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Research Article

Photodynamic Therapy for Pancreatic and Biliary Tract Carcinoma

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Abstract

The prognosis of patients with pancreatic and biliary tract cancer treated with conventional therapies such as stent insertion or chemotherapy is often poor, and new approaches are urgently needed. Surgery is the only curative treatment but is appropriate in less than 20% of cases, and even then it is associated with a 5-yr survival of less than 30% in selected series. Photodynamic therapy represents a novel treatment for pancreaticobiliary malignancy. It is a way of producing localized tissue necrosis with light, most conveniently from a low-power, red laser, after prior administration of a photosensitizing agent, thereby initiating a non-thermal cytotoxic effect and tissue necrosis. This review outlines the mechanisms of action of photodynamic therapy including direct cell death, vascular injury, and immune system activation, and summarizes the results of preclinical and clinical studies of photodynamic therapy for pancreaticobiliary malignancy.

Key Words: Pancreatic cancer; cholangiocarcinoma; ampullary carcinoma; mechanisms; photodynamic therapy.

Basic Principles of Photodynamic Therapy

Photodynamic therapy (PDT) is a way of producing localized tissue necrosis with light. A photosensitizer, which is a light-absorbing agent, is applied to tissue either topically or systemically. Ideally, the photosensitizer is retained selectively in tumor, to ensure safe destruction of tumor with minimal damage to adjacent normal tissue. Although animal and human studies of pancreatic and biliary tract cancer do indeed show some selectivity of uptake of the injected sensitizer *(1–4)*, this is rarely enough to make truly selective tumor destruction feasible. Therefore, some degree of normal tissue destruction has to be accepted provided safe healing can occur *(5)*.

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After administration of the photosensitizer, the tumor is irradiated with laser light at a wavelength compatible with the absorption spectrum of the drug, usually in the red or near-infrared region. This leads to excitation of the sensitizer from its ground state (singlet state) into a relatively long-lived electronically excited state (triplet state), via a short-lived excited singlet state *(6)* (*see* Fig. 1). In this excited state several processes can occur *(7,8)*. The excited sensitizer can react directly via a Type I photo-oxygenation process with substrate (e.g., protein, lipid), leading to free radical intermediates that react with oxygen to generate various reactive oxygen species. Alternatively, the triplet can transfer its energy directly to

