High-dose Photoirradiation of Esophageal Cancer

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Fifteen patients with locally advanced esophageal cancer were treated with phototherapy. Each patient had dysphagia and weight loss before therapy and could not be operated on because of the extent of the tumor or poor performance status. Patients received a photosensitizer (hematoporphyrin derivative) 72 hours before phototherapy and were then treated by light delivered by an argon pumped dye laser or gold metal vapor laser at powers up to 2.2 W and doses of 337 J/cm^2. Fourteen patients received 24 treatments. The results were *all* patients achieved a tumor response. The depth of response depended on the dose and dose rate of radiation. There were four of 24 local complications (mediastinitis 3, bronchoesophageal fistula 1). These occurred in patients treated with a power of greater than 1.5 W. There were two complete pathologic remissions in patients with locally advanced cancer. In conclusion, phototherapy is an effective alternative to other forms of palliation and potentially may be an alternative to surgery in selected cases of locally advanced esophageal cancer.

TREATMENT OF CARCINOMA of the esophagus is unsatisfactory. Although there has been recent improvement in the survival of patients treated by surgical resection,[1] the survival of patients with inoperable cancer is poor. Furthermore, radiotherapy, chemotherapy, or dilation and intubation often do not provide good palliation. There have been several reports on the use of laser therapy for the creation of a larger esophageal lumen to enable patients to swallow. This has been achieved either by directly coagulating tumor with an Nd Yag Laser or by photodynamic therapy using an argon pumped dye laser emitting light of 630 nm onto tumors presensitized with hematoporphyrin derivative (HpD).[2–9]

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HpD has been shown to selectively localize in many human and experimental tumors[4] and to sensitize them to kill by light of appropriate wavelength. Photodynamic therapy has been used to treat many human tumors, including recurrent breast cancer,[4] squamous carcinoma of the head and neck,[5] bronchial carcinoma,[6] gastrointestinal tract cancer,[7] and bladder cancer.[8] Complete and partial response rates of up to 60% have been reported in bronchial and gastrointestinal tract cancers. There have been two previous reports dealing specifically with esophageal cancer. McCaughan et al.[9] reported the results of 16 patients with advanced cancer and Hayata et al.[7] reported on the results of 12 patients with advanced cancer.

These studies have not attempted to identify the maximum tolerable dose of light for the phototherapy of esophageal cancer. Variable dose rates were used with powers of 90–400 mW and 200–1000 mW.[7,9] It is not clear whether dose rate is an important determinant of tumor kill, although it is clearly important for the kill produced by x-irradiation.[10] The dose of light delivered in one of the studies[7] was less than 150 J/cm^2; in the other study[9] insufficient information was provided to calculate the dose delivered.

The dosimetry in photodynamic therapy is poorly developed. Only the power output of the laser and the duration of therapy can be measured accurately. The surface area of the tumor can only be estimated and the delivery systems using fibers with a variety of tips provide variable distribution to the tumor. The absorbed dose of light cannot be measured. We describe a method

TABLE 1. *Characteristics of Patients with Esophageal Cancer*

Patient	Age (years)	Sex	Histology	Site	Length (cm)	Extra-esophageal Spread	Prior Treatment	ECOG Status
1	66	M	SCC	Lower 1/3	10	Mediastinal/hepatic	Radiotherapy	2
2	61	F	Adeno	Lower 1/3	3	Mediastinal	Surgery	1
3	82	F	Adeno	Lower 1/3	4	Nodal	None	4
4	61	F	Adeno	Lower 1/3	8	Mediastinal	Surgery/tube	2
5	72	F	SCC	Mid 1/3	5	Mediastinal/nodal	Radiotherapy	2
6	78	M	SCC	Lower 1/3	10	Mediastinal/hepatic	None	2
7	65	F	SCC	Mid 1/3	5	Mediastinal	None	2
8	60	F	SCC	Upper 1/3	5	Mediastinal	Radiotherapy	2
9	82	F	SCC	Mid 1/3	8	None	None	2
10	80	F	SCC	Mid 1/3	8	Mediastinal	None	2
11	57	F	SCC	Mid 1/3	9	Mediastinal	Radiotherapy	2
12	82	M	Adeno	Lower 1/3	10	Mediastinal	None	3
13	72	M	Adeno	Lower 1/3	6	None	None	2
14	59	M	SCC	Mid 1/3	10	Mediastinal	Surgery	2

