REVIEW

ANNALS OF SURGERY
Vol. 230, No. 1, 12–23

Current Concepts in Gastrointestinal Photodynamic Therapy

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Objective
To review current concepts of photodynamic therapy (PDT) applied to the treatment of tumors of the gastrointestinal tract.

Summary Background Data
PDT initially involves the uptake or production of a photosensitive compound by tumor cells. Subsequent activation of the photoreactive compound by a specific wavelength of light results in cell death, either directly or as a result of vascular compromise and/or apoptosis.

Methods
The authors selectively review current concepts relating to photosensitization, photoactivation, time of PDT application, tissue selectivity, sites of photodynamic action, PDT effects on normal tissue, limitations of PDT, toxicity of photosensitizers, application of principles of PDT to tumor detection, and current applications of PDT to tumors of the gastrointestinal tract.

Results
PDT is clearly effective for small cancers, but it is not yet clear in which cases such treatment is more effective than other currently acceptable approaches. The major side effect of PDT is cutaneous photosensitization. The major limitation of PDT is depth of tumor kill. As data from current and future clinical trials become available, a clearer perspective of where PDT fits in the treatment of cancers will be gained. Many issues regarding pharmacokinetic data of photosensitizers, newer technology involved in light sources, optimal treatment regimens that take advantage of the pharmacophysiology of photoablation, and light dosimetry still require solution. One can foresee application of differing sensitizers and light sources depending on the specific clinical situation. As technologic advances occur, interstitial PDT may have significant application.

Conclusions
PDT has a potentially important role either as a primary or adjuvant mode of treatment of tumors of the gastrointestinal tract.

Photodynamic therapy (PDT) is a form of cancer treatment that takes its origin from the concept of "photodynamic" cell death first described a century ago,[1] when Raab observed that the death of paramecia exposed to eosin was related to the intensity of room light. Clinically, PDT is based on two steps. The first involves the selective accumulation of a photosensitizer in the target tissue. The second involves activation of the photosensitizer with an appropriate wavelength of light. This results in selective tissue destruction by means of a photochemical reaction.[2] Current photosensitizers do not exhibit toxicity until they are activated by a specific wavelength of light corresponding to an absorbance band of the photosensitizer.[3] The concept that PDT can selectively destroy tissue has found applicability in the treatment of malignant and benign tumors involving the skin, gastrointestinal (GI) tract, retroperitoneum, genital and urinary systems, chest, central nervous system, and eye.[4–13]

PDT shows considerable promise as a primary treatment modality for localized superficial tumors[4,5,14] and is a potentially important form of adjuvant treatment for cancers of the GI tract.[8,9] The advantages of PDT include the low incidence of complications,[15] tumor responsiveness uncompromised by previous radiation or chemotherapy, subsequent use of radiation and/or chemotherapy, and repetition in multiple successive sessions. The use of photosensitive drugs has diagnostic applicability because photoreactive agents are also fluorescent, permitting tumor localization with a suitable imaging system.[16,17] The clinical applications of PDT are just emerging.

PHOTOSENSITIZATION

Malignant tissues can be photosensitized by either exogenous or endogenous means. Exogenous photosensitization

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Accepted for publication January 11, 1999.

is achieved through the administration of a photoreactive compound that is selectively retained in tumors. In contrast, endogenous photosensitization involves administration of a drug that is converted by the target tissue into a photoreactive compound.

The use of hematoporphyrin derivative (HPD) as an exogenous photosensitizer for the treatment of animal tumors ushered in the modern era of PDT in 1975. HPD is an unstable mixture of porphyrin monomers and oligomers joined by ether and ester linkages.[18–21] A more recently introduced and purer preparation of HPD (Photofrin) is now commercially available. Photofrin is an effective photosensitizer but has the undesirable side effect of prolonged skin photosensitization. This requires patients to avoid sunlight or bright incandescent light for as long as 4 to 6 weeks after receiving the drug to avoid burns.[22] Moreover, the efficiency of conversion of light to cytotoxic products is low, the degree of tumor localization is inferior to that obtained with newer photosensitizers, and the wavelength of light required (630 nm) to activate Photofrin penetrates tissue to only approximately 1 cm in depth.[23,24]

Newer exogenous photosensitizers have been formulated with a view toward minimizing instability and prolonged skin photosensitization and providing more efficient conversion of light to cytotoxic products at wavelengths that offer better tissue penetration (agents with a high extinction coefficient, $>$650 nm). The advantage of using a sensitizer with a higher extinction coefficient is that a lower drug dose can be used, thus minimizing systemic toxicity (if any). However, it is not yet clear how much of a greater depth of tumor kill occurs with the longer wavelengths of light[15] corresponding to the absorbance bands of the second-generation photosensitizers (chlorins, purpurins, tetra [m-hydroxyphenyl]chlorin, phthalocyanines, benzoporphyrins, and texaphyrins).

