Palliation of Esophageal Malignancy With Photoradiation Therapy

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Seven patients with severe or complete obstruction of the esophagus by malignancy were treated with photoradiation after presensitization of the tumor with intravenous hematoporphyrin derivative. The 625- to 635-nm therapeutic light was delivered from a tunable dye argon laser system coupled through quartz fibers, passed through the biopsy channel of a flexible esophagoscope, with local anesthesia. All tumors (adeno, squamous, and melanoma) responded, and swallowing was improved. Although tumor is still present, one patient is 11 months from initial treatment and is eating a regular diet. Another patient is 8 months from initial treatment and has no dysphagia. One patient died of aspiration of gastric tube feedings and 3 others died of their disease at 3 weeks, 3 months, and 6 months, respectively, from their initial treatment. Another patient died 11 months from his initial treatment due to a cardiac arrhythmia. During the 11 months after his initial treatment he continued to eat a regular diet.


The results of the management of patients with cancer of the esophagus continues to be dismal. Therefore, we report the results with seven patients with cancer of the esophagus treated by photoradiation of the tumor area after presentation of the tumor with intravenous hematoporphyrin derivative. This form of therapy was developed and promoted by Dougherty, at Roswell Park Memorial Institute and now is being evaluated in several institutions.

Since 1924,† it has been known that some tumors give off a red-orange fluorescence when exposed to ultraviolet light. Studies in 1942 showed systemic injections of hematoporphyrin derivative gave off this characteristic red fluorescence in rat tumors, but not in normal tissue.

In 1961, Lipson and associates‡ reported the use of hematoporphyrin derivative prepared from hemoglobin by treating it with a acetic–sulfuric acid solution. This gives a higher degree of fluorescence to the tumors. In 1968, Gregorie and colleagues§ reported the results of studies of 226 patients treated with the intravenous injection of hematoporphyrin derivative. They found a 75% to 85% correlation of the fluorescence with positive biopsy specimens of squamous tumors and adenocarcinomas. In 1972, Diamond et al.§ reported destruction of experimental tumors by exposure to white light after the systemic injection of hematoporphyrin derivative. Subsequently, Dougherty and colleagues‡ at Roswell Park Memorial Institute reported on their laboratory and clinical work that used various light systems.

Hematoporphyrin derivative disseminates throughout the entire body, including the neoplastic tissue. The clearance from normal cells is faster than from neoplastic cells. Therefore, after a period of time, there is a higher concentration of the dye remaining in the neoplastic tissue than in the adjacent normal tissue.

When the dye is activated by exposing it to red light (625–635 nm) the energy is absorbed by the hematoporphyrin derivative. This produces a photodynamic reaction. One mechanism of the reaction is the formation of singlet oxygen that destroys the cancer cells. Since there is little or no hematoporphyrin derivative in the normal cells at this time, there is little or no severe reaction in the normal tissue. Although the absorption spectrum for the dye is greater for the 405-nm wavelength, red light at approximately 630 nm is used, since it penetrates tissue to a greater depth.

Materials and Methods

Three milligrams of hematoporphyrin derivative (Photofrin Medical Inc., Cheektowaga, New York) per

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kg of body weight were injected as a single intravenous bolus 3 to 6 days before photoradiation. A 20-watt argon laser (Spectra Physics, model #171) provides optical energy that is directed onto Rhodamine-B dye circulated in a tunable dye laser (Spectra Physics model #375) without the tuning wedge. The ensuing red beam (625–635 nm) then is coupled to 400- or 600-μ quartz fibers. These are then inserted through the biopsy channel of a standard fiberoptic gastroscope. The power output on the tip of the fiber is measured with a Coherent radiometer (model #210).

Special cylinder-type fibers delivering the light 360° over a distance of 2 to 3 cm (Photofrin Medical Inc.) were used on some of the patients. The power delivered from this type fiber was measured by placing the side of the light dispersion area adjacent to the well of the Coherent #210 radiometer. All patients were treated with local anesthesia.