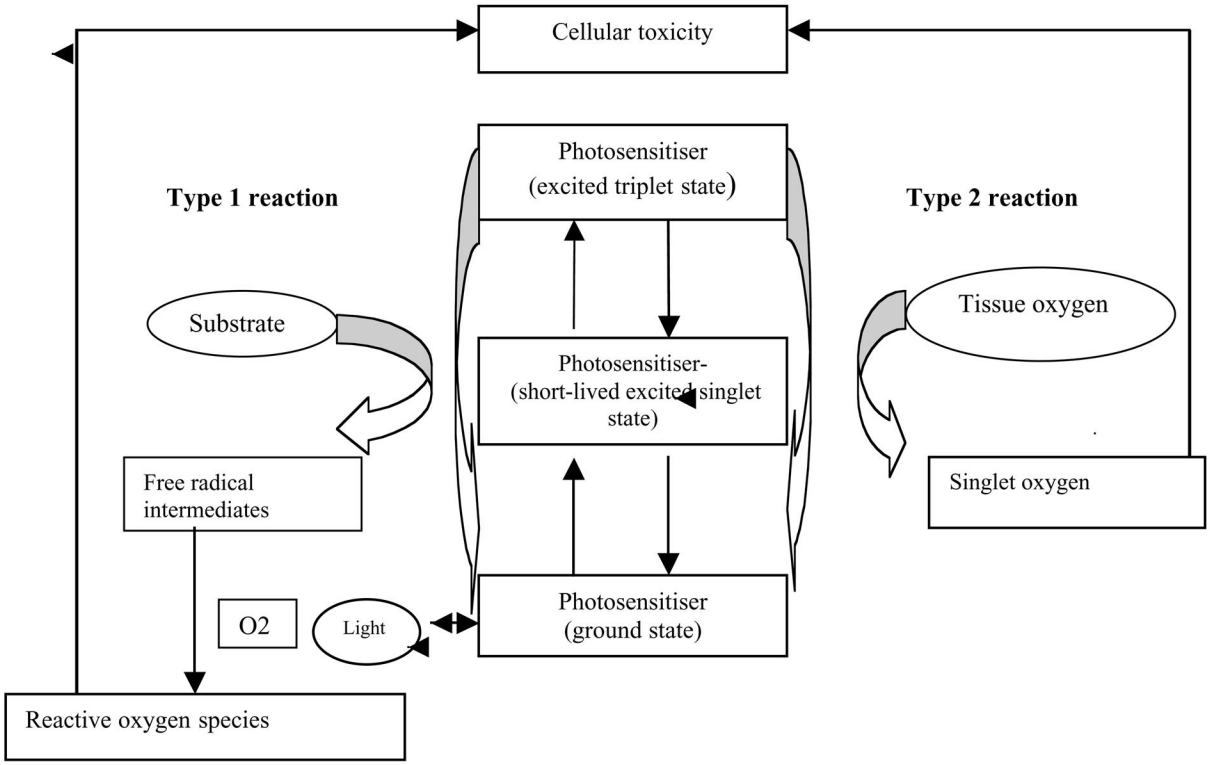

Fig. 1. Absorption of light by photosensitizer in the ground state results in excitation to triplet state. The excited photosensitizer can undergo either a Type I photo-oxygenation reaction with cell components, e.g., proteins and lipid, or a Type II reaction with oxygen. This generates singlet oxygen and reactive oxygen species which are responsible for cellular toxicity. [Adapted from Dolmans et al. *(8)* with permission from Nature Reviews. Website: (www.nature.com/reviews). *Cancer*, Vol. 3: pp. 380–387, © 2003 Macmillan Magazines Ltd.]

oxygen to form singlet oxygen (Type II reaction), which is assumed to be the key agent of cellular damage *(9,10)*. This moiety is highly cytotoxic, with a short half–life (<0.04 μs) and a short radius of action (<0.02 μm) *(11)*. As a result, only cells that are immediately adjacent to the areas of reactive oxygen species production are directly affected by PDT *(12)*.

An ideal photosensitizer for the treatment of pancreaticobiliary malignancy would have the following properties: (a) a strong absorption band in the red or near-infrared part of the spectrum, because human tissue transmits light of this wavelength most effectively; (b) a high selectivity for tumor tissue, and (c) poor retention of photosensitizer in the skin, thus limiting the duration of cutaneous photosensitivity. The first sensitizer to gain regulatory approval for PDT (as a treatment for bladder cancer) was porfimer sodium, which is a mixture of the most active porphyrin oligomers that comprise hematoporphyrin derivative (HpD). However, porfimer sodium has a number of limitations including its complexity (making it difficult to reproduce its composition), a relatively poor absorption of tissue penetrating red light, and the tendency to cause prolonged cutaneous photosensitivity. These limitations have led to the development of a variety of second-generation photosensitizers, which can be classified as (a) porphyrin-like macrocycles such as phthalocyanines *(4,13)* and chlorins *(2,14,15)*; (b) exogenous 5-aminolevulinic acid (ALA) that in turn enhances the production of endogenous protoporphyrin IX, which is photocytotoxic *(16,17)*; and (c) other structures, e.g., hypericin *(18)* and pheophorbide A *(3,19)*. In general, many of these compounds absorb red or near-infrared light more strongly than porfimer sodium, thus shortening treatment times, and are not retained in the skin for as long, thus decreasing the duration of cutaneous sensitivity.

Mechanisms of Action

At least three mechanisms for PDT-mediated tumor destruction have been proposed *(10)*. First, reactive oxygen species that are generated by PDT can kill tumor cells directly. Second, PDT damages the tumor-associated vasculature, which may lead to tumor infarction *(20)*. Finally, PDT can stimulate an immune response against tumor cells *(21)*. The relative importance of each mechanism in the treatment of pancreaticobiliary malignancy is unclear.

Direct Tumor Cell Death

Reactive oxygen species can cause direct photodamage to many biological molecules, including proteins, lipids, and nucleic acids *(22–24)*, at sites where the photosensitizer accumulates, either by apoptosis or necrosis. The intracellular localization of the photosensitizer determines in part the mechanism of cell death *(7)*. HpD and porfimer sodium both localize in mitochondria—owing to their hydrophobicity and their affinity for the same plasma binding site on the mitochondrial membrane *(25–27)*. More hydrophilic sensitizers, such as the phthlocyanines and many chlorins, enter cells via endocytosis and hence accumulate mainly in lysosomes. Damage to mitochondria generally leads to apoptosis, whereas plasma membrane and lysosomal damage can delay or even inhibit apoptosis and instead induces necrosis *(28–30)*. The extent of necrosis depends in part on the total dose of sensitizer administered, the time between the administration of the drug and light exposure, the total light exposure dose, and oxygen availability within the treated tissues.

Pancreatic carcinoma tissue treated with PDT undergoes both apoptosis and necrosis. In a pilot study of 16 patients with non-resectable pancreatic cancers (median diameter 4.0 cm), PDT using mesotetrahydroxyphenyl chlorin (mTHPC) safely achieved a radius of necrosis of 9 mm (range 7–11 mm) around each treatment point *(31)*. Conversely, in human pancreatic tumor cell lines in vitro and after grafting into athymic mice, apoptosis was shown to be the mechanism of cell death after exposure to low-dose pheophorbide A PDT *(19)*. Since hemoglobin acts as a shield against penetration of tissue by light, the authors postulated that gentle programmed cell death, by avoiding PDT-induced tumor hemorrhage *(3,4)*, may improve efficacy.