SCC = squamous cell carcinoma. ECOG = Eastern Clinical Oncology Group.

of applying light to an esophageal cancer that improves the accuracy of light delivery using a balloon filled with a light dispersing medium. We have undertaken a Phase 1 study of photodynamic therapy of advanced esophageal cancer using an argon pumped dye laser and a gold metal vapor laser. We have used high power levels up to 2.2 W and large doses up to 337 J/cm^2 to determine doses of light that are tolerable and whether the extent of tumor kill is dose related.

Patients and Methods

All patients gave informed consent before the study. Fourteen patients were admitted to the Phase 1 study. They were treated from March 1985 to September 1986. In the first half of the study patients were assessed as being unsuitable for any other form of therapy. In the second half of the study, photodynamic therapy was offered as an alternative to other forms of palliative therapy. The characteristics of the patients and tumor types are shown in Table 1. This study was approved by the Ethics Committee of the Royal Melbourne Hospital.

Technique of Photodynamic Therapy

An intravenous infusion of 2.5–5.0 mg/kg of HpD was administered to all patients 72 hours before laser therapy. HpD was obtained from the Pharmacy Department of Queen Elizabeth Hospital (Adelaide, South Australia) and was prepared by the acetylation of hematoporphyrin using the method described by Forbes et al.[11]

Hematologic and biochemical parameters were measured regularly after the infusion to assess and detect any toxic effects of the HpD. In five patients fluorescence was measured in the serum to assess peak levels and decay characteristics. Patients were screened from direct sunlight for up to 1 month. Laser light at 627–630 nm was generated using an argon pumped Rhodamine B dye laser (Spectra Physics, Model 164-05; argon laser, Model 375 dye laser, Spectra Physics, Mountain View, CA (9 patients, 16 therapies) or a gold metal vapor laser (Quentron, South Australia) (8 patients, 8 therapies). Light was delivered through a quartz fiber with a power output at the fiber tip varying from 0.5–2.2 W.

The quartz fiber was passed down a flexible endoscope (Olympus GIFQ, Olympus Optical Co., Ltd. Japan) and light directed towards the tumor. Eye protection was worn by the operator during this procedure.

To control the dose of light applied to the tumor, a light delivery system was devised as shown in Figure 1. This consisted of a polythene cannula with an attached thin-walled balloon that assumed an elongated shape measuring 8 × 1 cm in diameter when distended with 0.5% lipid emulsion (Intralipid®). The balloon was introduced into the lumen of the esophageal cancer *via* the fiberoptic endoscope after dilation of the cancer. With the balloon accurately in place within the tumor, the quartz fiber was moved from one end of the balloon to

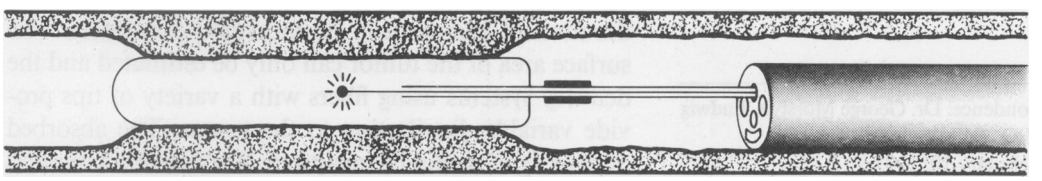


FIG. 1. Schema of delivering light to the tumor. The diagram shows the laser fiber in a balloon filled with Intralipid (0.5%) in the lumen of the esophagus.