The Laser Medical Research Foundation in collaboration with Grant Hospital Laser Center has treated 87 patients with various forms of malignancy by photoradiation, in accordance with strict Institutional Review Board guidelines. All patients are informed of the investigational nature of this therapy and have had, refused, or been ineligible for conventional surgery, chemotherapy, or x-ray therapy.

A summary of the results of seven patients with cancer of the esophagus is presented in Table 1.

**Case Reports**

**Case 1**

An 86-year-old white man could swallow only clear liquids because of a 5-cm-long melanoma (Fig. 1) encircling two-thirds of the circumference of the middle esophagus.

Three weeks after photoradiation with a 3-cm cylinder fiber delivering 200 mW to three areas for 10 minutes each, the
tumor was one half its original size and he was able to eat a regular diet.

Five weeks after a second treatment, the tumor covered only one fifth the circumference of the esophagus (Fig. 2).

Ten weeks after his second treatment, esophagoscopy showed the tumor enlarging and we elected to treat him with the Neodymium-Yttrium aluminum garnet (Nd:YAG) laser. Since then he has had three more treatments with the Nd:YAG laser.

Eleven months after his initial treatment, the tumor is 4 cm long and encircles one third of the circumference, but he has had no dysphagia, physical limitations, or weight loss since his initial treatment. He recently received his third photoradiation treatment.

Case 2
A 71-year-old black man received x-ray therapy for a cervical esophageal cancer in November, 1982. Increasing stenosis was controlled with dilatation, but on March 29, 1983, he had only a 2-mm opening that could not be mechanically dilated. Prior to seeing this patient, a jejunostomy feeding tube had been inserted since he had a previous subtotal gastrectomy.

A 7.6 mm diameter esophagoscope could not be passed beyond 18 cm and the tumor was photoradiated by inserting a 600-μm fiber into multiple areas of the tumor, delivering 1000 mW for 23 minutes. At the end of the procedure the tumor was edematous, soft, and easily dilated up to a #48 Fr. Maloney dilator. A #18 Salem sump passed into the stomach with return of gastric juice.

Two weeks later a 12.6-mm-diameter gastroscope passed easily to 25 cm. The tumor was necrotic and edematous and readily dilated to a #52 Fr. Maloney dilator.

Meanwhile, he had developed a jejunocutaneous fistula but a #18 Salem sump easily passed into his stomach. The patient died 3 weeks after photoradiation.

Case 3
A 65-year-old white man with complete obstruction of his distal esophagus by adenocarcinoma was not able to swallow his own saliva. Because of severe cardiopulmonary disease, he was not considered a candidate for surgery or x-ray therapy (Fig. 3). He refused chemotherapy. He first underwent photoradiation on November 24, 1982, by a cylinder-type fiber with a 2.5-cm-long diffusing area blindly passing through a pinpoint opening in the esophagus through the fiberoptic gastroscope. This delivered 300 mW from its sides, and 2 successive 2.5-cm areas were treated for 10 minutes each and a third area for 7 minutes.

Esophagoscopy 2 days later showed a pearly white reaction in the esophagus in the treatment area. There was a 4-mm opening in the esophagus and gastric juice was refluxing (Fig. 4). He was now able to eat ice cream. At 3 weeks he was eating a soft diet. Esophagoscopy showed whitish necrotic changes in the mucosa in the treated area with an opening that permitted a 7.8-mm diameter gastroscope to pass without difficulty (Fig. 5).
Ten weeks after therapy she had gained 10 pounds and was eating regular food.

Four months later the patient was retreated with a cylinder-type fiber, delivering 200 mW for 15 minutes to five successive areas from 25 to 40 cm. Six months after her first treatment, she was eating a regular diet and had gained 11 more pounds, but the tumor was still present and she was treated for a third time. Eight months from her first treatment the esophagus is open, but the tumor is still present.

