Role of Photodynamic Therapy in the Management of Gastrointestinal Cancer

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Abstract

Background: Surgery for cancer of the gastrointestinal tract is associated with high morbidity and mortality, especially in older patients. A significant proportion of patients cannot be cured and would be referred for palliative therapy. Others may have early cancer but are deemed unfit for surgery. Chemotherapy and external radiotherapy are suitable for only a proportion of patients. Therefore, photodynamic therapy may have a role in the management of these patients. It was the possibility of achieving selective tumour necrosis with sparing of normal tissue that made this treatment extremely appealing compared to other conventional tumour therapy.

Method: The literature is reviewed (after an extensive Medline search 1975–1997) regarding the scientific basis of photodynamic therapy and the clinical experience to date with this therapy in the management of malignancies of the gastrointestinal tract. Results and Conclusions: Photodynamic therapy holds the promise of an eradication form of treatment for early cancer especially for patients deemed unfit for other treatment. It may also prove a useful supplement to other techniques in order to eliminate small residual areas of tumour left after the main bulk has been removed by other methods. The use of photodynamic therapy in the palliative management of gastrointestinal tract cancer is likely to be limited.

Introduction

Photodynamic therapy (PDT) involves the interaction of light administered after the introduction of a photosensitising agent (dye).

In 1913 Meyer-Betz [1] injected himself with 200 mg haematoporphyrin (HPD) and within minutes of light exposure he developed severe pain and swelling confined to light-exposed areas.

In 1966, Lipson et al. [2] reported the use of HPD to treat cancer in patients with recurrent breast carcinoma with some evidence of response. In the 1990s there has been an increasing interest in PDT because of the development of more powerful sensitisers, more advanced light-delivery systems [3] and because of its increasing use in Barrett’s oesophagus.

There are four fundamental variables in the action of PDT, they are the target tissue, the oxygen intermediaries, the light source and the photosensitising agent. Earlier researchers hoped and sometimes found photosensitisers to have a greater affinity towards and accumulate in pre-malignant and malignant cells causing selective cell death.
The light wavelength and method of administration must be appropriate to initiate a photochemical reaction (table 1) [4–28].

Cell death is mediated by reactive intermediaries (such as singlet oxygen) [29] which are produced during photo-oxidation reactions within these cells [30] and at cell membrane sites [31]. Tumour affinity to the sensitisier may be influenced by manipulation of other co-factors such as pH [32].

In the 1970s Dougherty et al. [33] reported encouraging results in the control of local and regional recurrences of breast cancer using PDT (HPD as a photosensitiser). They also reported a high therapeutic ratio due to their observation of a higher uptake of HPD into malignant tissue compared to normal tissue. Further studies by the same group reported successes in the treatment of cancers of the colon, skin, endometrium and the prostate [34], which sparked off an increasing interest in PDT.

Apart from its use in the treatment of gastrointestinal tumours, PDT has been used in the treatment of malignancies in the brain [35], skin [36], ovaries [37], uterus [38], lungs [39], and oral cavity [40] for more than a decade. More recently, there has been considerable interest in the use of this therapy in the management of Barrett’s oesophagus [41–43] and intimal hyperplasia of peripheral arteries [44].

The aim of this review is to summarise the scientific basis of PDT and also to review the experimental and clinical experience to date relevant to cancer of the oesophagus, stomach and colon.

**Mechanism of Action**

**Direct Cell Death**

PDT increases the nuclear to cytoplasmic ratio and causes cytomegaly, both of which are thought to be intermediate processes leading to cell death [45–47].

As photofrin is absorbed into the cells, it is diffusely distributed through the cytoplasm and becomes bound primarily to mitochondrial membranes which initiate the cell changes induced by light exposure and are catalysed by membrane-bound enzymes such as cytochrome C oxidase and succinate dehydrogenase [48].

Cell death results from the production of oxygen free radicals in higher concentrations in tissues containing the photosensitiser, giving rise to a differential effect [49]. The role of reactive oxygen species has been further confirmed in in vitro cultures by incubating these cultures with different concentrations of sodium azide (reactive oxygen species scavenger) resulting in significant inhibition of cell death [28, 45].

