

## Role of Photodynamic Therapy in Gastroenterology

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### SUMMARY

**Photodynamic therapy (PDT) is a cancer treatment modality that combines the use of a photosensitizing agent and a photosensitizer (a drug that selectively accumulates and is preferentially retained in dysplastic or neoplastic cells). When activated by light of a specific wavelength in the presence of oxygen, the photoactive compound produces rapid cell death in the target tissue. Following health agency approvals throughout the world for various cancers and other diseases, PDT is gradually being accepted as a standard modality to be added to the medical practitioner's armamentarium. In Gastroenterology, PDT has been approved for the treatment of Barrett's esophagus and of early esophageal cancer, and as palliative therapy for advanced esophageal carcinoma whereas, superficial gastric cancer, non-resectable cholangiocarcinoma, and pancreatic carcinoma have been investigated in PDT trials. This article represents an extensive survey of literature to review the experience gained with PDT and to assess its clinical value in the management of gastrointestinal diseases.**

Photodynamic therapy (PDT) is a non-thermal, photochemical process. It uses the combination of a photosensitising drug (PS) and light to cause selective damage to the target tissue in a two step procedure.<sup>1-4</sup> A PS, administered intravenously, topically, or orally, preferentially accumulates in target tissue and remains inactive until exposed to light of a specific wavelength, suitable for the given PS. When light is delivered, the PS absorbs energy, and then transfers it to molecular oxygen to create an activated form of oxygen called singlet oxygen. It

is this singlet oxygen that reacts rapidly with cellular components to cause the cell death and tumor destruction. Damage of tissue occurs via several pathways including cell necrosis, apoptosis, and ischemia with vascular shutdown.<sup>1,5-6</sup> During the process, the PS is regenerated so that it acts catalytically, and many cycles of singlet-oxygen production can occur for each molecule of sensitizer. It is clear that the effectiveness of the procedure depends on the interaction of a PS, light, and oxygen. The targeting and selectivity of PDT is aided by several factors, the first of which is the delivery of light. By use of modern light delivery systems, light can be targeted accurately to the target tissue. In addition singlet oxygen generated by the activated PS has a very short life, and is deactivated before it can escape from the cell which produced it.<sup>4</sup>

Light has been used as a therapeutic agent for centuries, and was popular with the Greeks 3000 years ago, who advocated exposure to sunlight for restoration of health. In 1900, Oscar Raab, a medical student in Munich, discovered that acridine was toxic to paramecia.<sup>7</sup> Subsequent experiments showed that light and acridine together increased the toxic effect on the paramecium. This work was continued by his professor, who published clinical data on the treatment of skin conditions with eosin.<sup>7</sup> Hematoporphyrin derivate (HpD) was discovered in 1961. Since then, HpD and its partially purified derivative, porfimer sodium (Photofrin) have been studied in thousands of patients, especially in oncology. The main advantage for PDT use in oncology is their higher concentrations in tumour tissue than in surrounding healthy tissue. Although the exact mechanisms that drive this process are not fully understood, the abnormal physiology of tumours might contribute to the selectivity of PDT.<sup>4</sup> Furthermore, the healing of healthy tissue after PDT is very efficient, usually without scarring. Even if healthy tissue is damaged at the time of treatment, the cosmetic result after 2-3 months is usually excellent (a

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type of selectivity). The main disadvantages of PDT are difficulty in the establishment of the optimum variables for treatment and the problem of skin photosensitivity. However, greatly improved understanding of factors that control PDT and the identification of new PSs might overcome the present difficulties.

