Published in final edited form as:

Tech Gastrointest Endosc. 2010 January ; 12(1): . doi:10.1016/j.tgie.2010.01.009.

Role of Photodynamic Therapy for the Upper Gut

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Abstract

It may be questioned if PDT is still relevant for practicing gastroenterologists since other types of therapy have currently gained momentum. Important aspects of PDT that continue its development are it's intrinsic applicability to the luminal GI tract where there are often areas of mechanical narrowing, unusual topography, and difficult accessibility where a modality that does not require contact or optical visualization has advantages. Although not used as often in the upper gastrointestinal tract for it's original approved indications such as esophageal cancer or Barrett's esophagus, its value in biliary lesions appears to be well substantiated. In this paper, we will review its current application in the upper gastrointestinal tract.

History

Photodynamic therapy (PDT) has actually been in existence since the time of the ancient Egyptians, when it was recognized that the use of a sensitizing agent such as naturally occurring petroleum tar when applied to the skin and exposed to sunlight led to resolution of conditions such as psoriasis [1]. It was this early recognition that the interaction of light, a drug, and a human surface area could lead to beneficial results that led to further development of photodynamic therapy. Modern PDT using porphyrin agents began about 1967 with the initial description of hematoporphyrin derivative by Lipson in the gastrointestinal tract [2]. In its current iteration in the gastrointestinal tract, we still use primarily an injected drug, sodium porfimer, which is usually given 48 hours prior to light administration. Light is applied usually using some type of cylindrical diffusing fiber in the luminal GI tract which allows more uniform application. In addition, centering balloons have been developed to keep this light fiber in the center of the lumen to ensure more adequate distribution of light. The rationale for these centering balloons is to help provide even distribution of light in the lumen. If the fiber were eccentrically positioned, there would be far more light in the wall of the gastrointestinal tract that the fiber was closer to that the more distant wall that could lead to areas of over treatment and undertreatment. (Figure 1)

Subsequently, a photochemical process ensues which causes cell death and destruction of the treated tissue. This treatment has primarily applied to neoplastic tissue, although there have been a few indications for benign problems.

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The author reports no financial interests that might pose a conflict of interest in connection with the submitted manuscript.

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Mechanisms of Action

Photodynamic therapy is thought to result when photons interact with the photosensitizer causing elevation in the photosensitizer to a triplet state [3, 4]. This then interacts with molecular oxygen producing singlet oxygen that in turn has a very short half-life so it will cause cell death to any cells in the vicinity of the photosensitizer. The photosensitizers are usually fairly large molecules that contain chlorophyll or hemoglobin types of rings that can absorb light energy [5]. Modifications of these compounds are the basis of third generation photosensitizer.

A unique exception to this is the use of ALA (delta aminolevulinic acid) which is actually a pro-drug. It can be administered orally and subsequently is converted to protoporphyrin IX as part of the heme synthetic pathway. As protoporphyrin IX, this compound can then absorb light and act as a photosensitizer.

Generally, the signaling cascades that are triggered by photodynamic therapy include those for apoptosis. Soon after delivery of light, cells can undergo shrinkage in their size and activation of the Caspase 3A is noted [6–8]. There is both intrinsic and extrinsic activation of the apoptotic pathways. Some of this is dependent on the class of photosensitizers as some photosensitizers have been developed that can concentrate in cell organelle such as lysosomes or mitochondria to stimulate cell death.

In addition, there has been information suggesting that specific defects in known cell cycle checkpoint genes such as p16 can result in resistance to photodynamic therapy on a clinical basis. It is still unclear whether this is the result of cells that are actually more susceptible or less susceptible to photodynamic therapy or an indication that these patients have a more neoplastic disease course.

In addition to these mechanisms of action, there are also other mechanisms that work including ischemia which is produced by a preferential effect of the photosensitizers on the vascular supply of tumors. It can be well seen in implanted mouse tumor models that there is invasive constrictive effect soon after applications of light that causes ischemic damage to these tumors. In addition, there is direct cell toxicity from the photosensitizers as well. This ischemic affect, has been used to treat more benign conditions such as macular degeneration, primarily the “wet” form of macular degeneration where the photosensitizer vascular effects seem to decrease additional leakage of fluid from the capillaries and, thereby, maintain vision.

Current Equipment

In the United States the only clinically available laser system for gastrointestinal applications of photodynamic therapy are diode lasers. These have two watts of total output at 630 nanometers wavelength of red light which can activate sodium porfimer. This is the only photosensitizer available in the United States for gastrointestinal purposes. Although aminolevulinic acid is available, it is only used in cutaneous applications at this time. The oral formulation has not been approved in the United States, although it is available in Europe.