TABLE 2. *Results of Photodynamic Therapy in Esophageal Cancer*

Patient	HpD (mg/kg)	Power (W)	Total Dose J/cm²	Total Dose (J)	Length (cm)	Type of Laser	Ability to Swallow: Before Laser Therapy	Ability to Swallow: After Laser Therapy	Duration of Response (wks)	Complications	Survival (wks)	Time in Hospital (days)
1	2.5	0.5	1800	60	12	C	1	3	14	Fever day 1, sunburn 2 wks	19	30
2	2.5	1	1740	129	3	C	2	4	17	Sunburn 8 wks		7
	5.0	0.7	2562	190	3	C	2	4	26	None		3
	5.0	2.0	5400	337	6	C	2	4	24	None	67	5
3	2.5	1.0	3600	150	8	C	1	3	28	None	28	6
4	2.5	1.0	3600	150	8	C	1	2	4	Sunburn 2 wks	25	10
	2.5	1.0	2040	85	8	C	1	2	4			8
5	5.0	1.0	3000	191	5	C	2	4	1	Fever day 1		14
	2.5	1.0	3600	229	5	C	2	4	13	Fever day 3	13	14
6	5.0	0.9	3240	103	10	C	1	2	1	None	21	15
	2.5	1.3	4758	151	10	C	2	3	21	Fever day 2		
7	5.0	1.0	3900	207	6	C	2	2	3	Pain, fever day 7		2
	5.0	0.7	2562	136	6	C	2	3	12	Pain, fever day 7	60+	7
	5.0	2.0	3840	245	6	P	2	2	8	Fever day 4, mediastinitis		28
8	5.0	1.0	3000	191	5	C	2	2	2	Fever day 1	12	30
	5.0	1.7	3296	210	5	P	2	2	4	Fistual day 39		
9	5.0	1.8	4752	198	8	P	4	2	2	Death day 10	1	10
10	5.0	1.5	3150	125	8	C	3	3	2	None		8
	5.0	2.2	4780	190	8	P	3	3	2	Fever day 3	10	8
	5.0	1.5	6039	192	10	C	3	3	6	None		21
11	5.0	1.7	5392	191	9	P	3	4	14	Fever day 4	14+	13
12	5.0	1.8	4633	150	10	P	4	2	6	Pain and fever, day 2, fistula, abscess day 40	6	42
13	5.0	1.8	3098	155	6	P	3	2	3	None	5+	21
14	5.0	1.8	2181	72	10	P	4	4	2	Fever, pain day 10	4+	16

Dysphagia score:
1 = total obstruction.
2 = fluids.
3 = vitamized food.
4 = soft diet.
5 = normal.
C = continuous wave argon pumped dye laser.
P = pulsed gold metal vapor laser.

the other within the esophageal cancer resulting in light delivery to the whole tumor. The dosimetry was calculated assuming that the tumor was a cylinder with a diameter of 1 cm after the balloon was inflated within the lumen of the tumor. The length was determined by prior endoscopy. Doses of light between 60 and 337 J/cm² of tumor were delivered. This necessitated treatment times of 30–60 minutes. All patients in this series were treated under general anesthesia.

Assessment of Tumor Response

Before the laser therapy all the patients had endoscopic examination, the tumors were biopsied, photographed, and dilated if necessary, and the length of the tumor was measured. Barium meal and computed tomographic (CT) examinations of the thorax were obtained before treatment and 1 month after treatment. After laser therapy all patients had endoscopic examination at 48 hours and further photographs and biopsies were taken. This procedure was repeated 1 week and 2 weeks after therapy and when new symptoms such as dysphagia developed.

Results

The characteristics of the patients with esophageal cancer are shown in Table 1. Of the 14 patients, five had an adenocarcinoma and nine had a squamous cell carcinoma. Seven patients had lower-third tumors, six had mid-third tumors, and one had an upper-third tumor. Six patients had previous treatment, either radiotherapy or surgery. Twelve patients had advanced local mediastinal spread, and two patients had disease apparently confined to the esophagus on CT scan. All patients were deemed inoperable due to their clinical status or the stage of their tumor.

The details and results of the laser therapy are shown in Table 2. A total of 24 laser therapies were given to the

14 patients. In seven treatments, HpD was given at a dose of 2.5 mg/kg; in an additional 17 treatments, HpD was given at a dose of 5 mg/kg.

The gold metal vapor laser was used in eight of the 24 laser treatments. The mean power output at the fiber tip with this laser was 1.8 W (range: 1.7–2.2). The mean power output at the fiber tip of the argon pumped dye laser was 1.0 W (range: 0.5–2.0). The mean total dose of light was 3582 J (range: 1800–6039). The mean dose/cm^2 of tumor was 168 J/cm^2 (range: 60–337).