Endogenous photosensitization at present involves the oral administration of the prodrug aminolevulinic acid (ALA). ALA is absorbed into the bloodstream and converted by cellular enzymes to protoporphyrin IX (PpIX).[4,25–31] ALA is not a photosensitizer *per se*, but its metabolic end product, PpIX, is photoreactive. ALA is a naturally occurring amino acid that is the first committed intermediate in the heme biosynthetic pathway.[4,32] Heme exerts negative feedback on ALA synthase, the first and rate-limiting enzyme of the PpIX biosynthetic pathway. This inhibitory control can be bypassed in certain malignant cells exposed to excess ALA and results in the overproduction of PpIX. Adenocarcinomas tend to have an increase in porphobilinogen deaminase activity, which ultimately results in greater production of PpIX, and a decrease in ferrochelatase activity, which results in greater retention of PpIX by the tumor because of reduced conversion of PpIX to heme.[28–30,33–35] Further, hepatic synthesis of PpIX from ALA is quite efficient, and it is likely that there is subsequent transport of PpIX in the blood to peripheral sites.

PHOTOACTIVATION

The currently used photosensitizing drugs are porphyrins or porphyrin analogs. These molecules, with extended conjugated ring systems, have the ability to react with light and pass this energy along to oxygen molecules dissolved in tissues. This energy transfer process results in the transformation of oxygen to an activated electronic state (^1D_g) termed singlet oxygen.[36,37] This is a very reactive species that will oxidize the first molecule it encounters (amino acids, unsaturated fatty acids, or nucleic acids), ultimately resulting in cell damage if the sensitizer has concentrated in the neoplastic cell.[31]

The light source most frequently used to activate a photosensitizer is a laser, which energizes the sensitized cell to undergo a photooxidative reaction rather than photocoagulation or photothermal ablation, as occurs with conventional laser therapy.[38,39] The optimal dose of light used to activate a photosensitizer in human cancers is not known. Light dose is expressed as the delivered quantity in J/cm^2, but the absorbed dose depends on the spectrum of the light source, irradiation geometry, depth of penetration, light scattering in the tissue, concentration of the photosensitizer in the tissue, and hemorrhage within the tumor, as well as other factors, making the absorbed dose difficult to calculate.[24,40]

The photophysics of PDT dictate that it is a light- and oxygen-catalyzed process with no toxicity in the absence of oxygen; the level of tissue oxygenation must be adequate to sustain singlet oxygen formation.[41] Photosensitizing drugs are inert unless and until irradiated. PDT is dependent on both drug concentration and light dose (conc*J/cm^2),[42–46] with any tissue being susceptible to photodamage if the sensitizer and light dose are sufficiently high. A threshold PDT dose must be exceeded for necrosis to occur. Because photosensitizers are degraded (bleached) by light, a weaker response occurs at low drug concentrations. To obtain a PDT response at lower cellular drug concentrations, the light exposure must be increased. When the proper photosensitizer dose is used, differential uptake by tumor allows destruction of tumor and protection of normal tissue even at very high light doses because the level of photosensitizer in normal tissue is below the photodynamic threshold for necrosis.[47]

Thus, there are three variables at work that determine the PDT response: degradation of the sensitizer (bleaching), differential tissue uptake, and threshold effects. It is important to delay the irradiation step until a time when the ratio of drug level between malignant adjacent normal tissues is at a maximum.

TIME OF PDT APPLICATION

In general, there is greater flexibility in the timing of PDT treatment with exogenously administered photosensitizers because they do not require conversion by the target tissue into a photoreactive substance. PDT irradiation using Pho-

tofrin can be done 40 to 50 hours after administration of the drug, whereas secondary applications can be performed 96 to 120 hours after injection. In contrast, endogenous photosensitization with ALA relies on tumor synthesis of the photoreactive substance (PpIX), which results in various peak accumulation times of photoproduct among patients.[15] Thus, it becomes a practical point to know when the concentration of PpIX in the target tissue reaches a sufficient level for PDT to be effective, as well as when the tumor concentration of the sensitizer is substantially greater than that of the surrounding normal tissues. Tissue measurements of PpIX concentrations after ALA administration indicate that the time to peak occurrence of PpIX levels differs among patients for both normal and malignant tissues and ranges from 2.9 to 9 hours.[15] The variable peak accumulation of PpIX may explain why some adenocarcinomas of the GI tract appear to be unresponsive to PDT using ALA.[48]

Serial measurements of actual concentrations of PpIX before PDT are impractical because of the time involved for such determinations. However, one can take advantage of the fact that photosensitizers fluoresce. It has been shown in humans that >96% of fluorescing porphyrin after administration of ALA is PpIX.[9,49] Tissue concentrations of PpIX can be quantitated by applying spectrophotometric methodology.[9] This offers a practical means for determining the most favorable time for initiating irradiation, because relative changes in fluorescent signals correlate with changes in tissue concentrations of PpIX.[9] In contrast to ALA, spectrophotometric detection of peak Photofrin levels in tissue is not necessarily accurate because this product consists of several porphyrins, with widely varying yields in fluorescence.[50]