In experimental *(4,17)* and clinical studies of PDT *(31,32)* for pancreaticobiliary malignancy, complete tumor eradication has generally not been achievable. Reasons may include non-homogeneous distribution of photosensitizer within the tumor, decreased ability to kill tumor cells at increased distance from vascular supply *(33)*, reduction of tissue oxygen tension during and after illumination of photosensitized tissue *(34,35)*, and inadequate light doses at all relevant sites.

Vascular Cell Death

The viability of tumor cells depends on their blood supply *(36)*. PDT-related damage to the vascular endothelium leads to severe and persistent post-PDT tumor hypoxia *(37)*. These vascular effects are caused by reversible contraction of endothelial cells resulting in exposure of the basement membrane, vessel leakage, and thrombus formation *(10,38–40)*. These pathophysiological events may be mediated through the release of thromboxane *(41,42)* and inhibition of nitric oxide *(43)*, leading to ischemic death of tumor cells.

Immune System Activation

Another postulated mechanism of action of PDT is that, by causing necrosis of tumor cells with subsequent generation of inflammatory mediators, e.g., lipid fragments and metabolites of arachidonic acid *(6,44)*, immune responses to tumor are activated. Evidence for PDT-induced immune activation comes from initial studies more than 10 yr ago, which reported infiltration of lymphocytes, leukocytes, and macro phages into PDT–treated tissue *(6,44,45)*. In a rhabdomyosarcoma-bearing rat model, de Vree et al. showed that PDT resulted in accumulation of neutrophils around the tumor, thereby slowing growth. Depletion of neutrophils decreased the PDT-mediated effect on tumor growth *(46)*. More recently, the inflammatory cytokines interleukin IL-6 and IL-1 (but not TNF alpha) have been shown to be up-regulated in response to PDT *(47)*. The role of the adaptive immune response was investigated by Korbelik and colleagues in a study of PDT for mammary sarcoma in immunodeficient and normal mice. A significantly lower therapeutic effect was seen in immunodeficient mice, suggesting that the lack of an immune response was responsible for the difference in tumor cures *(48)*. This effect could be restored by adoptive transfer of T-lymphocytes of normal mice

into the immunodeficient mice. In a later study by the same group, sarcoma-bearing mice were selectively depleted of specific T cells. While initial tumor ablation by PDT was not affected, long-term tumor cure rates decreased markedly after T-cell depletion *(49)*. These results provide direct evidence that the contribution of T lymphocytes is essential for the maintenance of long-term control of PDT-treated tumors. However, the role of immune system activation in clinical studies of PDT for pancreaticobiliary malignancy remains largely unexplored.

Biliary Tract Carcinoma

Cholangiocarcinoma and cancer of the gall bladder are tumors of the biliary tract that are considered as one pathological entity [biliary tract carcinoma (BTC)]. Worldwide, BTC is the second most common primary liver cancer after hepatocellular carcinoma, accounting for 15% of all primary hepatic malignancies *(50)*. Overall, the incidence of BTC in Asia is 50 times higher than that in Europe, where it has been regarded as a rare tumor *(50,51)*. However, recent epidemiological data from the UK, US, Spain, and Australia have shown a steady and steep rise in mortality rates from intrahepatic cholangiocarcinoma (but not gallbladder cancer or extrahepatic bile duct cancer) over the last 20 yr, with smaller rises in France, Italy, and Japanese men *(52–55)*. In the UK since the mid 1990s, more deaths have been coded annually as being due to this tumor than to hepatocellular carcinoma. The cause of this rise is unknown and does not appear to be explained simply by improvements in diagnosis or changes in coding practice *(55)*. One hypothesis is that chronic and increasing exposure of biliary ductal epithelium to environmental chemical genotoxins in bile may play a role in the development of BTC *(56)*.

BTC has a poor prognosis, with similar incidence and mortality rates and an overall 5-yr survival of less than 5% *(57)*. Surgery is the only curative treatment for patients with BTC, but is appropriate in less than 20% of cases (Bismuth classification I–III) *(58)* and is associated with a 5-yr survival of 9–30% in selected series *(59–61)*. Conversely, more than 80% of patients are diagnosed with proximal strictures involving both sides of the liver (Bismuth type III—stenosis of at least one second order branch or Type IVℜ—bilobar involvement of second-order branches), or have vascular involvement or metastases precluding resection *(57)*. Although most patients can be palliated temporarily by endoscopic or percutaneous placement of one or more biliary stents *(62,63)*, the prognosis remains poor, with complex hilar lesions having a median survival of less than 6 mo *(57,64)*. Because the cause of death in BTC after successful stenting is commonly due to recurrent biliary obstruction and intrabiliary sepsis, a key issue of palliative therapy is that of control of locally progressive disease.

In theory, nonsurgical oncological approaches could have a beneficial impact on this disease. Uncontrolled studies suggest that intraluminal brachytherapy (iridium implants) *(65,66)*, sometimes combined with external-beam radiotherapy *(67,68)*, may prolong survival. However, the few controlled studies that have assessed this therapy have not found any significant clinical or survival advantage. In a retrospective comparison of endoscopic stenting alone with stenting and radiotherapy in 56 patients with irresectable cholangiocarcinoma from our unit *(69)*, there was a small survival advantage (11 vs 7 mo) in those with Bismuth III/IV strictures given radiotherapy, but length of hospital stay and stent change requirements were also significantly increased. In a preliminary report of 21 patients with biliary stents randomized to observation alone or brachytherapy, there was no advantage of brachytherapy over biliary drainage *(70)*.