The degree of necrosis of the cancer after laser therapy was estimated by visual grading of the macroscopic appearance of the tumor at the postlaser endoscopic examinations. The necrosis was graded as follows: G0: no tumor necrosis visible; G1: tumor necrosis but obvious viable tumor persisting (Fig. 2); G2: apparent total tumor necrosis (Fig. 3); G3: total tumor necrosis with a physical appearance of esophageal tumor slough (Fig. 4).

The relationship between tumor necrosis (G_0–G_3) and light dose and power output of the laser is shown in Figure 5. G_1 minimal tumor necrosis correlated significantly with the dose of light (Spearman rank correlation test, correlation coefficient 0.368, $p = 0.04$) G3 esophageal tumor slough correlates significantly with a power output of the laser of >1.5 W (Spearman rank correlation test, correlation coefficient 0.54, $p = 0.005$).

The palliation of the symptoms produced by the tumors was assessed by measuring the improvement of dysphagia after therapy (Table 2).

The ability to swallow was assessed before laser therapy and 2 weeks after laser therapy using a dysphagia scale, and all patients achieved measurable improvement in the severity of dysphagia. The duration of the response varied from 1 to 28 weeks with a median of 9.5 weeks. With respect to weight changes, seven of the 14 patients maintained their weight from the time of laser therapy to 1 month after the therapy despite a history of loss of weight in the 3 months before treatment. The remainder of the surviving patients showed modest declines in weight.

The in-hospital mortality rate was 14% with two patients dying after their therapy, both aged over 80 years. One of these patients was shown at postmortem examination to have complete necrosis of the esophageal cancer but also significant esophageal wall necrosis associated with thrombosis of an esophageal artery (Fig. 6). In this instance cardiac arrest occurred 13 days after therapy and the postmortem examination showed significant coronary artery disease. The second patient in whom bronchoesophageal fistula pneumonia developed died 4 weeks after the therapy, and at postmortem examination had an extensive esophageal and mediastinal tumor with massive necrosis of the esophageal portion of the tumor.

Survival Data

A number of complications occurred after the therapy and are listed in Table 2. Febrile episodes were common but settled with the institution of antibiotics. In one patient mediastinitis developed with pleural effusions demonstrated on CT scan. This patient was treated conservatively with full recovery and subsequently had a strictured area of the esophagus resected (8 months after laser treatment). Histologic examination of the specimen revealed complete eradication of the esophageal tumor with a dense fibrous scar formation. There has been no recurrence of tumor 1 year later. This patient had heavy irradiation to the neck and esophagus for a paraesophageal tumor 10 years before the development of the presumed radiation-induced proximal esophageal cancer.

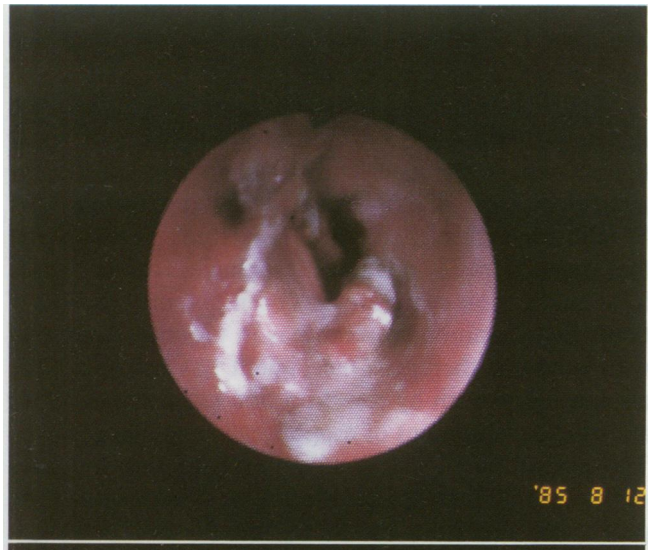
A laser power output of >1.5 W correlated significantly with the development of complications.