The development of PDT has progressed slowly but surely, and in some specialties of medicine (eg, dermatological oncology and ophthalmology), it is used widely. In gastroenterology, PDT has been approved for the treatment of Barrett's esophagus, for early esophageal cancer, and as palliative therapy for advanced esophageal carcinoma. Superficial gastric cancer, non-resectable cholangiocarcinoma, and pancreatic carcinoma have been investigated in PDT trials. Table 1 summarizes the characteristics of commonly used clinical sensitizers in gastroenterology. Most applications of PDT in Gastroenterology to date have used porphyrin sodium. Photofrin has been used mainly for the destruction of esophageal tumors, due to its depth of penetration and relative tumor selectivity. However, its use is complicated by a prolonged induced skin photosensitivity and a high incidence of stricture formation. Thus, two new sensitizers are of particular interest.<sup>7</sup> PDT with meta-tetrahydroxyphenyl chlorin (m-THPC) has been found to produce a biological effect similar to PDT with porphyrin sodium but the light doses required are much smaller and cutaneous photosensitivity lasts only 2-3 weeks. The 5-aminolevulinic acid (5-ALA) is a unique naturally occurring photosensitizer precursor. Living cells in the haem biosynthetic pathway synthesize it and then it is converted to different porphyrin intermediaries, including the photoactive protoporphyrin IX (PpIX). Administration of exogenous 5-ALA bypasses the negative feedback control of the pathway, resulting in excessive production of the photoactive agent. The major advantage of 5-ALA is its selective production by the mucosa in comparison to the muscularis, thereby producing highly specific mucosal photosensitization. Thus, it could destroy areas of abnormal mucosa without damaging underlying muscle layer and reduce the incidence of stricture formation.<sup>1</sup>

Lasers provide the most convenient source of light for PDT, as they produce monochromatic light of a known wavelength, light dosimetry is easy to calculate, and the light can be passed down an optical fiber.<sup>1,2,4</sup> The power of the source is important because it will determine treatment times. In clinical practice, diode lasers, which are small, portable, reliable, and inexpensive, are the most commonly used. However, their power output

is limited and they only emit light at a single wavelength, thus their use is specified for only a particular sensitizer. Many other types of lasers have been used, including argon-dye, KTP-dye, and metal vapor. These lasers allow the use of different sensitizers, as their wavelength is varied and could match the optimum absorption wavelength of the sensitizer. However, these systems are bulky, very expensive, and require technical expertise for use.

## ESOPHAGUS

### *Barrett's esophagus*

Light delivery for PDT and the eradication of Barrett's esophagus presents a challenge and different methods of light application have been used.<sup>9</sup> Light delivery systems are generally cylindrical diffusing fibers, positioned under endoscopic or fluoroscopic guidance within the lumen of esophagus. This technique has the disadvantage that it is not possible to flatten the esophageal folds to improve illumination of the entire treatment segment. Moreover, it is difficult to center the fiber within the lumen so as to avoid light delivery over only a limited distance. Thus, the use of these fibers may result in a non-uniform illumination or in a potential esophageal injury.<sup>10</sup> Modern light systems, using an applicator adapted to the shape of the esophagus, could flatten the mucosal folds of esophagus.<sup>9,11</sup> The use of a cylindrical nonelastic balloon-centering device flattens the folds, stabilizes the position of the light fiber, and may improve clinical outcome. However, it is important not to stretch the esophagus wall too much, as this decreases mucosal blood flow and reduce the PDT effect.

Photofrin has been commercially available since 1994 and has been used in four large studies for PDT in patients with Barrett's esophagus.<sup>12-15</sup> The number of patients recruited ranged from 26 to 84 and total elimination of Barrett's esophagus was found in a range from 35% to 50% of patients. Residual submucosal islands of Barrett's epithelium was detected in 0-6% of patients without development of dysplasia or neoplasia. The most problematic treatment complication was the development of strictures (range from 16% to 34%). The use of oral prednisone to reduce the incidence of stricture after porphyrin sodium PDT was not supported by one study.<sup>15</sup> The results of these studies led to a large, phase III randomised trial with porphyrin sodium.<sup>16</sup> The study included 208 patients with high-grade dysplastic Barrett's esophagus who were randomly allocated to treatment with PDT plus omeprazole (n=138) or omeprazole only (n=70). At a minimum follow-up of 24 months, 76.8%

of patients in the PDT group had high-grade dysplasia elimination compared with 38.6% of patients in the control, omeprazole group ( $p < 0.001$ ). Moreover, treatment with porfimer sodium was demonstrated to produce an up to twofold, statistically significant decrease in the development of adenocarcinoma (13% vs. 28%,  $p = 0.006$ ).