**Case 5**

A 65-year-old white woman had complete obstruction of her distal esophagus from adenocarcinoma. She previously had a gastrostomy, and attempts at esophageal dilatation had been unsuccessful. The tumor was photoradiated with 200 mW for 10 minutes with a cylinder fiber inserted into the tumor and 200 mW for 10 minutes directed onto the top of the tumor from a straight fiber tip. A total of 1000 mW was then delivered directly into the tumor with a 600-μ straight fiber tip for 10 minutes.

At the end of the treatment, the tumor showed obvious edema and necrosis and there was a small opening, which allowed a 12.6-mm-diameter gastroscope to pass easily into the stomach, and there was a whitish concentric area of inflammation from 27 to 40 cm. Ten weeks after therapy she had gained 10 pounds and was eating regular food.

Four months later the patient was retreated with a cylinder-type fiber, delivering 200 mW for 15 minutes to five successive areas from 25 to 40 cm. Six months after her first treatment, she was eating a regular diet and had gained 11 more pounds, but the tumor was still present and she was treated for a third time. Eight months from her first treatment the esophagus is open, but the tumor is still present.

**Case 4**

A 71-year-old white woman with a chronic brain disease was able to swallow only liquids because of a squamous cell carcinoma at 30 to 35 cm from the teeth. Five successive areas were treated with a cylinder-type fiber delivering 300 mW from its sides from 25 to 40 cm. Two weeks later, a 12.6-mm-diameter gastroscope passed easily into the stomach, and there was a whitish concentric area of inflammation from 27 to 40 cm. Ten weeks after therapy she had gained 10 pounds and was eating regular food.

Four months later the patient was retreated with a cylinder-type fiber, delivering 200 mW for 15 minutes to five successive areas from 25 to 40 cm. Six months after her first treatment, she was eating a regular diet and had gained 11 more pounds, but the tumor was still present and she was treated for a third time. Eight months from her first treatment the esophagus is open, but the tumor is still present.

**Case 5**

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easily dilated through a #48 Fr. Maloney dilator and enabled the passage of a 7.5-mm-diameter gastroscope into the stomach without difficulty. Gastric tube feedings were restarted, and 2 days after treatment the patient aspirated the tube feeding. She died from pneumonia 1 month after treatment.

Case 6

A 61-year-old black man was able to swallow only clear liquids due to distal obstruction of the esophagus from squamous cell cancer beginning at 35 cm. He was treated with a cylinder fiber delivering 300 mW from its sides for 10 minutes in two successive areas from 35 to 41 cm. A straight-tip fiber was then used to deliver 300 mW held above the tumor for 5 minutes.

Esophagoscopy 4 days later showed a pearly white edematous reaction beginning at 32 cm, and we were able to pass the gastroscope into the stomach without any difficulty. He now was swallowing a full liquid diet. Three weeks after treatment a barium swallow showed the tumor to be 8 cm long, with an opening of 1.3 cm, and he was eating a regular diet. He was retreated following a second injection of hematoporphyrin derivative.

In the 2 months after his first treatment he had gained 17 pounds and was eating hot dogs and steak. At 3 months, a barium swallow showed a 1.8-cm-diameter opening through a 6-cm-long tumor. He continued to eat a regular diet but refused any more hematoporphyrin derivative injections because of the activity limitations caused by the photosensitivity of the skin to sunlight. Accordingly, he was treated twice with the Nd:YAG laser. By 4 months he had developed difficulty swallowing and was admitted to another hospital where a gastrostomy was performed. He died 6 months after his first photoradiation treatment with widespread disease.

Case 7

A 75-year-old white man had an concentric adenocarcinoma of the esophagus that prevented the 7.6-mm-diameter gastroscope from passing 35 cm. Two successive areas were treated with a cylinder fiber delivering 300 mW for 10 minutes each and 1000 mW from a straight fiber inserted into multiple areas for 10 minutes. Two days later a 7.6-mm-diameter gastroscope was passed easily into the stomach and the tumor was edematous and friable from 30 to 36 cm. Four days after his initial treatment, the patient was retreated with 1000 mW from a straight fiber inserted in multiple areas for a total of 30 minutes.