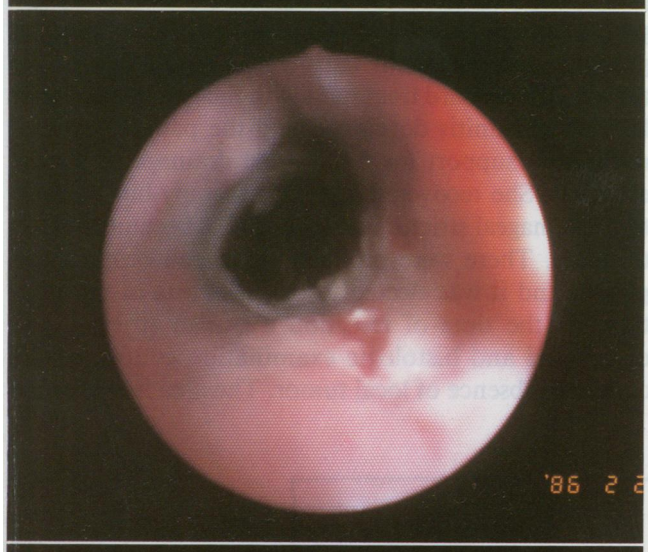
All patients received instructions to avoid direct sun. However, three patients showed a reaction to sunlight when inadvertently exposed. In two of these patients, their skin reaction developed in the hospital from light coming through the windows. In another patient, sun sensitivity developed after leaving the hospital. It was evident that this phenomenon of sun sensitivity persisted for several months after the therapy, and in one patient skin pigmentation developed that persisted for more than 6 months before fading. The basis for prolonged skin sensitivity is not clear. However, Figure 7 shows that HpD fluorescence can persist in the serum for up to 1 month. Similar findings were found in four other patients. There was no effect of HpD on liver or renal function as measured biochemically. To determine the effect of phototherapy on survival we compared the actuarial survival of all 14 patients with a previous series of patients treated for palliation nonsurgically (Fig. 8).[1] This survival has been stable in the hospital for 5 years. There was no significant difference between the curves.

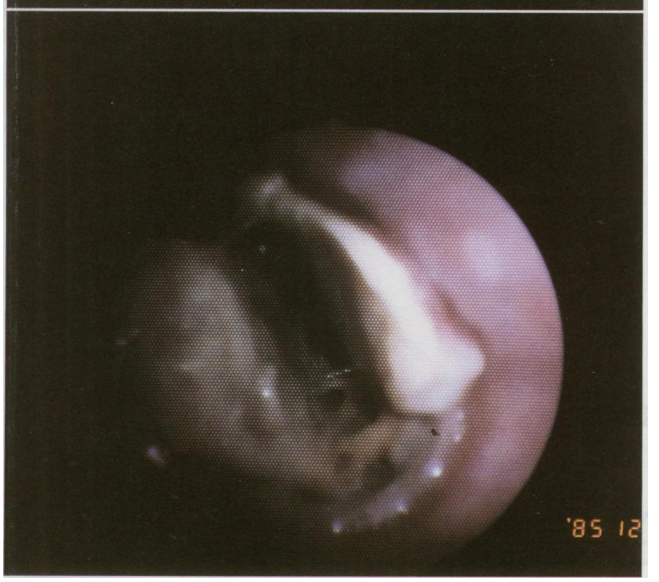
Discussion

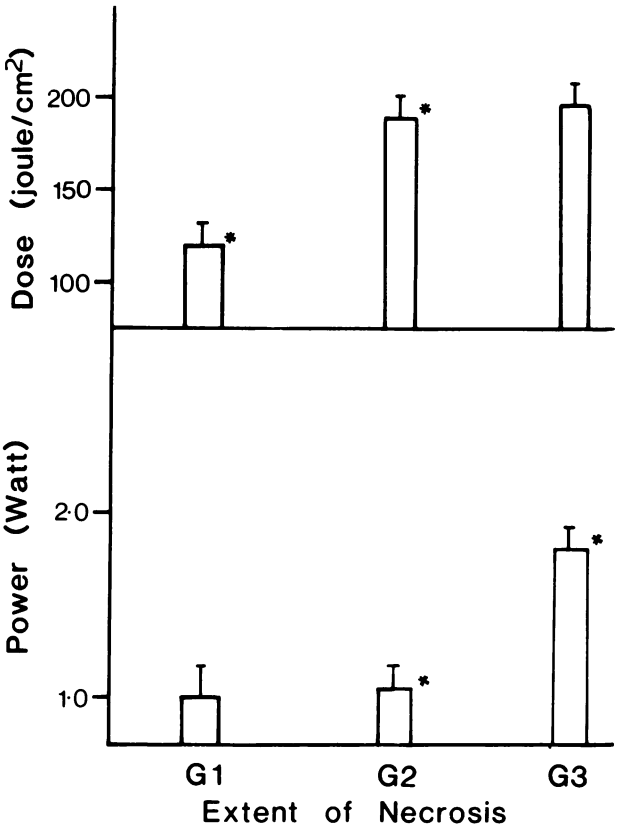
This study confirms that photodynamic therapy is an effective form of local therapy for esophageal cancer. All tumors treated showed some evidence of necrosis. In this group of patients there was no apparent difference in the response of squamous and adenocarcinomas.