The lasers that are available are fairly self-sufficient and contain an integrating sphere for measuring total power output that allow the unit to be calibrated at the desired outputs. The current diode lasers have built in treatment parameters for FDA approved indications such as lung cancer, esophageal cancer, and Barrett’s esophagus with high-grade dysplasia. By selecting one of these indications, the laser automatically inputs the correct parameters for therapy including the power required and the total amount of energy delivered. These parameters are very important for any applications since the delivery rate and the total

energy dose needed varies depending on tissue properties. For instance, in the gastrointestinal tract, dosages required for areas such as the biliary system are very high most likely due to the desmoplastic reaction produced by these tumors. This creates a great deal of light reflection that increases the amount of light needed to treat the cancer cells. It is also thought that the light is transmitted into areas of the biliary system that is not directly photoradiated and that the light reflected internally in the ducts leads to destruction of tumor cells and allows the secondary and even tertiary biliary ducts to remain patent allowing for better palliation from the progressive biliary disease.

The company that once made these lasers, Diomed, has been purchased by another company, Angiodynamics (Queensbury, New York). It is unclear if and how long these lasers will continue to be available for photodynamic therapy.

The newer photosensitizers that can reach into the near infrared or 680 nanometer wavelength will require new laser systems that are not currently approved for photodynamic therapy. These laser systems should be more robust as lasers in the near infrared are more cost-effective and have been created with very stable technologies to maintain their outputs. Generally speaking, diode lasers have a finite life expectancy because of the gradual breakdown of the photodiode arrays that produce the laser energy. Lasers generally have an anticipated life expectancy based upon hours of use.

The Diomed laser is operationally similar to the laser shown in Figure 2. There is a built in integrating sphere that can measure the laser output at the tip of the photoradiating device. This allows very easy calibration in a self contained unit. In addition, this provides a failsafe solution to not allow the system to operate if sufficient power output is not available. The laser can be programmed for the amount of energy to be delivered and records the time remaining during the treatment.

Methods

Light is delivered from a laser to the tissue using a diffusing fiber. The FDA approved fibers in the United States are limited to flexible fiberoptic cables with a semi-rigid cylindrical diffuser mounted at the end available in lengths from 1.0 centimeters in length to 5.0 centimeters. The length of the diffusing segment determines the length of the Barrett's esophagus that can be treated with a single light application. Thus, longer fibers are needed for longer lengths of Barrett's esophagus. At the current time, 5 centimeters of Barrett's esophagus can be treated with a single light application although more than one application of the fiber can be rendered (Figure 3).

There is the potential for overlap and possible stricture formation. This can be reduced by the use of "Optiguide PDT fibers". These are the fibers typically applied for esophageal or gastric PDT but due to their stiffness are difficult to use in the biliary tree. However, these fibers are not approved for human use in the United States. Centering type balloons are available in Europe but not available in the United States due to regulatory issues.

Current Clinical Applications

Esophageal Cancer

PDT was originally approved for the use in palliation of esophageal cancer based on a large multicenter randomized trial that was performed over 14 years ago [9]. This trial consisting of 110 patients treated with sodium porfimer based PDT and 108 treated with neodymium:yttrium-aluminum-garnet laser which was the standard for laser palliation in this time period. PDT delivered with a cylindrical diffusing fiber at a dose of 300 Joules/

centimeter fiber was found to be equivalent to the thermal laser in terms of palliation and was associated with much fewer complications. Although not commonly used for this application in this age of expandable metal stents, this treatment certainly has its place in those patients who have very tightly obstructing lesions that are difficult to stent. The tighter the lumen, the more effective the PDT since the dose of light is greater with a narrower lumen. PDT can also be effective in the situation where there is tumor overgrowth of a stent [10]. Primary palliation using PDT is less common since there is still the concern over the cutaneous photosensitivity produced by the drug that persists for over 4–8 weeks in some patients that can limit quality of life.

In patients who have reasonable life expectancies and also have good to excellent performance status, tumor ablation techniques such as PDT to alleviate dysphagia seem to be well tolerated. These patients are less likely to tolerate the traditional stents because of the discomfort, restrictions from bending over, as well as the reflux produced from stents predominately in the lower esophagus. In patients that are performing at a high level, PDT can provide a long duration of palliation from dysphagia without as many restrictions as stents. In patients who are debilitated and have a limited survival, stents are probably a better option.

Barrett's Esophagus

Although there has not been a randomized trial comparing the two modalities, it appears that radiofrequency ablation is able to be at least as effective as PDT and produce less complications. However, there is still a role for PDT in certain situations. As the randomized studies have shown, PDT is effective in reducing dysplasia in patients with high grade dysplasia in 77% of 208 patients treated in the largest multi-center prospective randomized trial of patients with high grade dysplasia [11]. It also resulted in a about a 50% reduction in cancer development in the treated group. These results have substantiated its efficacy and resulted in FDA approval for treatment of Barrett's esophagus with high-grade dysplasia.

The primary limitation to the use of PDT in Barrett's esophagus has been the stricture formation that occurs after multiple treatments. In patients who had been treated with photodynamic therapy, strictures appeared in 36% of patients treated with photodynamic therapy overall. However, if there was only one treatment, the stricture rate was limited to 12%. The use of a second treatment raised the stricture rate significantly to 30%. A single application of photodynamic therapy with elimination of residual tissue with other modalities such as mucosal resection or other ablation techniques is now favored for photodynamic therapy [12].

