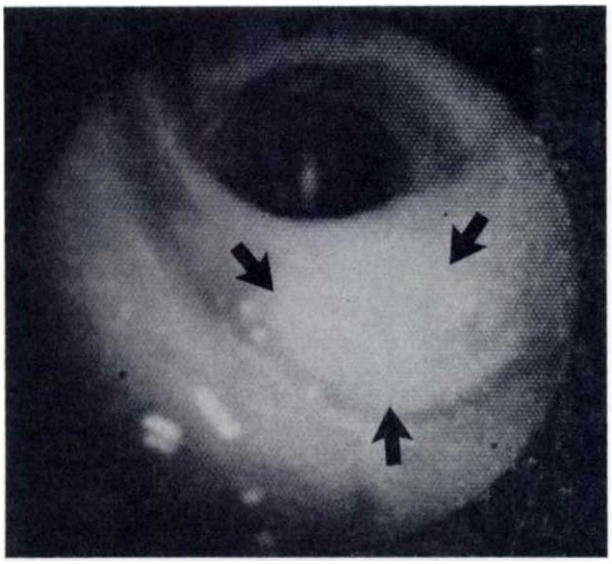

FIGURE 5, Case 4. Large amount of white gelatinous substance in necrotic tissue obtained for few days after PRT; shown are findings on day after treatment. Substance obstructed B9 and B10 bronchi despite the tumor's location in B9 bronchus. This substance should be removed to avoid obstructive pneumonia.

DISCUSSION

A system involving administration of Hpd followed by the laser photoradiation system was introduced by Dougherty et al[2] for therapy of malignant diseases. This pioneering work was performed primarily in very advanced cases. To clarify the therapeutic indications in early-stage cases, we applied a similar system in a successful canine lung cancer study.[11] Subsequently we applied the methodology established on the basis of the experimental data in human lung cancer cases including early-stage cases.

Responses were obtained in all cases (100 percent). In particular, the single case of early-stage lung cancer showed complete regression of the tumor, and the patient remained disease-free at 16 months after therapy. While this is only a single case, it does highlight the possible significance of Hpd and laser beam irradiation in the nonsurgical curative treatment of early-stage lung cancer. Lung cancer incidence is much higher in older age groups, and many cases have poor lung function due to fibrosis and emphysema, and also heart failures. In such cases, surgery can be contraindicated even in early-stage lung cancer, and conventional therapeutic options are limited to radiotherapy, systemic chemotherapy, and immunotherapy. Results in such cases are frequently unsatisfactory. From this point of view, this new PRT appears highly significant. However, the indications for this therapeutic modality are at present limited to those tumors visible by fiberoptic bronchoscopy and less than 1 cm in depth because of the problem of light penetration. Methods of implanting quartz fibers for deeper penetration are now under investigation. Dougherty et al[15] have demonstrated the effectiveness of this method. Resected specimens indicated that the light penetration was insufficient to penetrate through to the extrabronchial portion of tumors, even though remission of the endobronchial portion was obtained. These findings were observed in cases 4 and 5. In these cases 2.5 mg/kg body weight of Hpd was injected IV and PRT conditions were 200 mW from the fiber tip, for 10 to 40 minutes at 48 and 72 hours following the injection. Thus, greater power and light penetration are necessary in advanced cases.