This form of therapy produced reasonable palliation in patients who were close to having or had complete obstruction. The degree of palliation appeared to be at least as good as that produced by other forms of therapy. The eventual place for photodynamic therapy as a palliative treatment of advanced esophageal cancer is still to be established. It is likely that certain groups of pa-









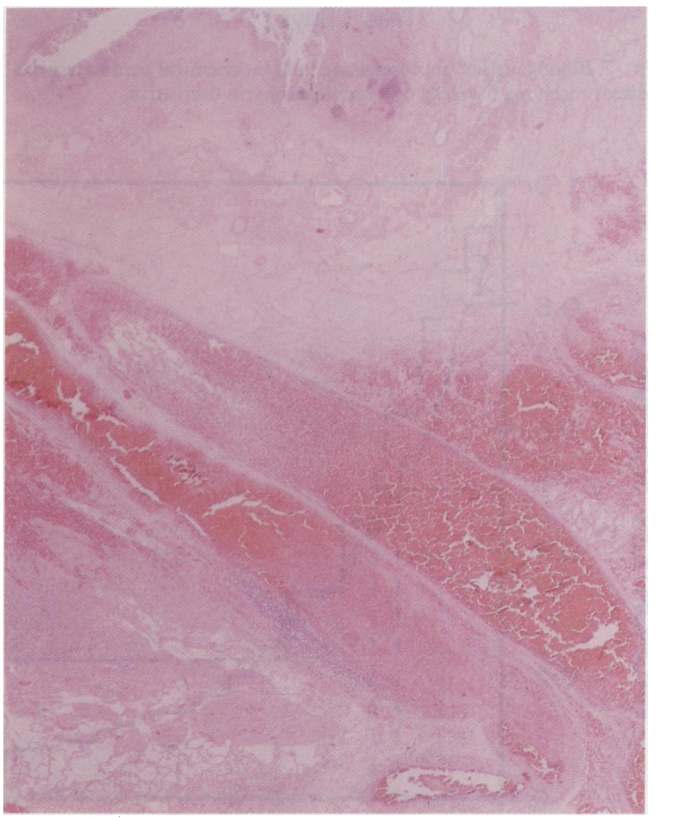


FIG. 2. *Top left.* G_1: minimal necrosis with macroscopic viable tumor. FIG. 3. *Middle left.* G_2: intermediate necrosis: macroscopic total tumor necrosis. FIG. 4. *Bottom left.* G_3: maximal necrosis: esophageal slough. FIG. 5. *Top right.* Extent of macroscopic tumor necrosis as a function of dose of light and power output of laser. Points of significance ($p < 0.05$) marked with asterisks. FIG. 6. *Bottom right.* Thrombosis of esophageal artery and vein after photoirradiation therapy.