TISSUE SELECTIVITY

The precise mechanism whereby the porphyrinlike molecules localize in neoplastic cells is not clear. Localization at sites of wound healing, embryonic tissues, and certain organs (liver, spleen, pituitary, kidney) generally occurs. Many of the photosensitizing drugs show a marked affinity for the low-density lipoprotein (LDL) in plasma, which implicates an LDL-directed pathway of biodistribution,[17,51,52] especially in view of the elevated levels of LDL receptors expressed in tissues that preferentially accumulate porphyrinlike molecules. The finding that some effective sensitizers bind only to high-density lipoprotein suggests that there may be multiple localization mechanisms.[53] A common element in tissues that selectively concentrate photosensitizing drugs is a high level of metabolic activity. However, it is not known how this might enhance the uptake of sensitizers, especially those that do not show significant binding to lipoproteins.

SITES OF PHOTODYNAMIC ACTION

The effective sensitizers tend to concentrate in both tumor and tumor vasculature, along with the normal vasculature in the vicinity of a neoplastic lesion. The precise biodistribution pattern depends on the properties of the sensitizer. An important advance in the field came with the discovery that the phototoxic effect can cause both a direct tumor cell kill and a vascular shutdown, which also promotes tumor destruction.[54,55] The degrees of tumor and vascular photodamage may depend not only on the particular sensitizer but also on the method of light dosimetry.

PDT using Photofrin results in the destruction of the tumor vasculature, an effect that appears to be selective, even in regions of tumor where the photosensitizer concentration is similar to that in normal adjacent tissue.[55] Thus, the effect of Photofrin may be mainly an indirect one, derived from the destruction of the tumor vasculature.[56] It is not clear if this effect of Photofrin is universal with respect to all tumor types affected by the drug.

Vascular destruction itself, without any contribution from direct tumor cell kill, can lead to cures of experimental tumors. Given the importance of oxygen availability to phototoxicity, the rapid formation of hypoxic cells resulting from vascular damage increases the likelihood that some tumor cells will escape direct photodestruction.[57,58] If a photodynamic agent has primarily vascular effects, hypoxic but still viable cells may persist at the interface of necrotic and well-perfused regions.[59] Thus, it is clear from the mechanism of PDT-induced photodamage with Photofrin that tumor oxygenation plays a role with regard to efficacy. However, with lower photosensitizer doses and certain second-generation sensitizers, many of which presumably exert less severe acute effects on the vasculature than Photofrin, this mechanism for oxygen limitation and treatment may be less important. If the light dose is decreased, oxygen consumption is lowered and appropriate tumor tissue levels of oxygen can be maintained. Another approach involves the fractionation of light delivery; by using short (in the order of 20 to 50 seconds) light and dark intervals, sufficient reoxygenation may occur during dark periods.

A proposed advantage of chemically induced porphyria with ALA is that the phototoxic effect relies primarily on direct cell kill, whereas other photosensitizing agents appear to rely more on vascular effects.[38,60–62] However, it is becoming apparent that ALA has definite vascular effects, but the data are difficult to compare because of the number of confounding technical variables involved in these studies. For example, the vascular effects are related to the duration and intensity of the light source used to activate PpIX.[63] Adding to the controversy are magnetic resonance spectroscopic studies suggesting that direct cellular damage from PDT *per se* occurs well before the changes observed with tumor hypoxia, which usually occur later and are mostly attributable to vascular damage.[64] If this is the case,

it suggests that cellular destruction caused by PDT occurs by a dual synergistic mechanism.

Reports that PDT rapidly induces apoptosis, both *in vitro*[65,66] and *in vivo*,[67,68] provide new information on the mechanisms of phototoxicity. Malignant cell types often exhibit an impaired ability to undergo apoptosis, an effect associated with an enhanced ability to survive chemotherapy with many common antitumor agents.[69,70] The apoptotic response to these drugs may determine whether cell death occurs.[71] If apoptosis is a major mode of phototoxicity, the broad responsiveness pattern of PDT suggests that PDT induces apoptosis in almost any cell, perhaps at such a stage that circumvents the faulty signaling sometimes associated with neoplasia.[72]

EFFECTS ON NORMAL TISSUE

Photosensitizers are not completely specific for malignant tissue. As a result, there will always be some photosensitization of normal tissues. In the case of ALA, this effect is mainly caused by the relatively slow conversion of PpIX to heme, which is not photosensitive. However, photodestruction can be avoided by relying on bleaching of the photosensitizer. Most sensitizers undergo rapid photobleaching on irradiation. A low concentration of a photosensitizer can be photobleached before the photodynamic threshold for tissue damage occurs. This phenomenon makes it possible to "overdose" the treatment field to get maximum light penetration without causing serious damage to normal tissue. However, malignant cells will be destroyed only if sufficient sensitizer accumulates so that there is a loss of viability before photobleaching can reduce the sensitizer concentration to a nontoxic level.[4,41,42,45,47] Thus, an efficient photosensitizer will have a much greater concentration in the target tissue than in surrounding normal tissue to avoid significant damage to the latter.