A systematic review of over 65 disparate studies of chemotherapy and/or radiation in BTC *(64)*, and a recent UK consensus document on the diagnosis and treatment of cholangiocarcinoma *(51)*, concluded that there was no strong evidence of survival benefit. To date, most studies have been small and have lacked a control group (level II evidence or less) *(71)* or sufficient power to test for differences in survival and at present there is no established treatment for advanced biliary cancer other than stenting and best supportive care.

Photodynamic Therapy in BTC

Porfimer Sodium PDT

HpD is the product mixture formed upon solubilizing hematoporphyrin in aqueous media (sulfuric and acetic acids). It consists of a mixture of mono-, di-, and oligomers, all containing the porphyrin moiety. As the oligomeric fraction appeared to be largely responsible for phototoxicity, purification methods were developed to remove part of the mono-

and dimers *(72)* resulting in the commercial product Photofrin (porfimer sodium).

In 1998, Pahernik and colleagues demonstrated the potential of porfimer sodium as a photosensitizer for BTC, using quantitative fluorescence microscopy and digital image analysis of cryosections to analyze normal and malignant bile duct tissue *(1)*. They reported an approximately twofold selective accumulation of porfimer sodium in human BTC over normal tissue. In an experimental model of nude mice inoculated with a cholangiocarcinoma cell line, Wong Kee Song and colleagues achieved a reduction of up to 60% of tumor volume after PDT with hematoporphyrin *(15)*. The first human study of PDT in BTC was reported by McCaughan and colleagues in 1991 *(73)*, who gave repeated PDT using dihematoporphyrin to a patient with histologically proven adenocarcinoma of the common bile duct. The patient responded well to a total of seven PDT treatments performed via a percutaneous access, but after 2 yr developed an unrelated endometrial carcinoma and died of pleural metastases after 4 yr.

This case report stimulated phase II studies of palliative endoscopic and percutaneous PDT for BTC *(74–76)*. In all of the studies, the patients were photosensitized intravenously with porfimer sodium (Photofrin®, Axcan Pharma Inc., Mount-Saint-Hiliare, Canada), followed by endoscopic illumination of the tumor with laser light at 630 nm. In two phase II studies from Germany of 9 *(74)* and 23 patients *(75)* with histologically proven cholangiocarcinoma (Bismuth type III 2, Bismuth IV 30), endoscopic stenting plus PDT (repeated if there was evidence of tumor reduction or endoscopic biopsies of hilar strictures remained positive) resulted in an improvement in cholestasis, quality of life, and survival compared with historical controls treated with stenting alone. Ortner et al. *(74)* demonstrated a median survival of 439 d in their study group, while Berr et al. *(75)* reported a median survival of 340 d and a 6-mo survival of 91% after diagnosis, compared with an expected survival of 50%. The 30-d mortality in the two studies was 0 and 4%, respectively. Similar findings were reported in a recent study from Bonn *(78)*. In 24 patients with histologically proven cholangiocarcinoma (Bismuth III 2, Bismuth IV 22) treated with a single course of PDT followed by metal stent insertion, the 30- and 60-d mortality was zero and the median survival post-PDT was approx 300 d.

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In the study by Ortner et al., the mean change in the diameter of the bile duct at the area of greatest stenosis was 1.2 ± SD 1.0 mm before to 5.9 ± 1.3 mm after PDT ($p < 0.001$), as a result of stricture dilatation by the endoprostheses and/or tumor debulking by PDT. An apparent reduction in tumor mass was also seen in some intrahepatic ducts not directly illuminated with laser light. In the series by Berr et al. *(75)*, 11 of the 23 patients presented with occlusion of either the left or right bile duct. The initial PDT reopened the occluded lobar duct in all of them, as well as an average of three segmental ducts. A potential explanation for these observations is that enough light to activate the photosensitizer reached affected areas by light propagation in the bile or through the hepatic parenchyma. Alternatively, as discussed earlier, PDT has been shown in animal models to induce a variety of immunologic responses that could potentially affect tumor growth in regions outside the treatment zone *(15,33,79)*. Adverse events related to PDT were minor (mainly cholangitis and photosensitivity). A UK phase II study of 35 patients using similar methodology has also been completed *(80)*.

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These phase II data have been supported by the results of a recent multicenter, randomized, controlled trial of repeated PDT with stenting (mean 2.4 sessions) vs stenting alone for irresectable cholangiocarcinoma *(32)*. The trial was discontinued early by the monitoring committee after 39 patients had been randomized owing to a marked survival advantage in the PDT group, with a median survival at the time of publication of 493 d compared with 98 d in the stent alone group ($p < 0.0001$). A further 31 patients with advanced disease (1 tumor stage III, 13 stage IVa, 17 stage IVb disease) who declined or had exclusion criteria for randomization were also treated with PDT plus stenting, and had a median survival of 426 d.