### Table 1. List of photosensitisers used

<table>
<thead>
<tr>
<th>Photosensitiser</th>
<th>Peak wavelength nm</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-Aminolaevulinic acid (5ALA)</td>
<td>632</td>
<td>Limited tissue penetration, can be taken orally, low skin photosensitivity</td>
</tr>
<tr>
<td>HpD/Photofrin</td>
<td>630</td>
<td>Instability at room temperature, long skin photosensitivity</td>
</tr>
<tr>
<td>Profimer sodium</td>
<td>630</td>
<td>Long skin photosensitivity (&gt;6 weeks)</td>
</tr>
<tr>
<td>Phthalocyanines (Pc)</td>
<td>675–700</td>
<td>Second-generation photosensitisers</td>
</tr>
<tr>
<td>Zn II Phthalocyanine</td>
<td>675–700</td>
<td>Strong light absorption and deep tissue penetration</td>
</tr>
<tr>
<td>Aluminium sulphonated Pc (AISPc)</td>
<td>675</td>
<td>High tumour selectivity and cytotoxicity, water insoluble</td>
</tr>
<tr>
<td>Benzo[10]-porphyrin derivatives</td>
<td>690</td>
<td>Low skin photosensitivity</td>
</tr>
<tr>
<td>Mesotetrahydroxyphenylchlorin (mTHPC)</td>
<td>652</td>
<td>High selectivity for tumour cells (1:14?), suitable for irradiation with diode laser</td>
</tr>
<tr>
<td>Mono-L-aspartyle chlorin e6(NPe6)</td>
<td>664</td>
<td>Low skin photosensitivity, limited clinical experience</td>
</tr>
<tr>
<td>Indocyanine green</td>
<td>790–805</td>
<td>No clinical experience reported (mostly used in cell cultures), little or no skin photosensitivity</td>
</tr>
</tbody>
</table>
Photodynamic Therapy in the Management of Gastrointestinal Cancer

Vascular-Mediated Response
PDT induces ischaemia in cell cultures [50, 51] and treated tissues. This is possibly mediated by prostaglandin E2 [52] or high tissue thromboxane release [53], both of which have been found in elevated levels in cells undergoing PDT. In animal experiments, PDT markedly decreases vascular perfusion in tumours and increases tissue hypoxia [54].

Secondary tumour cell death is induced by vascular shutdown [55].

Overholt et al. [56] observed in a canine oesophagus model that the delivery of PDT via a large balloon (2–3.5 cm in diameter) results in reduced tissue injury. They concluded that excessive pressure on the oesophageal wall reduces the therapeutic effect.

Immunological Response
Photodynamic therapy is associated with increased production of tumour necrosis factor, interleukin-1β and interleukin 2, which suggests that it may elicit a local macrophage response [57, 58].

The combination of photosensitisers with low-density lipoproteins has been shown to enhance delivery to tumours in mice [59, 60]. Tumour-associated macrophages are largely responsible for the higher concentration of photosensitisers in tumour cells because of phagocytosis of aggregates or by scavenging of modified lipoproteins [61, 62].

Light Source
Laser produces a high-intensity energy of a defined wavelength which can be directed to a specific area, and making the laser the most suitable light source for PDT. Optical fibre modifications such as a microlens, a radially diffusing tip or a balloon-diffuser system can be used to adapt the light irradiation to the shape of the target tissue.

The balloon-diffuser (fig. 1) system has been shown to be successful in centering the rays of radiation and providing a uniform circumferential and predictable light delivery which minimises the 'hill and valley' effect due to organ folds (especially oesophageal folds) [63–65]. The possibility of contact laser techniques may allow more exact targeting of radiation. The continuous wave dye laser (optically pumped by a krypton or argon ion) and the pulsed dye laser (optically pumped by N2, excimer, or Nd-YAG laser) are both used [66]. A recent study tested the use of a 'Versa-Light' using a xenon lamp in order to find a cheaper alternative to laser therapy [67]. This was tested in animals and used in the treatment of an inoperable rectal cancer in 1 patient. It was thought to be a safe, cheap and effective light source. However, an endoscopic mode of delivery is yet to become available. This light source might be popular because many centres do not have dye laser, the laser equipments are heavy to transport between hospitals and they require complicated electric and cooling installations. This light source has a spectral emission in the 600- to 720-nm region, matching closely the absorption spectra of
existing photosensitisers. Therefore, further work is required to establish the efficacy of this light source and to develop the technology for endoscopic delivery.

New advances in diode laser technology promise considerable simplification for PDT light delivery. These systems could be compact, easily transportable, require only 108 V power and are considerably less expensive than current PDT laser systems [68]. However, the diode laser available to date has a limited wavelength spectrum, therefore, limiting the type of photosensitiser which can be successfully employed.