Three weeks after his first treatment he was anorexic, but able to swallow. The 11-mm-diameter gastroscope passed easily into his stomach and dilation to a #50 Fr. Maloney dilator was possible. He died 10 weeks after treatment, due to widespread disease.

Discussion

Palliation of patients with esophageal malignancy remains a desperate challenge with no truly effective modality. Survival is usually measured in terms of weeks, with unimaginable suffering from the disease and therapies.8-10

With photoradiation therapy delivered through a fiberoptic esophagoscope and topical anesthesia, we have been able to palliate patients up to 11 months, while they resume or continue eating normally. Except for the limitation of sunlight exposure for 2 months after the hematoporphyrin derivative injection, they have maintained a normal life-style. We have not had any adverse reactions from over 100 injections of hematoporphyrin derivative.

A cylinder-type fiber delivering 200 to 300 mW from its sides appears to provide the best light distribution for treating concentric lesions. A straight-tip fiber delivering 1000 mW inserted directly into exophytic tumors causes immediate changes, and the hard tumor becomes edematous and soft. At the end of the treatment, Maloney dilators and nasogastric tubes frequently pass tumors that previously were completely obstructing and could not be dilated by any type of dilators.

The posttreatment side effects have been relatively minimal: (1) burning epigastric or retrosternal pain similar to esophagitis, easily controlled with antacids and codeine for 3 or 4 days; (2) expectoration of necrotic tumor for approximately 1 week; and (3) edema that may require esophagoscopy and dilatation with Maloney dilators 1 or 2 weeks after treatment.

Management of these patients by repeated dilatations and/or insertion of prostheses may be associated with a procedure-related mortality rate of up to 20%.11,12,13 In addition, there are the complications due to a foreign-body tube in the esophagus.

Recanalization of the esophagus with a Nd:YAG laser14 has been technically more difficult, in our hands, than photoradiation. In case of complete or almost complete obstruction, the tumor must be destroyed from the top down and it is difficult to know exactly which direction to go so as not to perforate the esophagus. If the fiber tip is too close to the esophagoscope, the esophagoscope will burn. The treated tumor does not immediately disintegrate, but remains as hard, coagulated tissue and must be removed mechanically. Perforation occurs in 10% to 20% of the cases.14

With photoradiation, a cylinder fiber can be inserted through a narrow opening and the entire tumor can be treated at one time. With a straight-tip fiber delivering 1000 mW directly into the tumor, the hard tumor becomes edematous and soft and can be dilated easily with Maloney dilators.

While photoradiation of the esophageal tumors is promising, many questions need to be answered, some of which are:

(1) What is the optimum power and duration of treatment?
What is the optimum time for retreatment?

Would corticosteroids help control the edema or would they be deleterious?

Should it be combined with x-ray and/or chemotherapy?

Would prior “debulking” with the Nd:YAG laser be beneficial since the light for photoradiation only penetrates a maximum of 1.5 cm?

Conclusions

Preliminary studies show photoradiation therapy of esophageal malignancies after presensitization with hematoporphyrin derivative to be a relatively simple way to provide palliation with minimal risk. Nutrition and management of secretions are the two main problems these patients have until they die of their disease. With photoradiation, we have been able to control these problems and permit the patients to lead otherwise relatively normal lives.

There are numerous advantages of photoradiation. The operative risk is minimal, and it has the ability to destroy the tumor as well as to increase the size of the esophageal lumen. It can be repeated indefinitely, there is no conflict with x-ray and/or chemotherapy, and no foreign-body prostheses are involved. It is easier to perform than Nd:YAG. In addition, patients who are not malnourished can be treated as outpatients. The main complication has been the necessity of avoiding bright sunlight for up to 2 months after injection of the hematoporphyrin derivative.

REFERENCES