Despite these impressive results, PDT for advanced cholangiocarcinoma is clearly not curative, as 90% of patients in the PDT arm had died by the end of the study. An accompanying editorial outlined some of the limitations of this study, which included the failure to adequately relieve bile duct obstruction with stenting alone *(81)*. It is therefore unclear if PDT will also improve the survival of the majority of patients whose cholestasis can be relieved, at least temporarily, by biliary stenting. Moreover, whether PDT is a better method of palliation than biliary

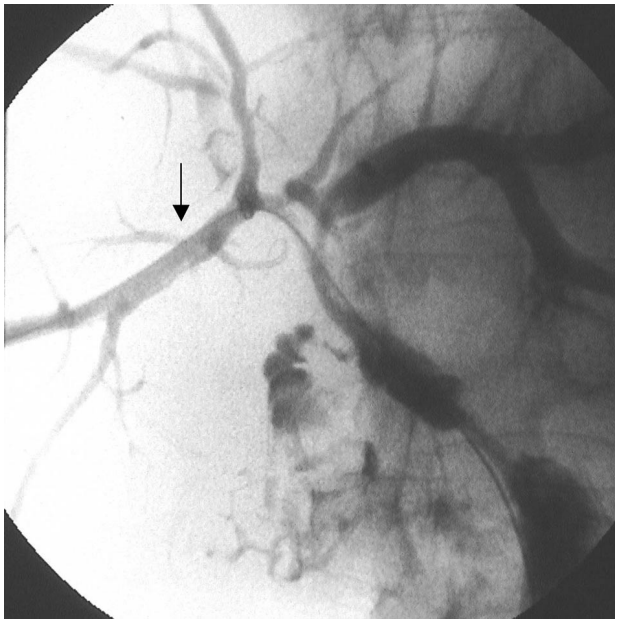

Fig. 2. Percutaneous cholangiogram showing a laser fiber (arrow) placed across a malignant stricture of the right and common hepatic duct. Gallbladder stones and a percutaneous left-sided internal–external biliary drain are also present.

metal stents, which have longer rates of stent patency than plastic endoprostheses but have not been shown to increase survival in patients with advanced pancreaticobiliary malignancy *(82–86)*, is also unknown. It is generally accepted that a metal biliary stent is more cost-effective than a plastic stent if the patient is likely to survive longer than 4 to 6 mo *(87,88)*. Similar analyses will be required in order to determine the place of PDT in the treatment of patients with BTC.

Technique

PDT for biliary cancer is performed either at the time of therapeutic ERCP or via a percutaneous transhepatic approach, or both. After diagnosis, patients undergo endoscopic and/or percutaneous drainage and insertion of endoprostheses into the right and left intrahepatic system. Following successful endoprosthesis placement and histological or cytological confirmation of cancer, patients receive 2 mg/kg bodyweight porfimer sodium, intravenously, 48 h before laser activation. Patients remain in a darkened area of the ward for 2 to 3 d after injection, followed by readaptation to normal indoor light by d 5. If more intense exposure is necessary during this period, patients are advised to wear protective covering and sunglasses, and to avoid direct exposure to sunlight for at least 1 mo after photosensitization.

At 48 h after photosensitisation, the endoprostheses are removed at repeat ERCP and intraluminal photoactivation is performed. In our Unit, this is done using a laser quartz fiber with cylindrical diffuser tip (20–50 mm length, 400 μm core diameter) with an X-ray marker on both sides of the diffuser—inserted either through a translucent endoscopic catheter introduced proximally above the strictures, or by placing the laser fiber directly across the stricture (*see* Fig. 2).

Photoactivation is performed at 630 nm using a light dose of 180 J/cm^2, which requires an irradiation time of approx 10–12 min per treated biliary segment. All patients receive oxygen via a nasal catheter during the procedure as part of standard endoscopic practice, which in theory also optimizes the PDT effect. Where tumor length exceeds the maximal diffuser length, overlap of treated fields is avoided by pulling the fiber back in controlled stages or using an opaque catheter to shield part of the fiber. After illumination of the first section of tumor length, the laser fiber is pulled back under radiological control using the markers viewed on the X-ray screen to the next segment of bile duct. In Bismuth IV strictures, a guidewire is inserted into the duct while treating one side, before repeating treatment on the other side. In the case of multiple intrahepatic strictures, second-order branches that are accessible endoscopically and associated with obstructed liver segments are also treated. A new set of endoprostheses is inserted after completion of treatment.

Other Photosensitizers

Photodynamic therapy with Foscan® (mTHPC: meso-tetrahydroxyphenyl chlorin; Biolitec Pharma Incorporated, Germany) has been used successfully to clear biliary metal stents blocked by malignant ingrowth *(89)*. The only major complications that occurred using this treatment were in patients whose tumors invaded large arteries, whereas infiltration of smaller vessels did not seem to contraindicate PDT.