Severely atypical squamous metaplasia has been

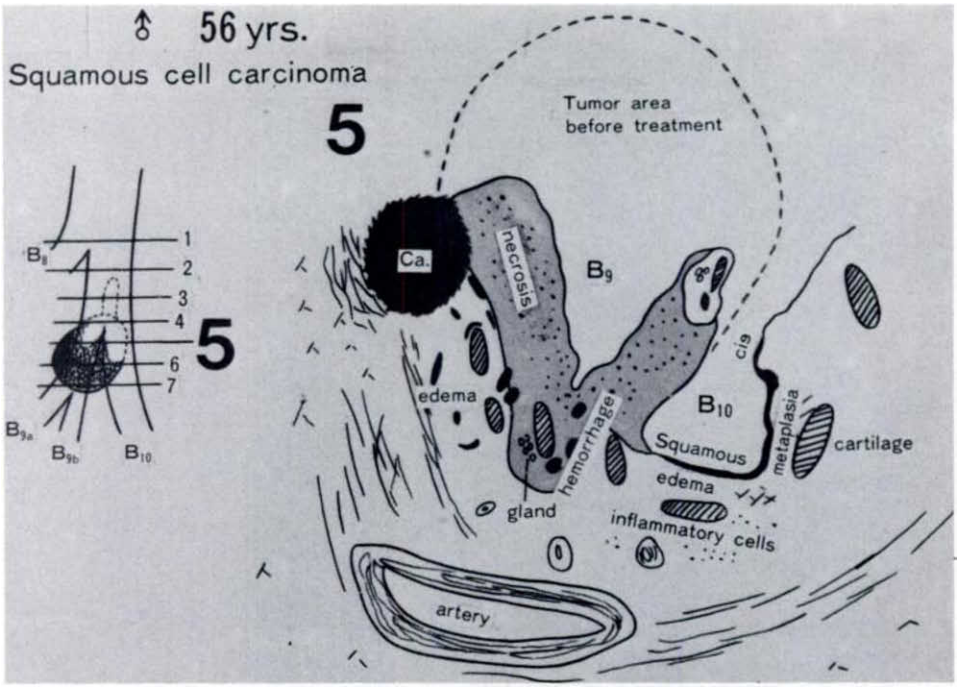

FIGURE 6, Case 4. Schema of the resected specimen. The tumor had mostly disappeared except beyond the bronchial cartilage. *Ca*, remaining viable cancer tissue.

recognized in the carcinogenetic process in a canine model and has been suggested as one of the possible precursors of squamous cell carcinoma.[9] It has also been associated with a high incidence of lung cancer in uranium workers.[10] In the case included in the present series a diagnosis of severely atypical squamous metaplasia was reached after brushing cytology originally yielded findings suspicious of malignancy. Nevertheless, the patient requested PRT because there are no harmful effects on normal epithelium.[8] It was decided to accede to the patient's request. The fact that subsequently no abnormal cytologic findings were recognized suggests the possibility of the future use of this modality in the treatment of such precursors to malignancy, thus preventing the development of pulmonary squamous cell carcinoma. This case revealed only slight macroscopic change after therapy, contrary to the cases of malignant tumors, possibly due to lower Hpd absorption by squamous metaplasia than by malignant tumors.

Although partial responses were obtained in all cases, in advanced cases this procedure should not be expected to result in complete response. However, since opening of the bronchus was obtained in 50 percent of cases of bronchial obstruction by tumors following this procedure, it can be effective in improving clinical performance and dyspnea and obstructive pneumonia.

In this clinical trial in lung cancer patients, the light dosage varied from 90 to 400 mW from the fiber tip. The effective response depended on the light penetration, which in turn depended on the light output. To maximize effectiveness it is neces-

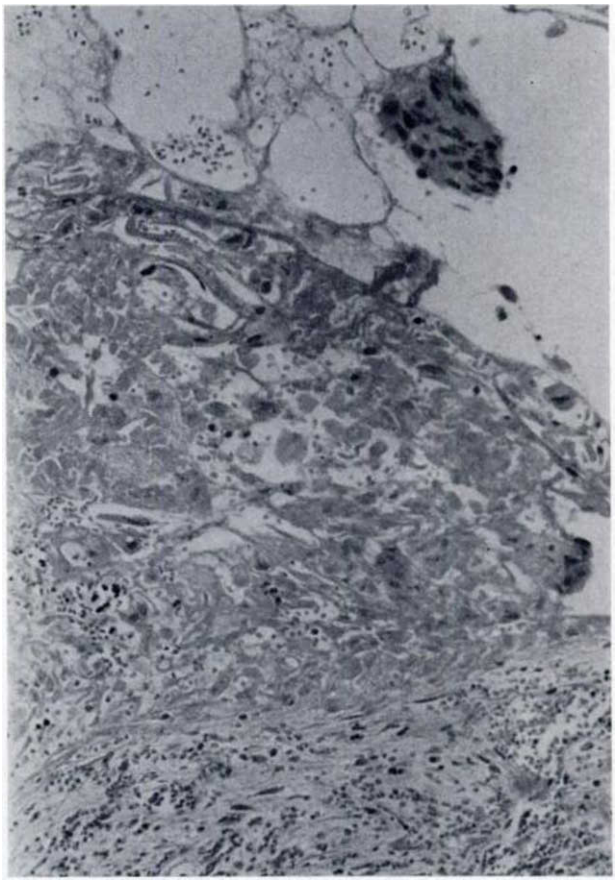

FIGURE 7, Case 4. Histopathology of tumor tissue showed degeneration of tumor cells (×200).

sary to remove intraprocedurally necrotic tissue, since necrosis, which occurs immediately due to PRT, absorbs red light and diminishes light penetration into the tumor tissue.

In case 6, which showed stenosis of the right main bronchus with submucosal invasion and compression from an extrabronchial tumor, the stenotic portion improved one month after PRT. In this case, necrotic changes were not seen during the irradiation. Therefore, the light penetration is considered to have been sufficient to decrease the tumor size.

In the description of the mechanism of tumor destruction by Weishaupt et al,[6] singlet oxygen produced by activation of Hpd under exposure to red light was suggested as causing the oxidation of the cancer cell. The location of Hpd in tumor tissue in human cases is unclear. It is likely that Hpd is absorbed into the cytoplasm or adheres to the cytoplasmic membrane, according to our previous experiments using cultured cancer cells.[12,13] Gomer et al[14] suggested that Hpd was located in the interstitial tissue between cancer cells.