**Tissue Effects and Side Effects of PDT**

Although the principle behind photodynamic therapy may be different from that used in thermal or laser treatment, the overall tissue effects observed at the site of treatment are rather similar [16]. In the first 72 h after PDT oedema develops [69]. When the necrotic tissue finally sloughs, perforation remains a risk.

Adverse effects such as nausea, epigastric pain, anorexia, chest discomfort, atrial fibrillation, heart failure, transient elevation of white cell count and temperature, pleural effusion, pulmonary oedema and aspiration pneumonia are all rare, but have been reported after PDT [70–73].

When treating superficial oesophageal malignant strictures, post-treatment oesophageal strictures have been reported in a significant minority of patients especially with the use of the older photosensitisers such as HPD (though some of these symptoms might have been secondary to the original pathology rather than the treatment employed).

The reported rate of post-treatment strictures is variable and depends on the tissue involved, the light intensity and the photosensitiser used.

Overholt and Panjehpour [74] reported the treatment of 36 patients with superficial oesophageal cancer and Barrett’s oesophagus. Although this group reported an excellent response rate, the rate of stricture formation was 58%. This may be due to the use of sodium porfimer (a strong photosensitiser) in the treatment of superficial lesions. Such a high stricture formation rate is becoming increasingly unacceptable.

Skin photosensitivity is commonly reported in most studies using most photosensitisers. Recently, it has been claimed that skin photosensitivity is significantly reduced when using 5-aminolaevulinic acid (5ALA) [75]. Recently Verspaget et al. [76] reported that in cell cultures PDT causes an intrinsic immunosuppressive effect manifesting in a reduction in natural killer cell activity. No assessment of a possible immunological reaction to PDT in man has been reported.

Further selectivity of the photosensitiser to tumour cells, possibly by combining them with other factors such as serum albumin labelled with tumour-specific monoclonal antibodies or lipoproteins [77] or by injecting them directly into the tumour itself, would allow greater tumour destruction and minimise complications such as skin photosensitivity [78].

Amano et al. [78] examined the hypothesis that intratumour (IT) injection of photosensitiser may carry the advantages of decreasing skin photosensitivity and increasing the tumour concentration of the photosensitiser (thereby increasing tumour destruction). This work was carried out in an animal model of bladder tumour using HPD. It was found that for up to 96 h after IT versus intraperitoneal injections, the porphyrin levels in the tumour were 3–15 times greater with IT injections. The concentrations in skin and other tissues (muscle, liver, kidney, spleen, bladder and blood) were 1.3–10 times lower after IT injection.

Veenhuizen et al. [79] conducted a similar study and found that local administration of HPD resulted in tissue damage in a dose-dependent manner. Maximal effect was achieved at 6–24 h after injection with no systemic absorption.

Veenhuizen et al. [79] compared intravenous with intraperitoneal delivery of the photosensitiser photofrin in an animal model of colon cancer. They found no difference in tumour uptake or efficacy but found that a combination of PDT and the hypoxic toxin mitomycin C proved superior to PDT alone in tumour destruction.

More recently WongKeeSong et al. [80] presented the case of a patient with oesophageal cancer treated by PDT (using intra-lesional injection of porfimer sodium) with satisfactory outcome.

These are interesting studies but the extrapolation of these findings into greater tumour destruction and lesser skin photosensitivity in man is yet to be established. Finally it must be acknowledged that IT injection of the photosensitiser can only be applied to easily accessible single lesion tumours.

Rabeiz et al. [81, 82] advanced the idea that tetrabpyrrole modulators such as 1,10-phenanthroline if added to 5ALA can result in greater accumulation of protoporphyrin IX and subsequent cell lysis (on exposure to light) in vitro and in vivo (animal model of solid tumour; BALB/c mice; p < 0.05) compared to using 5ALA alone.
More recently an encouraging report of the successful use of another pro-drug, the ALA pentyl ester, which was shown to increase the uptake of 5ALA and its greater conversion into PpIX, has been reported [83].

If as anticipated, biological modulators act synergistically with 5ALA resulting in an increased concentration of synthesised photosensitiser and hence leading to a greater tumour destruction upon exposure to light, the search must continue for a safe, non-toxic modulator to enhance sensitiser-mediated PDT. Numerous possible modulators are available which may be used safely in man. This issue we believe merits further investigations.