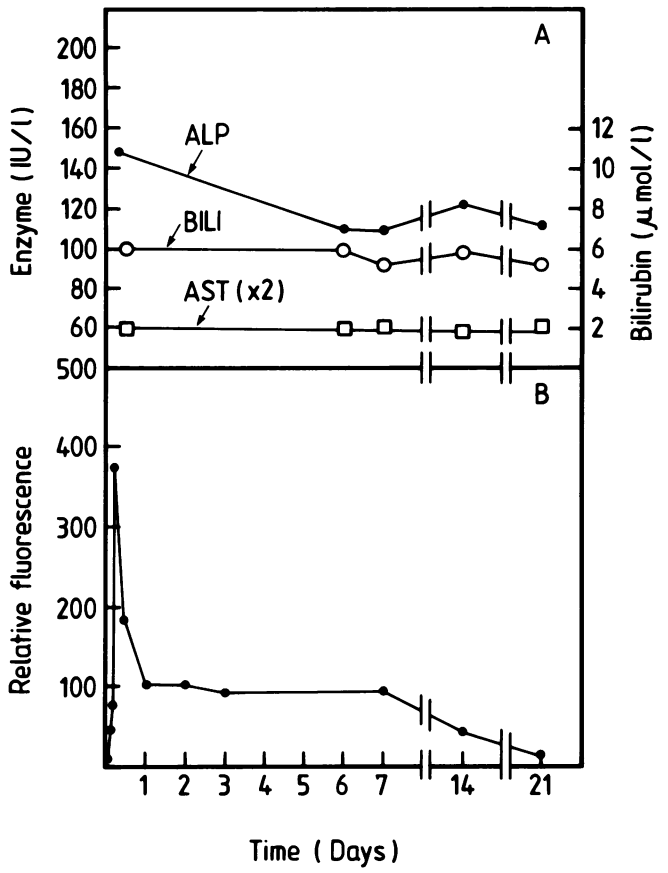


FIG. 7. Blood levels of photosensitizer and biochemical parameters in a patient receiving 5 mg/kg of hematoporphyrin derivative.

tients will be better treated with this form of therapy than others. Further studies are needed to compare the various methods of palliation.

Of particular interest is the ability of photoirradiation therapy to produce complete eradication of local tumors. There are reports in the literature of the complete eradication of early esophageal and gastric cancers by photodynamic therapy.[6,7] This study includes the first cases of locally advanced esophageal cancer where local eradication of tumors has been obtained. Both patients had squamous carcinomas in the mid-esophagus with no prior therapy. One patient has had complete eradication proven by resection of a persisting stricture after the development of esophageal slough (grade G3). This patient had a locally advanced tumor on the basis of thickening in the mediastinum on CT scan but poor pulmonary function, and frailty initially precluded surgery. The patient received two treatments with the argon pumped dye laser with fairly rapid recurrence of the tumor. After a third treatment with the gold metal vapor laser mediastinitis developed and the patient required respiratory support for 5 days and drainage of pleural effusions. She recovered after this therapy but a persistent esophageal stricture developed that became difficult to dilate. There were problems with endoscoping this patient and it was elected to risk resection of the stricture. At the time of resection a benign stricture was discovered and histologic examination confirmed the complete absence of local tumor. The area in which the