The major side effect is skin photosensitivity. Slight sunburn was recognized in 11 of 14 cases (78.5 percent). The patients were told to stay in shady parts of the hospital building during the day for about two weeks. However, slight sunburn, even under room lamp exposure, was observed in ten cases. In a single patient who refused to stay in the shade, serious side effects were observed.

No major complications such as bleeding were observed. However, it is obvious that great care must be exercised in employing this therapy if invasion to the pulmonary artery or large vessels is suspected.

For optimum therapeutic effect, sufficient amounts of both Hpd and light are required in the tumor tissue. Laser beams therefore appear most suitable for this procedure, because they can provide sufficient doses of light at the desired wavelength of 630 nm. To achieve higher concentrations of Hpd in tumor tissue, it may be possible to infuse Hpd into the blood supply of the tumor. Methods such as implanting quartz fibers into the tumor to achieve better light irradiation distribution are possible,[15] in addition to using materials such as drugs with properties similar to Hpd but with greater tumor uptake.

To date satisfactory results were obtained in the single early-stage lung cancer case treated by Hpd and laser beam PRT. Unfortunately, most cases of lung cancer are detected at advanced stages, and there are difficulties in the estimation of the precise extent, size, and the depth of the tumor. Evaluation of lymph node involvement and metastasis prior to treatment can also be difficult. Therefore, it is not easy to evaluate precisely the tumor response after PRT. However, it appears that in cases of advanced carcinoma, other therapeutic modalities, such as combined systemic chemotherapy, radiation therapy, and immunotherapy, are thought to be necessary.

This therapeutic method also may hold potential for the treatment of widespread lymph node involvement that cannot be resected intraoperatively.

While the full extent of the indications and effectiveness of Hpd administration plus photoradiation therapy remain to be established, our experience has shown that it is effective in palliation of the conditions of advanced lung cancer cases, and has achieved a 16-month period of disease-free survival in a case of early-stage lung cancer.

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References

1 Dougherty TJ, Kaufman JH, Goldfarb A, et al. Photoradiation therapy for the treatment of malignant tumors. Cancer Res 1978; 38:2628-35

2 Dougherty TJ, Lawrence G, Kaufman JH, et al. Photoradiation in the treatment of recurrent breast carcinoma. J Natl Cancer Inst 1979; 62:231-37

3 Figge FHJ, Weiland GS, Manganiello LOJ. Cancer detection and therapy: affinity of neoplastic, embryonic, and traumatized tissues for porphyrins and metalloporphyrins. Proc Soc Exp Biol Med 1948; 68:640-41

4 Lipson RL, Baldes EJ. The photodynamic properties of a particular hematoporphyrin derivative. Arch Dermatol 1960; 82:508-16

5 Profio AE, Doiron DR. A feasibility study of the use of fluorescence bronchoscopy for localization of small lung tumors. Phys Med Biol 1977; 22:949-57

6 Weishaup KR, Gomer CJ, Dougherty TJ. Identification of singlet oxygen as the cytotoxic agent in photo-inactivation of a murine tumor. Cancer Res 1976; 36:2326-29

7 Dougherty TJ, Grindey GB, Fiel R, et al. Photoradiation therapy: II. Cure of animal tumors with hematoporphyrin and light. J Natl Cancer Inst 1975; 55:115-21

8 Hayata Y, Kato H, Konaka C, et al. Hematoporphyrin derivative and photoirradiation therapy with argon dye laser for the treatment of experimentally induced central type lung cancers in dogs (Japanese). Igakunoayumi 1981; 116:203-15

9 Kato H, Hayata Y, Konaka C, et al. Lung cancer histogenesis following in vivo bronchial injections of 20-methylcholanthren in dogs. Rec Prog Cancer Res, Springer-Verlag (in press)

10 Saccomanno G, Archer VE, Auerbach O, et al. Development of carcinoma of the lung as reflected in exfoliated cells. Cancer 1974; 33:256-70

11 Hayata Y, Kato H, Ono J, et al. Fluorescence fiberoptic

bronchoscopy for diagnosis of early stage lung cancer. Rec Prog Cancer Res, Springer-Verlag (in press)
12 Kato H. The role of sputum cytology in mass survey for lung cancer (Japanese). Thorac Surg 1979; 32:601-04
13 Kato H, Konaka C, Hayata Y, et al. Cancer localization by detection of fluorescence by means of HpD administration and krypton ion laser photoradiation in canine lung cancer (Japanese). Lung Cancer (in press)
14 Gomer CJ, Dougherty TJ. Determination of [^{3}H]- and [^{14}C]-hematoporphyrin derivative distribution in malignant and normal tissue. Cancer Res 1979; 39:146-51
15 Dougherty TJ, Thoma RE, et al. Photoradiation therapy for treatment of tumors in pet cats and dogs. Cancer Res 1981; 401-04

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