Zoepf et al. treated eight patients with nonresectable bile duct cancer, using Photosan-3 (a hematoporphyrin derivative). Plastic stents were re-inserted post-treatment. After 4 wk, there was a

marked reduction in bile duct stenoses and bilirubin levels, with two infectious complications but no mortality *(90)*. At the time of publication, the median survival was 119 d (range 52–443 d), with five patients still alive. A smaller study by the same group of four patients with bile duct cancer treated with 5-ALA revealed superficial fibrinoid necrosis at cholangioscopy performed 72 h after treatment, but no significant reduction in bile duct stenoses *(16)*.

Neoadjuvant PDT Before Curative Resection

After attempted curative resection of hilar bile duct carcinoma, there is an 80% probability of local recurrence and a 5-yr survival rate of approx 20% *(51)*. Berr et al. proposed that preoperative local ablation of infiltrating tumor and dysplastic epithelium with PDT may increase the rate of cure after resection *(91)*. A 72-yr-old man underwent photofrin PDT to a Bismuth type II bile duct cancer, followed by surgical resection on d 23. Twenty-two hours after administration of porfimer sodium, biopsies from the adenocarcinoma exhibited 2.4-fold enrichment of porfimer-specific fluorescence as compared with the adjacent normal bile duct epithelium. In serial cross-sections of the surgical specimen, there was complete tumor necrosis with pigmentation of photodegraded photosensitizer to a depth of 4 mm, while in the outer layer of the wall (at 5–8 mm depth) viable cancer cell nests without degraded photosensitizer were seen. Normal tissue suffered very little phototoxic damage, with no evidence of necrosis or inflammation within either the connective or muscular tissue in the treated tumor or the bile duct mucosa and muscular layer at the tumor-free resection margin. None of the 20 lymph nodes removed contained metastatic tumor. Eighteen months after surgery, neither tumor recurrence nor stricture formation was found at the pretreated bilioenteric anastomosis.

In a subsequent series of seven patients with advanced proximal bile duct cancer treated with neoadjuvant PDT by the same group *(92)*, R0 resection (histologically negative margins) was achieved in all patients and tumor recurred in only two patients 6 and 9 mo after surgery, with a 1-yr recurrence-free survival of 83%. Four patients developed minor surgical complications (two patients had a bile leak and one a subdiaphragmatic hematoma), but no functionally relevant stricture formation was observed at the biliary–enteric anastomoses during a median follow-up period of 15 mo. Viable tumor cells were not found in the inner 4 mm layer of the surgical specimens. The authors concluded that neoadjuvant PDT of localized BTC with porfimer sodium is safe and needs to be evaluated prospectively to determine whether it reduces the rates of positive resection margins and local disease recurrence after attempted curative resection.

PDT for Ampullary Carcinoma

PDT has also been used with palliative intent in patients with carcinoma of the ampulla of Vater unsuitable for pancreaticoduodenectomy. In a series from The Royal London Hospital *(93)*, 10 patients were treated endoscopically with PDT after hematoporphyrin derivative had been given intravenously 48 h beforehand. The tumors were treated by three or four light applications at different sites on the tumor at each session, and treatment repeated up to five times (median 2) at 3–6 mo intervals. The sole complication was moderate skin photosensitivity in three patients, with no evidence of significant damage to the duodenum. In three of the four patients with small tumors confined to the ampulla but who were unfit for surgery, endoscopic biopsies post-PDT were negative for malignancy and endoscopic stents were no longer required for 8–12 mo, by which time macroscopic tumor had recurred. In all three patients with local spread <3 cm in diameter, there was an appreciable response with reduced tumor bulk but macroscopic tumor remained, while only one of three patients with advanced disease had a temporary reduction in tumor size. The authors concluded that PDT causes safe and effective tumor destruction in patients with ampullary carcinoma with periods of clinical remission for tumors confined to the ampulla, and with refinements in technique may prove curative for small tumors.

Pancreatic Adenocarcinoma

Worldwide, adenocarcinoma of the pancreas is one of the top 10 leading causes of cancer death, and ranks fourth as a cause of cancer death in the UK and the US *(94,95)*. In series from specialized centers, over 10% may be resectable at presentation *(96)*, but in larger population-based studies the number undergoing resection with curative intent may be as low as 3% *(97)*. Even after resection,

median survival is only 10–20 mo and no more than 5–20% of resected patients survive 5 yr *(98)*. Options available for the treatment of inoperable patients are largely limited to chemotherapy, radiotherapy, or some combination of the two. Gemcitabine is probably the most useful single agent for symptomatic relief, although no agent has been shown to have a convincing benefit on survival *(99)*. Overall, the long-term prognosis of the disease is poor with a 1-yr survival rate of no more than 10%. For non-metastatic disease, median survival is 6–10 mo, although for those with metastatic disease at presentation median survival is only 3–6 mo *(100)*. Given these dismal results, a minimally invasive treatment capable of local destruction of tumor tissue with low morbidity may have a place in the treatment of this disease.