Photodynamic therapy for Barrett's esophagus is currently performed by first administering sodium porfimer intravenously at a concentration of 2 milligrams per kilogram body weight 48 hours prior to photoradiation. The patient is then sedated for a routine endoscopy and the diffusing fiber is placed through the working channel. The diffuser section is placed in the area opposing the Barrett's mucosa and light is delivered at a power output at 400 milliwatts per centimeter fiber for a total energy of 200 joules per centimeter diffuser. The goal is to keep the fiber centered within the lumen and to keep the areas being photoradiated relatively focused during the procedure. If more than one application of light is performed, care must be made to ensure that the overlap is limited.

The primary areas where photodynamic therapy can be applied are those which other therapies have failed, the presence of a stricture that cannot be traversed by the balloon devices used for radiofrequency ablation, areas of the gastrointestinal tract in which a contact method cannot be applied i.e. the cardia of the stomach. In these situations, PDT is often the only ablative method that can be applied to Barrett's esophagus.

Photodynamic therapy in conjunction with mucosal resection has been found to produce long-term survival benefits comparable with esophagectomy [13]. These ablative therapies are also more cost-effective than esophagectomy in the treatment of Barrett's esophagus with high-grade dysplasia [14].

Cholangiocarcinoma

Initial reports of the use of photodynamic therapy for biliary tumors have been very encouraging. Photodynamic therapy for cholangiocarcinoma Bismuth staged III–IV with jaundice that was unresponsive to stenting led to a very significant increase in survival as well as relief of jaundice in a small number of patients [15]. Subsequent randomized prospective studies confirmed this observation with statistically and clinically significant increases in survival of 493 days in the treated group as compared to only 98 days in a control group of patients with obstructive jaundice [16]. The sample size was also small in this study since the differences were so great it was terminated early due to ethical concerns. Although other groups have reported similar findings, this study clearly had one of the best reported survivals in the literature.

The technique used by Ortnier in her studies involved a flexible cylindrical diffusing fiber which is not available for clinical use in the United States although available in Europe from two different sources. The lack of this fiber means that the semi-rigid fiber used for esophageal work can be implemented though this is difficult to use and the fibers can easily be broken. The esophageal fibers must be placed within an introducer catheter which in our case, has been the Howell Introducer (Cook Medical, Bloomington, Indiana) which protects the diffuser as it is passed retrograde through the papilla to the lesion [17]. Even with the use of this fiber, roughly 1 in three fibers are broken in the attempt. Cholangiocarcinoma are treated at similar power as the esophagus, 400 milliwatts per centimeter fiber but are dosed with much more light. It has been found that a dose of 180 Joules per square centimeter of tumor is needed for the treatment to be successful. It has also been found that if the treatment can be performed soon after diagnosis, there is increased survival which does not seem to be simply the result of lead time bias (Figure 4).

Evidence-based reviews of the literature have found that photodynamic therapy clearly superior to studies involving brachytherapy and stenting in terms of survival though not as good as liver transplantation in patients who are good candidates [18].

Future Directions

Photodynamic therapy has its advantage in being able to be placed into areas where other therapies cannot access. The biliary system is a key example but other lesions that are of interest to gastroenterologists include pancreatic cancers and other non-luminal lesions [19, 20]. The treatment of these lesions is still in the exploratory phase but with the use of EUS guidance and the development of smaller and more flexible fibers, most locations in the mediastinum and abdominal cavity are now treatable. The fibers can be built that are as narrow as a .035 guidewire and can easily be safely passed through the wall of the gastrointestinal tract for photoradiation.

The phototoxicity of this agent can also be obviated by the use of newly developed sunscreens that can effectively eliminate photosensitivity. In addition, new photosensitizers under development clear the system much faster so the period of photosensitivity has decreased from months to days.

All of these developments lead to the possibility of using photodynamic therapy to eliminate residual cancer, small foci of metastasis, or even primary lesions that are within reach of the

gastrointestinal tract. The future of PDT will most likely depend upon further studies in these areas.

Acknowledgments

This work was supported by grants from the NCI R01CA111603, R21CA122426, R01CA097048 as well as contributions from the Mayo Foundation.

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Fiber Centering

Figure 1.

If the cylindrical diffusing fiber is eccentrically placed in the lumen, there is a tendency to over treat the closer portion of the wall and undertreat the more distant wall. This is the rationale for using devices such as centering balloons.

Figure 2.

This is a typical laser diode based photodynamic therapy laser with touch screen for operational control and connectors for the laser fiber. There is also a remote control for activating/inactivating the laser output. As required by regulations, these lasers do contain emergency power shut off switches. (Sinolaser System & Equipment Co., Ltd., model PDT 635S).

Figure 3.
This is an endoscopic view of a bare fiber placed through the working channel of an endoscope in the esophagus. The red glowing area is the cylindrical diffusing fiber.

Figure 4.
Positioning of a cylindrical diffusing fiber using an introducing catheter into the common bile duct for PDT of a cholangiocarcinoma.