LIMITATIONS

The major limiting factor in using PDT is the depth of tumor kill. The depth of penetration of 630 nm light (used for Photofrin and ALA) in tissue ranges from 0.2 to 2 cm.[55,73–76] The mean depth of destruction of rectal and sigmoid adenocarcinomas in patients receiving Photofrin amounts to 0.6 cm, with a range of 0.3 to 1.5 cm, after intraluminal insertion of an optical fiber 1 mm into the tumor.[77] Among factors that limit light penetration are the presence of blood clot and necrosis within the tumor and absorption of light by the photosensitizer itself (a phenomenon called self-shielding). Precise depths of tumor destruction are difficult to determine because of sloughing, and the actual extent of destruction may be variable because of the effects of PDT on blood flow. However, given the relatively small extent of tumor destruction, it appears that the main benefit of PDT at present for tumors may be fourfold:

- Local control of microscopic deposits remaining after what appears to be a curative resection
- Removal of relatively small deposits remaining after debulking surgery
- Primary treatment for small lesions
- Palliative treatment.

More promising are some newer experimental photoreactive agents that are sensitive to longer wavelengths of light (>650 nm). This results in deeper tissue penetration than the 630 to 633 nm wavelength required to activate Photofrin and PpIX, but just how much greater depth of tumor kill results is unclear. The therapeutic depth may in fact be greater than the depth of light penetration, a phenomenon that may relate to additional vascular injury.[78]

Another limitation is the expense of not only purchase but also maintenance of the equipment (especially lasers) necessary to apply PDT. However, photodiode technology is rapidly advancing to the point that more powerful sources are available and, as a result, equipment costs will lessen. Although photodiodes do not have as sharply defined wavelengths as lasers, this may be of some advantage. For example, activation of PpIX results in the formation of a photoproduct, photoprotoporphyrin, which is photoreactive at a wavelength of approximately 670 nm.[79] This and the 630 nm absorbance band can be incorporated within photodiode wavelengths. As the technology of light-emitting diodes increases, interstitial treatment of tumors will also become more practical.

TOXICITY OF PHOTOSENSITIZERS

The toxicity of PDT is site-specific and dependent on the organ being irradiated and the selectivity of the photosensitizer for target tissue over normal tissue. However, there are also reactions related to the sensitizer *per se* that are independent of those related to the treatment site. A universal and clinically important adverse effect of PDT is cutaneous photosensitization, which can lead to sunburns.[80] Most photosensitizing agents are not concentrated *per se* in the skin, but low concentrations can be found in the skin for several weeks. For example, Photofrin cannot be bleached sufficiently to achieve photoprotection of the skin.[81] Although the mean duration of photosensitization after Photofrin injection is 4 to 6 weeks, Photofrin can be found in human serum 1 year or more after administration.[82] It is not known if this is associated with any risk. Cutaneous photosensitization is not prevented by using sunscreen because it is primarily visible, rather than ultraviolet, light that activates the photosensitizer.

In contrast to Photofrin, ALA-induced PpIX is almost completely cleared from human plasma by 48 hours after oral administration.[15] An occasional patient has been reported to develop mild cutaneous phototoxicity as late as 48 hours after receiving ALA.[83] Cutaneous phototoxic reactions in patients taking ALA can be avoided by exposure to

only subdued light for 48 hours, preventing more than momentary exposure to photodiode monitors (*e.g.*, a pulse oximeter),[84] and filtering operating room lights to prevent nonspecific photoactivation of PpIX.[15] Oral intake of ALA causes mild nausea or vomiting in almost a quarter of patients, as well as transient and variable abnormalities of liver function tests in approximately one third of patients. ALA administration also can cause a decrease in peripheral vascular resistance and thus can cause hypotension, a side effect not necessarily limited to ALA.[85]

TUMOR DETECTION

Excitation of photosensitizer by an incident photon produces reemission of a fluorescent photon, which can be used to localize the reaction.[80] This might enable detection of metastases not ordinarily evident.[86] There appears to be a correlation between the presence of local tumor and local fluorescence. Success has been reported in examining potential treatment fields exposed to Photofrin using ultraviolet light.[4,86,87] Gross detection of fluorescence using ultraviolet light works with Photofrin and ALA-induced PpIX, but this requires subjective assessment using the eye as well as the fact that the ultraviolet spectrum does not include the peak excitation wavelength (410 nm) of PpIX.[88] More sensitive detection of PpIX can be accomplished in patients by employing spectrophotofluorometric technology, which allows for the use of specific excitation wavelengths.[16] Application of this principle may ultimately lead to a relatively simple method for detecting tumor spread and directing site-specific rather than random biopsies to determine the stage of the tumor. However, the intensity of the fluorescent signal produced from tissue containing PpIX is affected by several variables, including blood flow, desmoplasia, pigment distribution, and keratin thickness.[16]