PDT in Pancreatic Cancer: Animal studies

In contrast to biliary tract carcinoma, PDT of the pancreas has been less well studied in humans, partly because of concerns related to the many vital structures in the vicinity of the pancreas that could be vulnerable to local insults, and the theoretical risks of pancreatitis, fistulation and inappropriate release of pancreatic secretions. However, a great deal of experimental work has been undertaken, mainly in hamsters, to study PDT effects on the pancreas and surrounding tissues as well as on tumors transplanted into the pancreas *(2–4,13,14,17,101)*. In general, there was necrosis in normal pancreas and stomach, which healed without serious adverse effects. The tissue that was most vulnerable with all photosensitizers was the duodenum, with sealed duodenal perforations and late duodenal stenosis seen in some animals. In the aorta, there was endothelial and medial smooth muscle cell necrosis, but this did not lead to any thrombotic events or weakening of the arterial wall. A recent pilot study of endoscopic ultrasound (EUS)–guided photodynamic therapy of the pancreas in a porcine model, found that this technique was safe and feasible and could induce small areas of necrosis (mean: 3.6 mm^2; range:1–14) in normal pancreas *(102)*.

Studies of treatment of chemically induced pancreatic cancers transplanted into the hamster pancreas showed that it was possible to achieve tumor necrosis, with the only significant complication again being duodenal damage (sealed perforation or stenosis) when the site treated was close to the duodenal wall *(3,4,17,101)*. Unlike tumors in the luminal gut, some selectivity of tumor necrosis was found relative to the effect in the surrounding normal pancreas *(2)*. This was noted using aluminum sulfonated phthalocyanine (AlS_2Pc), even though the selectivity of uptake in these tumors was only 2–3:1. The reasons for this are unclear. It has been postulated that normal pancreas may be protected from the effects of PDT via singlet oxygen–quenching agents, e.g., glutathione *(103)*, that act as intracellular scavengers *(4)*, or that there is neutralization of the photosensitizer by an unknown biochemical pathway*(3)*. In a randomized, controlled study of implanted pancreatic cancers in hamsters treated with ALA, PDT tumor necrosis up to 8 mm deep was achieved and there was a significant increase in the survival time of treated animals compared with untreated controls *(17)*.

PDT in Pancreatic Cancer: Clinical Studies

The lack of serious complications in these animal studies (apart from the duodenal effects that were thought to be a consequence of the very thin wall of the hamster duodenum) led to our Unit conducting the first clinical trial of PDT in locally advanced pancreatic cancer, published in 2002 *(31)*. The photosensitizer used was mTHPC, because the experimental work had shown that this gave the largest zone of necrosis around each treatment site (up to 12 mm in diameter), and also because this drug requires the lowest light doses and therefore the shortest treatment times.

Technique

With the aims of assessing technical feasibility, safety, and efficacy, 16 patients with locally advanced cancers in the head of the pancreas were treated with mTHPC via percutaneous needles placed under CT guidance. The documented maximum tumor diameter prior to PDT was 2.5–6.0 cm (median 4.0) and tumor volume was 3–63 cm^3 (median 27). The patients received 0.15 mg/kg bodyweight mTHPC, intravenously, 72 h before laser activation. Patients remained in a darkened area of the ward for the first 24 h, with the level of light kept below 100 lux (equivalent to a single 60 W bulb). On each subsequent day the permitted light exposure was increased by 100

lux so that by d 3 low level indoor lighting was acceptable and by d 7 normal indoor lighting was safe.

Treatment was undertaken 3 d after photosensitization under subdued lighting conditions. After prophylactic antibiotics and intravenous sedation, the anterior abdominal wall was infiltrated with local anaesthetic. Up to six 19 G needles were inserted into the deepest part of the tumor by the radiologist using a combination of ultrasound and CT guidance, with the tips of the needles separated by about 1.5 cm, the number being determined by the size and position of the tumor.

The light source used was a diode laser delivering red light at 652 nm. Using a beam splitter, the light was divided equally between up to four 0.4 mm core diameter optical fibers with plain cleaved tips. When all of the needles had been confirmed as correctly sited in the tumor, a fiber was passed down to the tip of each needle to leave 3 mm of bare fiber in direct contact with the tumor during delivery of the therapeutic light. In patients requiring six needles, the last two sites were illuminated after the first four rather than concurrently. Prior to use, the system was calibrated to deliver 100 mW at the tip of each fiber. This power setting was used to minimize photocoagulation of blood around the fiber tips, which can reduce the amount of light delivered to the target site. After delivery of the planned light dose at the initial sites, the needles and fibers were pulled back under CT control in approx 1 cm steps as required to cover the entire tumor and the same light dose delivered at each position. The light dose delivered at each site was kept at 20 J for each patient.