The PS 5-ALA is used extensively for PDT in Europe where it is inexpensive and readily available. Small and non-randomised trials of PDT with oral 5-ALA have shown encouraging results, with regeneration of healthy epithelium.<sup>17-21</sup> Recently, in a prospective double blinded study, 36 patients with dysplastic Barrett's esophagus were randomly treated with 30mg/kg oral 5-ALA or placebo.<sup>22</sup> 5-ALA was activated by green light (514 nm) in order to enhance superficial mucosal damage but avoid stricture formation. In the 5-ALA group, 16 of 18 patients responded, with a median decrease in columnar epithelial area of 30%, whereas, a 10% decrease in area was seen in only 2 of 18 patients in the placebo group. No dysplasia was seen in the treated area of any patient in the PDT group, but persistent low-grade dysplasia was seen in 12 patients ( $p < 0.001$ ) in the placebo group. A recent trial studied the topical administration of 5-ALA with red-light PDT in 14 patients with or without low-grade dysplasia.<sup>23</sup> Although dysplasia was eliminated in all patients and skin photosensitivity was reduced, further studies should be performed before topical administration becomes an alternative approach for 5-ALA PDT therapy. However, there is some concern that after PDT with 5-ALA, submucosal islands of Barrett's epithelium may remain.<sup>2</sup>

Two small studies, with 4 and 3 patients respectively, used m-THPC as a sensitiser.<sup>24,25</sup> These studies suggested the capability of this potent sensitiser to eliminate columnar esophageal mucosa, reduce the length of the Barrett's segment, and downgrade the histological classification of dysplasia. Precise control of the light dose is critical, since the use of this agent may be associated with severe strictures and tissue necrosis.

### *Esophageal carcinoma*

**Advanced carcinoma:** Porfimer sodium is licenced for palliation of patients with completely obstructing esophageal cancer, or for patients with partial obstruction who cannot be treated satisfactorily with Nd:YAG laser therapy.<sup>26</sup>

In an early prospective, multicentre, study Photofrin-PDT was compared with Nd:YAG laser in patients with advanced esophageal cancer.<sup>27</sup> Median survival and relief of dysphagia was similar, but the latter was prolonged at

1 month for those receiving PDT (32% vs. 20%,  $p < 0.05$ ); Nine complete tumour responses occurred after PDT and two after Nd:YAG. Significantly more perforations occurred in the Nd:YAG group (1% vs. 7%,  $p < 0.05$ ).

**Early adenocarcinoma:** Five studies using HpD or Photofrin have been conducted, and four of them showed that PDT is capable for eradicating early esophageal cancers.<sup>12,14,15,28,29</sup> The number of patients recruited ranged from 13 to 62 and most of them presented with superficial cancer (stage Tis-T2). A complete response rate of 44-100% was found over a follow-up of 12-57 months in patients with Tis or T1 carcinoma. Patients with more advanced disease had a lower complete response (0-100%) and the median survival decreased (from 12 months for stage II to 3.5 months for stage IV).

In a recent study, photofrin-PDT with supplementary Nd:YAG photoablation and continuous treatment with omeprazole reduced the length of Barrett's mucosa and eliminated high-grade dysplasia.<sup>30</sup> For 103 patients with Barrett's with high-grade dysplasia, low-grade dysplasia, or early stage carcinoma, intention-to-treat success rates were 77.5%, 92.9%, and 44.4%, respectively. Strictures occurred in 30% of patients, overall.