**PDT in the Treatment of Oesophageal Cancer**

Malignant stenosis of the oesophagus is common and unfortunately curative treatment is possible in only a small percentage of patients. The 5-year survival remains poor [84]. Therefore, many patients who cannot be cured should be referred for palliative therapy. Operative treatment is associated with high morbidity and mortality [85]. Chemotherapy and external radiotherapy are associated with complications and only a proportion of patients respond to these techniques [86]. Therefore, photodynamic therapy may have a role in the management of both early cancers and inoperable malignant oesophageal strictures [87–92].

**Early Cancer**

Fujimaki and Nakayama [91] reported the treatment of 11 patients with early oesophageal cancer using PDT. Nine patients remained in remission by the end of the study (median follow-up 13–48 months). However, 1 patient developed a recurrence 18 months later. One broncho-oesophageal fistula and one oesophageal stenosis occurred.

McCaughan et al. [93] conducted a prospective study (between 1982 and 1994) in which 77 patients with oesophageal cancer (not suitable for more radical therapy) were treated with PDT. Follow-up was 100%. They used argon dye laser therapy, initial treatment was with a haematoporphyrin derivative as the photosensitiser and latterly dye haematoporphyrin ether, injected intravenously 1–3 days before treatment. They found that for those in clinical stage 1, the estimated 5-year survival was 62%. This is comparable with other reports of 5-year survival after surgery (ranging between 46 and 70%) [94–99]. Four patients developed fistulas, but all had advanced squamous cell carcinoma and had received different therapies prior to PDT. Four patients developed strictures, manageable by bouginage. This study looked at patients who were otherwise unfit for any other form of treatment such as radical surgery, chemotherapy etc., and, therefore, they were at high risk of complications. The use of a first-generation photosensitiser was the only agent available and, therefore, photosensitivity of the skin was inevitable. However, despite the number of reported complications it is fair to point out that other treatment regimes are associated with their share of post-treatment complications [100, 101].

Monnier et al. [92] treated 15 patients with superficial oesophageal cancer by a mixture of bouginage and photodynamic therapy and reported an initial remission rate of 80%, three recurrences developed within 3 months of treatment. The remaining 12 patients remained in remission (follow-up range 6–60 months). Two oesophageal perforations and one stenosis were reported in this study.

Spinelli et al. [102] reported the treatment of 20 patients with superficial oesophageal cancer by PDT. 79% showed a response. The overall result showed a remission rate of 73% and the treatment was particularly good (remission rate of 86%) in tumours which were <1 cm in diameter.

Sibille et al. [103] reported the treatment of 123 patients with small oesophageal tumours (0.5–4 cm in diameter) who were not fit for surgery. A remission rate of 87% at 6 months with an overall 5-year disease-specific survival rate of 74% was reported. This was a very encouraging report with results comparable or superior to other modalities of treatment. Others have reported similar experience (table 2) [74, 104–107].

In China and Japan where it appears that the rate of detection of early oesophageal and gastric cancer is higher than that in the West, photodynamic therapy has been used in the treatment of early cancer [90, 108, 109]. The numbers of patients involved in these studies are small and the follow-up period is limited (maximum of 19–41 months).

Kato et al. [109] reported the treatment of 66 patients with oesophageal cancer, remission was achieved in 80% with no recurrence (during the follow-up period of up to 36 months). The patients with early oesophageal cancer had an encouraging tumour-free follow-up [110].
Advancing Cancer

McCaughan et al. [111, 112] treated 56 patients with inoperable oesophageal cancer. In all patients tumour diminution occurred and swallowing improved (an increase in the patent diameter of the oesophagus from 6 to 9 mm). Using 5ALA and low-dose PDT, Regula et al. [106] reported the treatment of 18 patients with colorectal, duodenal and oesophageal tumours. This resulted in superficial mucosal necrosis with fibrinous exudation. The group was disappointed with the fact that the depth of necrosis was very limited using 5ALA; however, this was a pilot study using a relatively low dose of PDT in a small number of patients. They suggested that the use of 5ALA in PDT might be more appropriate in the treatment of relatively superficial abnormalities such as Barrett’s oesophagus than for the treatment of cancer.

Jin et al. [110] reported the treatment of 207 patients with advanced gastrointestinal tumours (121 inoperable and 86 recurrent) with PDT (using HPD). Remission was achieved in 16.4% of advanced cancers of the oesophagus, cardia and body of the stomach. They suggested that when cancer is < 50 mm in diameter, PDT could be curative.