APPROVED APPLICATIONS

PDT has been approved for the prophylactic treatment of recurrent papillary bladder cancer and for palliation in obstructing or near-obstructing esophageal cancer in Canada. PDT also has been approved for early and obstructive lung and esophageal cancer in the Netherlands. Approval for PDT has been given in Japan for early-stage lung, gastric, and cervical cancer, including cervical dysplasia. The U.S. Food & Drug Administration approved Photofrin for palliation in partially and totaling obstructing esophageal cancers not treatable with thermal laser therapy[89] and early-stage lung cancer. Approvals for PDT are currently being sought in 11 additional countries in Europe.

The clinical use of PDT is still in its infancy. The majority of treated tumors respond with unpredictable depths of necrosis using a variety of photosensitizers. This is complicated by the dependence of PDT on numerous complex variables: photosensitizer localization, tissue concentration, oxygenation and blood flow, target tissue optical properties, activation wavelength, power density, light source, tumor thickness, and treatment regimen.[90] In general, most reports of PDT are anecdotal or preliminary and include patients with different types of tumors and different stages and those in whom standard therapies have failed. Further, many treatment parameters are not comparable, including many different photosensitizer dosages, light dosimetry, laser technique, and time of illumination. These variables make it difficult to interpret the various data. Although numerous reports have shown that PDT can cause significant tumor destruction,[7,91–95] there are few randomized trials or palliative protocols. Recently, there has been a trend in clinical PDT research to use PDT as an adjunct to curative surgery to aid in controlling locoregional recurrence.

ESOPHAGUS

Cancer Palliation

Cure for esophageal cancer remains surgical, although the disease is resectable in only a few patients (39%).[96] In the majority of cases, palliation of dysphagia is the only achievable goal with many methods currently in use. The earliest clinical reports of PDT for palliation in esophageal cancer date to the mid-1980s.[94,97,98] Average patient survival in these studies was 7.7 months for those with adenocarcinoma and 5.8 months for those with squamous cell carcinoma.

Although dysphagia is relieved in most patients where the intent was palliation,[99–104] it is difficult to make further conclusions from these studies. Confounding variables in the interpretation of these studies include the photosensitizer used and the dose, as well as light dosimetry. Moreover, there have been concerns that the treatment effects were thermal rather than photochemical.[105] Distinction between thermal and photosensitizer activation is important, but dosimetry studies have shown that there is a relation between light dose, thermal effects, and the depth of tumor necrosis.[100]

Another confounding factor in some of these studies arises from the fact that many of the patients underwent concurrent radiation, chemotherapy, or laser therapy, making it is impossible to determine which of the treatments contributed to outcome. Adding to the confusion is imprecision in the reporting of tumor staging. Many reports describe tumors only as “early” or “advanced” or simply describe the length of tumor involvement within the esophagus.

Two prospective, randomized trials have been completed comparing PDT with Nd:YAG thermal ablation for palliation of advanced esophageal cancer.[104,106] One study randomized 42 patients at one center; the larger study included 236 patients from 24 centers. Results of the smaller study revealed that both PDT and Nd:YAG treatments improved dysphagia, but PDT was significantly better at improving esophageal grade, dietary performance, and patient weight.

The duration of these improvements was significantly longer with PDT than Nd:YAG—84 and 53 days, respectively. The larger trial resulted in equal improvement in dysphagia grades for both the PDT and the Nd:YAG groups, but the improvement was significantly better at 1 month after treatment with PDT. The two treatments were identical in a number of other parameters: endoscopies per patient, palliation of adenocarcinoma and squamous cell carcinoma, palliation of upper and lower esophageal tumors, and survival. The most frequent complication in both studies was sunburn, which occurred in 18% to 19% of patients randomized to PDT. Esophageal perforation occurred more commonly with Nd:YAG than with PDT—7% and 1%, respectively.

In general, PDT has been shown to relieve dysphagia in the majority of reported patients[104,106] and with lower complication and death rates than the alternatives. Complications after PDT typically center on phototoxicity, which has been reported in 0% to 60% of patients. Other mild side effects include substernal chest pain, fever, and nausea. Major complications, which typically occur in $<$10% of cases, include esophageal perforation, tracheoesophageal fistula, aspiration, and esophageal stricture. There have been no deaths over the wide range of studies. PDT appears to compare favorably with conventional nonstenting methods of palliation and to have some advantage over Nd:YAG laser treatment. Anecdotally, we have found PDT useful before placement of expandable metal stents, as well as in the treatment of subsequent tumor ingrowth between the interstices of such stents.