In a retrospective review, the combination of endoscopic mucosal resection (EMR) and PDT was a viable less morbid alternative to standard esophagectomy in patients presenting with early Barrett's esophageal adenocarcinoma.<sup>31</sup> Eighty-three percent of patients (20/24) in the EMR/PDT group and all the patients (64/64) in the surgery group remained free of cancer over a follow-up of 12 and 19 months, respectively. However, the complication rate after surgery was significantly higher compared to EMR/PDT group (31% vs. 4%,  $p < 0.01$ ).

**Squamous cell carcinoma:** HpD or Photofrin have been also used for treatment of squamous cell carcinoma.<sup>31,32</sup> These studies were able to demonstrate complete remission in 50-92% of patients with superficial tumors. A palliative effect was also found in patients with advanced cancer, as significant remission were obtained in 40-60% of patients, while partial remissions were observed in 50-75% of patients. There was no recurrence in responder patients after a follow-up ranged from 6-85 months.

PDT with m-THPC was applied in patients with in situ squamous cell cancers of the esophagus with no recurrence in 83% of patients after a mean follow-up of 15.3 months, whereas only one of patients with T1 and T2 cancers showed complete response.<sup>39-41</sup> In a small study, comparing m-THPC, HpD, and porfimer sodium,

cure was achieved in 84% of early cancers (Tis, T1) at a mean follow-up of 2 years.<sup>39</sup> Differences in the efficiency of treatment and the complication rate were similar for the different sensitizers. The efficacy of 5-ALA compared with HpD in patients with advanced esophageal carcinoma was reported in one study.<sup>42</sup> Based on improvement in dysphagia and reduction of tumor stenosis, HpD was significantly more effective than 5-ALA PDT.

*Complications:* Aside from skin phototoxicity (10%), the primary complication of PDT has been the formation of esophageal strictures during the healing procedure. The incidence of stricture formation has been reported over a broad range from 4.8% to 53%.<sup>43</sup> Fortunately, the majority of them are mild and respond to endoscopic dilatation. Other complications include esophagotracheal fistula and occult esophageal perforation, both of which are common with the use of m-THPC but uncommon with porfimer sodium.<sup>41</sup> Minor complications include candida esophagitis (3.2%) and symptomatic pleural effusion (3.2%).

## GASTRIC CANCER

PDT effect on gastric cancer has been investigated in trials including small numbers of patients. HpD has been used as a sensitizer in 3 early studies; two recruited patients with early gastric cancer and one patient with advanced disease.<sup>44-46</sup> Local cure was reported in 7 of 8 and in 2 of 2 patients with early cancer, whereas partial response was observed in patients with advanced gastric cancer.

In a recent study, 22 patients with superficial early gastric cancer received PDT with m-THPC.<sup>47</sup> Complete remission was achieved in 16/22 (73%) of patients: 13/16 (80%) with intestinal type of cancer and 3/6 (50%) with diffuse type carcinoma. The mean follow-up period was 12 and 20 months, respectively.

## CHOLANGIOCARCINOMA

PDT has been developed as an acceptable palliative therapy for perihilar cholangiocarcinomas (CC). There is no reason to apply PDT to intrahepatic peripheral CCs, which usually are multifocal or bulky when non-resectable, or to distal extrahepatic CCs, which are best managed by curative resection or palliative insertion of a metal stent.<sup>48</sup> There are five small, prospective, non-randomized studies of PDT for CC with survival data (49-53).<sup>49-53</sup> Overall, these trials demonstrated that when PDT was used repeatedly, a significant extension in the medi-

an survival time in the range of > 9 to 14.4 months could be expected. Moreover, all trials have shown a remarkable reduction of cholestasis, and improvement in quality of life, even in patients in poor condition. A recent prospective, randomized, controlled study confirmed the above mentioned results.<sup>54</sup> Thirty-nine patients were randomly assigned to receive PDT with porfimer sodium plus endoprosthesis insertion or endoprosthesis insertion only. PDT with plastic stents resulted in prolongation of survival (493 vs. 98 days,  $p < 0.0001$ ), with a low rate of adverse side effects. It also improved biliary drainage and quality of life, and decreased symptoms.