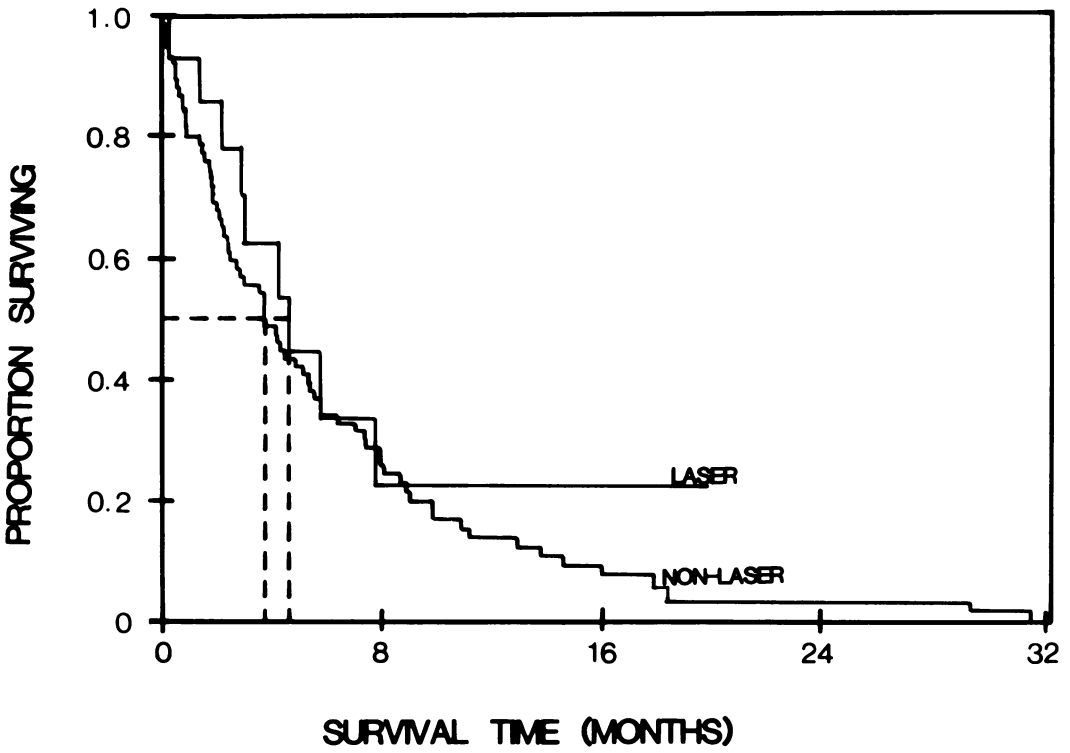


FIG. 8. Survival of all photoirradiation patients (laser) compared with patients treated for palliation before availability of photoirradiation.

tumor was previously noted was surrounded by a dense scar surmounted by a small shallow ulcer. This patient has remained tumor free for more than 12 months. The second instance where complete eradication was seen occurred in one patient who died 14 days after therapy and in whom at autopsy there was total necrosis of the tumor.

The ability to produce local eradication of advanced tumors raises the possibility of developing this form of therapy as a first-line form of treatment for Stage 1 esophageal cancer. However, increasing the effectiveness of the local therapy in this situation demands the development of techniques to support both the patient and the esophageal wall during the postoperative period when tumor necrosis is maximal and the repair processes have not developed sufficiently to maintain the integrity of the esophageal wall. Appropriate management may require antibiotics, nil by mouth, parenteral nutrition, and occasionally temporary intubation to splint the esophagus. This introduces a new dimension in the field of surgical oncology rather akin to the problems seen in the use of chemotherapy without surgery in lymphomas affecting the gastrointestinal tract to avoid perforation.

An important attribute of photodynamic therapy previously reported is the selectivity of cell damage. In this group of patients, however, it was evident that the selectivity was not absolute. There was generally a sharp demarkation between tumor necrosis and the proximal esophageal mucosa. However, in both the resected case and the autopsy specimen there was evidence of normal tissues deep to the tumor or close to the tumor showing necrosis. The histologic changes were characteristic after phototherapy with severe fibrinoid necrosis noted in blood vessels close to the tumor. This would suggest that a vascular phenomenon was significant in producing at least part of the necrosis. This may also be a factor in producing the damage to the normal esophageal wall. These vascular changes can resolve as was evident from the resected specimen of the eradicated cancer where recanalization of previously thrombosed vessels was seen. A vascular basis for the damage induced by phototherapy has previously been suggested based on *in vivo* experiments in small animals.[12]

A major problem with the assessment of the effectiveness of photodynamic therapy relates to the difficulties with dosimetry. Although the balloon system as described improves light delivery to the tumor, there may still be variation in the dose of light delivered to various parts of the tumor and the problem of a geographic miss also exists. This lack of precision makes it difficult to define the optimal doses of light for various tumors. In this study substantial variations in the dosage of light to the various areas of the tumor may have been responsible for variations in necrosis in various parts of the tumor. However a direct dose-response relationship was demonstrated in this study by comparing very low doses with higher doses of light. Extent of tumor necrosis also correlated with the presence of significant complications and occurred where the pulsed laser was used with a power output of greater than 1.5 W. There is an obvious need to clarify the problem of dose response. Our data suggest that for the therapy of esophageal cancers, lasers with a higher power may not be necessary since a limit determined by normal tissue tolerance may have been reached.

There is no systemic toxicity from phototherapy apart from the problem of sun sensitivity. This was found to be a persistent problem extending for 2–3 months from the time of laser therapy, and in some patients was associated with mild skin pigmentation. The development of photosensitizers with a shorter half-life would reduce this problem.

Acknowledgments

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