Curative Intent

During early attempts to palliate esophageal cancer with PDT, an occasional patient was found to be tumor-free on follow-up. Such patients tended to have early tumors or were otherwise found to have medical contraindications or refused to undergo surgery. Soon thereafter, PDT studies with the aim of treating early esophageal cancer with curative intent were undertaken. One of the earliest of these studies treated six patients with "early-stage superficial" cancers; four patients had a complete response up to 41 months after treatment.[99] However, three of those four also underwent radiation therapy, and the exact TNM staging was not given. Other studies with similar results followed: 11 complete responses out of 24 patients monitored for 10.8 months;[101] 11 of 14 (79%) at 27 months;[102] and 16 of 22 (73%) at 3 months.[103] Although these initial results appear promising, interpretation is limited by the small numbers of patients, imprecise tumor staging, different photosensitizers and light doses, limited follow-up, and concurrent treatments given in addition to PDT.

A large retrospective study attempted to overcome some of the limitations of previous studies by including only patients who were accurately staged.[83] One hundred twenty-three patients were treated, and 67 underwent multimodal therapy in addition to PDT. The overall complete response rate was 87% at 6 months; the 5-year survival rate was 25% and the 5-year disease-specific survival rate was 74%. These results were the same for patients who underwent PDT alone compared with those who also underwent multimodal therapy in addition to PDT. Similar survival rates were noted when comparing the type of cancer (squamous or adenocarcinoma). Complications included cutaneous phototoxicity (13%) and esophageal stricture formation (33%). Although these results do not match the success of surgery for early esophageal cancer, PDT is an acceptable alternative for patients with medical contraindications and for those who refuse surgery. Randomized trials are certainly necessary before PDT can be recommended as primary treatment for early esophageal cancer.

Barrett's Esophagus

There is little dispute that the currently accepted treatment is esophagectomy for Barrett's esophagus with high-grade dysplasia or adenocarcinoma. Patients who undergo resection for high-grade dysplasia alone have an incidence of adenocarcinoma in the specimen ranging from 0% to 75%, with 50% being the average.[107] The goal of resection is to remove not only the foci of dysplasia and/or cancer, but also all of the abnormal mucosa, because Barrett's metaplasia is a premalignant lesion with a 10% risk of progression to invasive carcinoma.[108] A recent metaanalysis of outcomes after surgery confirmed a 5-year survival rate of 82% for patients with stage I adenocarcinoma in the specimen.[109]

Despite the success of surgery, it is not without its risks: an average mortality rate of 4% and a morbidity rate approaching 75%, with long hospital stays and high cost.[107,109–111] PDT has been proposed as an alternative to surgery and was initially used to treat Barrett's in patients who were not surgical candidates.[112] PDT was found to decrease not only the grade of dysplasia but also the extent of Barrett's mucosa. Further studies of PDT specifically intended to treat Barrett's dysplasia in addition to Barrett's with early carcinoma included small groups of patients with any combination of low-grade dysplasia, high-grade dysplasia, or early cancer.[111,113–116] The largest series included 45 patients: 10 with low-grade dysplasia, 20 with high-grade, and 15 with cancer.[116] Of the 15 with cancer, one was staged at T2 and the rest were T1 or Tis. At 6 months of follow-up, all 10 patients with low-grade dysplasia were found to be free of dysplasia, and 6 had persistent Barrett's epithelium. Of those with prior high-grade dysplasia, 2 continued to have high-grade dysplasia and 8 had low-grade; the remaining 10 were free of any dysplasia, and 7 had persistent metaplasia. All patients with previous cancer were found to be cancer-free, and only one had persistent low-grade dysplasia. These results have been accomplished in an outpatient or short-stay setting with mild complications such as chest pain and fever. The most worrisome complication was esophageal stricture development after

healing of ablated mucosa. This occurred in 33% to 58% of patients and almost always required dilation.[109,116]

The use of PDT in the treatment of Barrett's must be tempered by its failure to eliminate the abnormal mucosa. This necessitates continued surveillance endoscopies—a necessity clearly eliminated in patients undergoing esophagectomy. Further, there are several reports of new squamous epithelium simply growing superficially over the persistent Barrett's epithelium after PDT. Whether these "hidden" islands of Barrett's can subsequently progress to dysplasia or invasive cancer is not known. The patients in these studies were maintained on a proton pump inhibitor throughout the post-PDT follow-up period, which raises the issue that the regression in Barrett's mucosa was a consequence of prolonged acid suppression rather than PDT.[111] Although a theoretical concern, it is probably unlikely: numerous reports demonstrate the lack of success of omeprazole at eliminating Barrett's.[114,117,118] Despite the debate, it is believed that suppressive acid therapy must be maintained after PDT for Barrett's esophagus.