PDT has been also used as an adjuvant therapy for non-resectable CCs in two studies; in one study before<sup>55</sup> and in the other one after surgery.<sup>56</sup> Cholestasis parameters after PDT decreased significantly and the 1-year recurrence free survival rate was 83% in patients treated with adjuvant PDT before surgery.<sup>55</sup> In 8 patients with remnant or recurrent bile duct carcinoma after surgery, PDT was applied as palliative therapy showing a better survival benefit.<sup>56</sup>

In CCs photofrin has been used as PS. It was injected intravenously, and photoactivation was performed during endoscopic retrograde cholangiography (ERC) after a retention time of 24 to 48 hours. A translucent ERC catheter was inserted into the tumor stenosis, through which a cylindrical light diffuser was placed. The fibre was connected to a diode laser or a tunable dye laser and stepwise illumination with laser light was performed.<sup>48</sup>

## PANCREATIC CANCER

There was only one clinical study in the literature for PDT in patients with pancreatic cancer.<sup>57</sup> It was a phase I study using PDT with m-THPC to treat 16 patients with inoperable pancreatic adenocarcinomas (2.5-6 cm in diameter) localised to the region of the head of the pancreas. All the patients presented with obstructive jaundice which was satisfactorily relieved by insertion of a biliary endoprosthesis prior to further treatment. Light was delivered to the cancer percutaneously: four needles were inserted into the pancreas under ultrasound guidance and their positions checked with a computerised tomography scan; then, a laser fibre was passed through each needle to deliver red light at 652 nm. The light dose delivered at each site varied from 20 to 40 Joules. The median survival time after PDT was 9.5 months (range 4-30). Seven of 16 (44%) patients were alive one year after treatment. Three patients developed

duodenal obstruction during follow-up that may be related to treatment and two patients with tumour involving the gastroduodenal artery had significant gastrointestinal bleeds requiring transfusion (controlled without surgery).

These promising early results justify larger trials to assess the influence of PDT on the course of the disease alone or in combination with chemotherapy and/or radiation. According to this first report of the clinical use of PDT, the technique may be of value for treating localised cancers in patients who are poor candidates for definitive surgery or in whom the location of the tumour makes pancreatic resection inappropriate.

## COLON AND RECTUM

In view of the frequency of colorectal cancer there are only few reports of PDT for tumours at this site, probably due to the fact that surgical treatment has a good outcome for this cancer. There is a review of 71 patients with rectal cancer treated with photofrin-PDT. A complete and partial response was observed in 35% and 44% of patients, respectively, whereas, 21% of patients had no response.<sup>58</sup> In a recent small study, PDT for colon cancer using three different PS (5-ALA, Photofrin, and m-THPC) has been performed.<sup>59</sup> Using 5-ALA, the necrosis was only superficial, as expected. Four patients treated with photofrin showed deeper necrosis (complete response in 1 case of colon cancer, and 50% reduction in size in 3 cases with 1-1.5 cm adenomatous polyps). Two patients with rectal adenomas treated with m-THPC showed 60-80% reduction in size.

PDT has been used to treat adenomatous polyps.<sup>60</sup> Eight patients with nine colosigmoid villous adenomas treated with photofrin-PDT, and 7 adenomas were eradicated, whereas substantial necrosis was produced in the other adenomas, but they were not completely destroyed. No local complications were seen. In 6 patients with familial adenomatous polyposis, who were unsuitable for surgery, complete response was observed using photofrin-PDT.<sup>61</sup> PDT was also a successful method of relieving tenesmus and pain and controlling haemorrhage due to radiation proctitis.<sup>62</sup>

## CONCLUSIONS

In conclusion, PDT is now considered a safe and effective treatment for different types of gastrointestinal tumors. It has been approved for the treatment of Barrett's esophagus and of early esophageal cancer, and

as palliative therapy for advanced esophageal carcinoma. Further studies should address the influence of PDT on the course of tumors such as superficial gastric cancer, non-resectable cholangiocarcinoma, and pancreatic carcinoma.

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