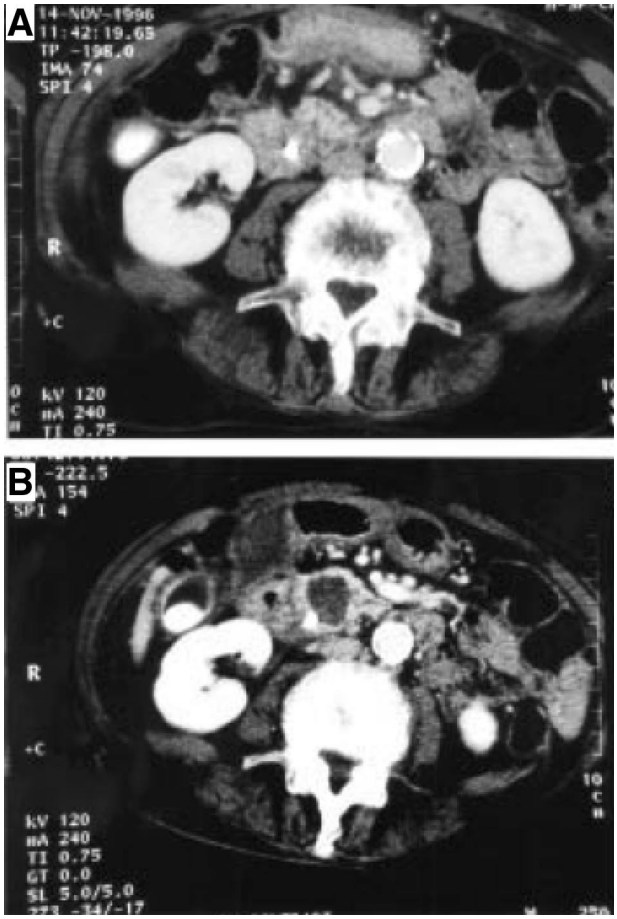

Fig. 3. Contrast enhanced computerized tomography scans of a patient: **(A)** prior to mTHPC PDT, showing a 2.5 cm carcinoma in the head of the pancreas, and **(B)** 4 d after PDT, showing a large new area of non-enhancement. This patient had a biliary stent in place at the time of treatment. Technically, this tumor was thought to be operable but the general condition of the patient was considered to be too poor. [From Bown et al. *(31)*, *Gut* 2002; 50:549–557, with permission from the BMJ Publishing Group.]

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Results

On contrast-enhanced CT scans taken a few days after PDT (Fig. 3), all patients had a new non-enhancing area in the pancreas (up to 6.5 cm diameter) consistent with tumor necrosis, which was confirmed on biopsy in the first patient. The median volume of necrosis produced by PDT was 36 cm^3 (range, 9.0–60.0 cm^3). Transient procedure-related pain requiring opiate analgesia was the most common side effect. Ten patients experienced a temporary paralytic ileus but most were drinking normally by 48 h and none developed pancreatitis. There was no treatment-related mortality, but two patients with gastroduodenal artery involvement had hemodynamically significant bleeds requiring transfusion and/or embolization. Two others with major duodenal wall involvement developed significant PDT-induced duodenal stenosis requiring enteral stent placement. In the patients, the treatment shrank the area of viable tumor, and tumor did not regrow at the site of PDT necrosis but often regrew from the edges of the treated areas. In 14 cases, the late stages of the disease were dominated by local tumor invasion and lymphadenopathy. In the other two patients, multiple liver metastases were detected soon after PDT

and their subsequent clinical course was dominated by this development. Median survival for all patients from the time of diagnosis was 12.5 mo (range 6–34 mo). Seven of the 16 (44%) patients were alive 1 yr after PDT, nine (56%) were alive 1 yr after diagnosis and two patients survived 2 yr.

These preliminary results suggest that the technique is feasible and safe for local debulking of pancreatic cancer. The survival times compare favorably with the median survival of 6–10 mo from diagnosis in patients with non-metastatic locally advanced disease reported in other series *(100)*. However, randomized controlled studies will be required to assess the true influence of PDT on survival, and its potential additional role to palliative chemotherapy in the management of this disease. The use of modified selection criteria, such as excluding patients with tumor encasement of a major artery or the duodenum, would also be expected to reduce the risk of major complications and allow treated areas to heal safely.

Conclusion

Photodynamic therapy is a promising novel treatment, which may improve the survival of patients with biliary tract cancer and appears to be safe and feasible for the treatment of locally advanced pancreatic cancer. However, the vast majority of patients will not be cured of malignancy and improvements in efficacy are needed. Technical aspects of future studies will be to match the distribution of laser effects to the extent of diseased tissue being treated, and ideally to extend the treated area beyond the tumor margins identified on pretreatment scans while ensuring that treated areas heal safely without unacceptable effects on structure or function. This requires good imaging to establish the extent of disease and ensuring that appropriate light doses are delivered to all relevant sites. Much current research is focusing on ways to achieve complete tumor necrosis by monitoring PDT in real time during light delivery. Other approaches include better delivery of photosensitizers to tumor tissue, the development of new photosensitizers with enhanced tumor specificity, and optimisation of the drug–light interval. Future work should also explore the combination of PDT with chemotherapy, surgery, and other emerging novel therapies.

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