Given the good long-term results after surgery, along with the fact that it eliminates the need for repeated endoscopies and acid suppression, we believe surgery should remain the preferred treatment for high-grade dysplasia and associated carcinoma.[109] Currently, PDT cannot reliably eliminate high-grade dysplasia or Barrett's mucosa to a degree whereby it could be used routinely. However, the lower morbidity and mortality rates make it well suited for nonoperative candidates with few other options and for continued clinical trials aimed at improving its efficacy.

STOMACH

As with esophageal cancer, PDT for gastric cancer is performed using an endoscopic laser-light delivery system. Most of the reports of PDT for gastric cancer are included in larger reports of PDT for various upper GI cancers, such as esophageal, cardia region, and gastric. Therefore, it is difficult to isolate and interpret the results solely for gastric cancers, because few studies have focused only on the stomach. The data currently available for gastric cancer are very similar to those for early esophageal cancer in that they involve small series of patients with short follow-up, a variety of tumor stages, different light dosimetry, and different means of evaluating tumor response.[99,101,113,119,120] In addition to confirming the feasibility and safety of the procedure, these studies obtained mixed success in terms of tumor response: some report complete histologic response in "advanced" tumors,[121] whereas others report only partial response in "early" tumors.[92] Unfortunately, the analysis of PDT for gastric cancer is plagued by mixed and varied results with low patient numbers and inadequate follow-up.

Some of the treatment failures among patients with early tumors have been blamed on poor light delivery.[92] This is a reasonable assumption because the gastric rugae and mucosal folds can shadow other areas from light. Gastric tumors may also spread over a large surface area, making light delivery even more difficult. If light delivery can be improved, and if gastric tumors can be detected early enough, then PDT may play a role in their treatment. However, it is doubtful that it will ever be the primary treatment, except in early gastric cancer.

PANCREAS

Thus far, PDT applied to pancreatic cancers has never been limited, despite multiple studies using different photosensitizers showing photodynamic destruction of rodent pancreatic cancer.[122–128] The transition to clinical trials has not been made for a number of reasons: some are based on animal studies, and others are more theoretical. One of the most worrisome side effects in animals has been duodenal perforation. This has occurred in most studies (although only in a small percentage of treated animals) and is related to the thin nature of the rodent duodenum. Further, mucosa is known to concentrate photosensitizers and is subsequently irradiated because of its juxtaposition to the treated tissue. Bile duct obstruction is another complication, but it is not as common.[127,128] This is thought to be secondary to edema of pancreatic tissue surrounding the treated area, especially near the ampulla of Vater, because it resolves spontaneously within 7 days.

Theoretical concerns for human application include the fact that pancreatic cancer is a bulky, solid organ tumor. This makes light penetration into the tumor limited, at least until interstitial light delivery can be improved. Benefit from PDT may lie in "sterilizing" the margins of resection of microscopic residual tumor. The complications seen after animal treatment may be very real for human treatment as well, even though the human duodenum is thicker and the pancreas larger, making overlapping light delivery less of a concern.[127,128] Bile duct obstruction in humans could be avoided by the insertion of a biliary stent.[127,128] Further potential complications include pancreatic edema and/or pancreatitis, secondary infection of necrotic pancreatic tumor, cholangitis secondary to biliary obstruction, and even pancreatic fistula.

HEPATOBILIARY

Very little data exist on the clinical application of PDT for hepatobiliary disease. A case report in 1991 described the successful palliation of cholangiocarcinoma in one patient using multiple PDT sessions over a period of years.[129] More recently, PDT has been used to palliate advanced, inoperable cholangiocarcinoma in a series of nine patients.[130] Patients were selected to undergo PDT for persistent hyperbilirubinemia after successful endoscopic stent placement. The nine were compared with four patients who were similarly stented but who did not receive PDT. PDT improved hyperbilirubinemia by at least 50% compared with the non-PDT controls. All PDT was performed using

an endoscopically guided laser fiber, which avoids the need for percutaneous drains or manipulations. After PDT, mean bilirubin levels fell significantly (from 31.8 to 10.3 mmol/L) and remained low at the 2-month follow-up. Quality of life was improved when compared with the four successfully stented patients. The peritreatment mortality rate was nil after PDT, with a 1-year survival rate of 77% and a median survival of 439 days. The significant complications were pleural effusion and sepsis in two patients. Although survival data for the four control patients were not given, historical data would predict a 30-day survival rate of 32% to 75%, with a median survival of 62 to 70 days. The inference is that PDT offers a chance for palliation, in terms of both survival and quality of life.

COLORECTAL

Only a handful of papers describe PDT for colon and rectal cancer; this is surprising when one considers the incidence of this disease.[77,101,115,131] The reports are again anecdotal and limited in terms of numbers of patients and scope. Some pilot studies have enrolled a small number of inoperable patients with colorectal adenocarcinoma who were all subsequently treated endoscopically. Tumor necrosis has been reported to occur as deep as 15 mm,[77] and complete responses to the treatment have been achieved in 50% of patients at 15 months of follow-up.[101] Good palliation of symptoms such as bleeding and constipation has also been possible in seven of ten patients.[77] Further, site-specific complications can occur, including post-PDT stenosis, hemorrhage from necrotic tumor, and colon perforation. Because many of these complications have followed the treatment of very large or circumferential tumors, and because treatment failures have occurred more commonly with large tumors, some authors have suggested limiting PDT to smaller lesions with less circumferential involvement.