The palliative treatment of dysphagia caused by malignant strictures, using stents [113] or laser therapy [114], is now very successful, easy to perform and has a low complication rate. Few researchers compared these modalities with PDT. Heier et al. [115] compared the use of PDT with Nd-YAG laser in the management of obstructing oesophageal cancer. In a randomised trial involving 52 patients (32 received PDT, 20 received Nd-YAG), both modalities relieved dysphagia but PDT resulted in a longer duration of response (p < 0.008).

Furthermore, PDT may have a role to play in the treatment of tumour ingrowth in expandable oesophageal stents. Eight such patients were treated for this problem by Scheider et al. [116] with success.

PDT in Gastric Cancer

The use of PDT in treating gastric cancer is technically more complicated owing to gastric folds, peristalsis and the shape of the stomach itself which may allow limited access to specific areas of abnormality. Earlier reports of the use of PDT in the treatment of gastric cancer were disappointing [48, 90, 109, 117, 118], suggesting that PDT is only useful in the treatment of superficial cancer. The most encouraging result in recent years is that reported by Kato et al. [109]. They treated 133 cases of
gastric cancer (120 of which were early tumours) and initial remission was achieved in 100% of patients, but recurrences occurred in 22.2% of treated patients (follow-up was up to 3 years).

Kasugai [119] reported the treatment of 81 gastric cancer patients with PDT showing a remission rate ranging from 85 to 98% in patients who were followed up for a period of 3–5 years.

Spinelli et al. [102] reported treatment with PDT of patients with early gastric cancer (n = 13). The response rate was 71%, and in those who responded the remission rate was 85% (follow-up period of 3–58 months).

PDT in Colorectal Cancer

Photodynamic therapy has been in use in colorectal cancer for the last 10 years. However, the number of reports of patients treated by this modality is small. Dohmoto et al. [120] reviewed the reported cases and found that, in 71 patients with rectal cancer treated by PDT, 35% had a complete response, 44% had a partial response and 21% had no response.

In the absence of large prospective or even retrospective reports or randomised controlled trials comparing this modality with other palliative treatments or radical treatment of rectal cancer, no conclusion can be drawn about the efficacy of PDT in the management of rectal tumours. However, these early reports are very encouraging.

Conclusions

PDT is a promising technique for producing local in situ ablation of small areas of premalignant and malignant lesions in the gastrointestinal tract, with accuracy and safe healing.

PDT is best indicated for local treatment of mucosal and submucosal cancer that cannot be treated by operation. In Japan where the percentage of early (often mucosal) gastric cancer detected exceeds 50%, PDT is becoming a useful alternative or addition to endoscopic mucosal resection as a form of eradication therapy of these early tumours.

PDT allows exposure of a large area of mucosa and therefore may decrease the number of treatments required compared to laser.

Up till recently the clinical and experimental experience with PDT (using established photosensitisers) demonstrated that tissue penetration and the necrotic effect of PDT is probably limited to 5–10 mm, making it less suitable for bulky tumours and more suitable for early tumours or high-grade dysplasia. However, more recently, new photosensitisers, such as mTHPC, have been shown to result in a deeper necrotic effect after interacting with light. In the treatment of prostatic cancer, unpublished reports suggest that tumours of <3 cm in size could be destroyed using interstitial PDT. Pilot trials are now in progress in Germany examining the efficacy of intravesical injection of the photosensitiser (with or without) and the addition of a pro-drug. If, as it is hoped, a preferential enhancement of photosensitiser uptake by malignant tissue leading to greater tumour destruction while sparing normal tissue is reported, then the way will be open for greater use of PDT in treating larger gastrointestinal lesions in patients deemed unfit for radical surgery.

The role of PDT as a primary method of palliating malignant oesophageal strictures is less certain. This is because other methods of palliating dysphagia (such as stents and laser) are extremely successful and have fewer complications. However, PDT may be useful in treating tumour ingrowth over oesophageal stents without undermining the stent in situ.

PDT holds the promise of an eradication form of treatment for early cancer especially for patients deemed unfit for other treatment. Furthermore, PDT might prove a useful supplement to other techniques in order to eliminate small residual areas of tumour left after the main bulk has been removed by other methods.

The ideal photosensitiser, light source, and the long-term effects (including side effects) of PDT are still not clearly identified. But, PDT will undoubtedly play a significant role in endoscopic gastroenterology in the years to come.
References


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