PDT has been performed on smaller lesions, namely adenomas.[132,133] The first such study included eight patients with nine sessile villous adenomas, all but one of which recurred after Nd:YAG thermal ablation. After a follow-up period of 9 to 56 months, a biopsy was performed, and it was found that seven of the nine adenomas had been completely eradicated. The only complication was one skin burn. Another study involved the treatment of large recurrent intestinal polyps in six patients with familial adenomatous polyposis. Of the two patients with colonic polyps, one was found to show a complete response to treatment, and no complications were reported.

Use of the Nd:YAG laser to ablate adenomas is an alternative in nonoperative candidates. Although it successfully removes the lesion in 84% to 93% of cases with low morbidity and mortality rates (1% to 5% and 0%, respectively), the progression to invasive cancer after treatment is 5.7% to 9.1%.[102,103,134] This cancer risk is most likely related to incomplete destruction of dysplastic epithelium. This may be an area where PDT is applicable, especially if it can be shown to eliminate cancer progression. PDT offers the potential of more tumor-specific photochemical injury, which allows for more complete necrosis of microscopic foci of dysplasia not visually evident and thereby missed during Nd:YAG therapy.

INTRAABDOMINAL

The vast majority of PDT procedures for tumors of the GI tract are performed using an endoscope. In fact, all studies discussed thus far have delivered light through a port using a fiberoptic cable. Although convenient for the patient, the tumor obviously must be endoscopically accessible. However, several phase I studies have been published to assess the feasibility of intraoperative PDT for tumors accessible only by laparotomy.[8,9,15,86,87] The first of these involved 11 patients with pelvic recurrence of colorectal adenocarcinoma.[86] In five patients, after tumor debulking was performed, PDT was used to treat the residual margins. The other six tumors were found to be unresectable at exploration; only PDT of the tumor was performed, without resection. No major side effects or complications resulted, and tumor shrinkage was documented by subsequent CT scans. However, patient outcome or survival did not improve, which is not surprising given the patient selection. Significantly, five patients had marked pain relief—a result not expected or explained.

Another study used PDT to treat recurrent retroperitoneal sarcomas in ten patients.[87] After resection of the tumor, a Wood's lamp was used to induce fluorescence in any residual tumor that was not obvious to the naked eye. Any fluorescent areas were then resected. In this way, photodiagnosis helped determine the extent of resection. No complications were reported; however, as with the previous study, no survival benefit was seen.

The treatment of disseminated intraperitoneal cancer has been attempted by one group.[8,9] A total of 39 patients with carcinomatosis secondary to ovarian cancer or sarcoma were treated by debulking all tumor >5 mm, followed by PDT of the entire peritoneal surface. Light was delivered through fiberoptic cables inserted into the abdominal cavity, which was filled with lipid medium to diffuse light. Shadowed areas, such as the diaphragm, were irradiated using a light diffusing wand. Using escalating drug and light doses, the maximum tolerable light dose was calculated. As the light dose exceeded this maximum, there was an increase in the rate of complications: small bowel and gastric perforations, prolonged intubation secondary to sympathetic pleural effusions, and colonic fistulas. Nine patients were free of disease up to 43 months. Whether these responses were secondary to the PDT or the debulking is uncertain because there were no controls. A disadvantage to this approach includes an average anesthesia time of 8.5 hours, reflecting the time necessary to deliver sufficient light to the entire peritoneal surface. These results are important because they

show that PDT can be performed on abdominal tumors and can be used despite previous or subsequent treatments (*i.e.*, chemotherapy and radiation).

The largest intraabdominal PDT study to date involved 42 patients with a variety of GI tumors.[15] Because this was primarily a toxicity study, treatment effects were not reported. It showed that photosensitization with ALA-induced PpIX was safe, caused no skin burns, and produced good selective accumulation of the photosensitizer within the tumors, all of which were adenocarcinomas of the GI tract. Further, PDT of the residual surgical field and/or metastatic disease was not associated with apparent complications.

CONCLUSION

PDT is clearly effective for small cancers, but it is not yet clear in which cases such treatment is more effective than other currently acceptable approaches. As data from additional clinical trials become available, we will gain a clearer perspective of where PDT fits in the treatment of cancers. Many issues regarding the pharmacokinetic data of photosensitizers, newer technology involved in light sources, optimal treatment regimens that take advantage of the pharmacophysiology of photoablation, and light dosimetry, still require solution. One can foresee the application of differing sensitizers and light sources depending on the specific clinical situation. As technologic advances occur, interstitial PDT may have significant application.

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