*Editorial*

# Photodynamic therapy and pancreatic cancer

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Pancreatic cancer is one of the top 10 leading causes of cancer death worldwide.[1] In population based studies, only a few pancreatic cancer (2.6%) are suitable for surgery and even after resection, the median survival is only 12-18 months.[2-3] Options available for the treatment of inoperable patients are largely limited to radiotherapy, chemotherapy or a combination. Unfortunately, no therapy has been shown of convincing benefit on survival.[4] The long term prognosis of the disease is poor, with a one year survival rate of no more than approximately 10%.[5]

Photodynamic therapy (PDT) is a form of cancer treatment, which involves the local activation of a preadministered photosensitiser by light of a wavelength matched to the absorption characteristics of the photosensitiser. The activated photosensitiser causes to the production of cytotoxic singlet oxygen. As the biological effect is photochemical and not thermal, there is little damage to connective tissues such as collagen and elastin, which helps to maintain the mechanichal integrity of the gastrointestinal tract. Furthermore, as the light used is non-ionising, PDT does not carry the cumulative toxicity associated with radiotherapy. Once a PDT treated area has healed, it can be treated again if necessary. Unfortunately, although there is some selectivity in tumour uptake, there is essentially always necrosis in adjacent normal tissue.[6-7]

Although most work on PDT has been on lesions in the wall of hollow organs or on the skin, recent interest has examined its potential for treating lesions of solid organs such as the pancreas. Experimental studies on normal hamsters, using three photosensitisers (5-ALA, AlS2Pc, mTHPC), have been performed. The results were broadly similar with all three. Necrosis was produced in the normal pancreas, stomach, duodenum and the common bile duct, but this healed, with the exception of the duodenum, where some free and sealed perforations were seen. These perforations may be related to the thin nature of the rodent wall.[8-10] In the arteries, there was endothelial loss and loss of smooth muscle but the endothelium regenerated within a few days. There was no risk of thrombosis, no reduction in the mechanical strength of the arterial wall and no evidence of aneurysm formation.[11]

Several groups have undertaken experiments on cancers transplanted into the hamster pancreas using different photosensitisers such as the partly purified derivatives of haematoporphyrin (dihaematoporphyrin and porfimer sodium), 5-ALA, AlSPc and mTHPC. All of them had the possibility of producing necrosis in the cancer and there was even some selectivity of effect between the cancer and the adjacent normal pancreas. This was thought to be due not to selectivity of retention of the photosensitiser but to a costituent of the normal pancreas that reacted with singlet oxygen, perhaps glutathione, that was not present in the cancer. Duodenal perforation occurred in a small percentage of treated animals with all the photosensitisers but these seemed well tolerated. Bile duct obstruction was another complication, but it was less common. This is thought to be secondary to edema of pancreatic tissue surrounding the treated area, especially near the ampulla of Vater, because it resolved spontaneously within 7 days.[12-15]

A theoretical concern for human application is the fact that pancreatic cancer is a bulky, solid organ tumour. This probably means light penetration into the tumour is limited.

The only clinical study in the literature is that of Bown *et al*,[16] which was a phase I study using PDT to treat pancreatic cancers in patients who were considered unsuitable for surgery. Sixteen patients with cancers

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localised in the region of the head of the pancreas were studied. All the cases were confirmed by histology or cytology to be adenocarcinomas. Ten men and six women, aged 46-77 years were included. All had presented with obstructive jaundice which had been satisfactory relieved by insertion of a biliary endoprosthesis prior to further treatment. The cancers were not all small, with a maximum diameter at the time of treatment of 2.5-6.0 cm Patients were photosensitised with 0.15 mg/kg meso-tetrahydroxyphenyl chlorin (mTHPC) by slow intravenous injection three days prior to light delivery. 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. Contrast enhanced spiral CT scans were performed 3-5 days after PDT with flexible duodenoscopy being performed approximately one week after treatment. In all cases, CT scans, after PDT treatment, showed a substantial tumour necrosis which, in some cases, covered all the tumour visible on CT. The median survival time after PDT was 9.5 months (range 4-30). Seven of the 16 (44%) patients were alive one year after treatment. There was no treatment related mortality, most patients were out of hospital in less than 10 days after treatment and morbidity was less than would be expected after surgery. All patients had abdominal pain after the procedure, most requiring opiate analgesia for the first few days, but none had clinical evidence of pancreatitis. PDT did not exacerbate any abnormalities of glucose tolerance other than in the first few days after treatment. In the first 6 weeks after PDT only three patients had a normal appearing duodenum endoscopically. In three patients there was a breakdown of the wall between the duodenum and common bile duct but there were no free duodenal perforations. Two patients with tumours 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 the 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. However, care is required for tumours invading the duodenal wall or involving the gastroduodenal artery.

## REFERENCES


1. Parkin DM, Pisani P, Ferlay J. Global cancer statistics. CA Cancer J Clin 1999; 49: 33-64
2. Bramhall SR, Allum WH, Jones AG, *et al*. Treatment and survival in 13.500 patients with pancreatic cancer and incidence of the disease in the epidimiological study. Br J Surg 1995; 82: 111-115
3. Yeo CJ, Cameron JL, Lillemoe KD, *et al*. Pancreaticoduodenectomy for cancer of the head of the pancreas. 201 patients. Ann Surg 1995; 221: 59-66
4. DiMagno EP, Reber HA, Tempero MA. AGA technical review on the epidemiology, diagnosis and treatment of pancreatic ductal adenocarcinoma. American Gastroenterological Association. Gastroenterology 1999; 117: 1464-1484
5. Hawes RH, Xiong Q, Waxman I, *et al*. A multispecialty approach to the diagnosis and management of pancreatic cancer. Am J Gastroenterol 2000; 95: 17-31
6. Dougherty TJ, Gomer CJ, Henderson BW, *et al*. Photodynamic therapy. J Natl Cancer Inst 1998; 90: 889-905
7. Barr H, Tralau CJ, Boulos PB, *et al*. The contrasting mechanisms of colonic collagen damage between photodynamic and thermal injury. Photochem Photobiol 1987; 46: 795-800
8. Nuutinen PJ, Chatlani PT, Bedwell J, *et al*. Distribution and photodynamic effect of disulphonated aluminium phthalocyanine in the pancreas and adjacent tissues in the Syrian golden hamster. Br J Cancer 1991; 64:1108-1115
9. Ravi B, Regula J, Buonaccorsi GA, *et al*. Sensitization and photodynamic therapy of normal pancreas, duodenum and bile ducts in the hamster using 5-aminolaevulinic acid. Lasers Med Sci 1996; 11:11-21
10. Milkvy P, Messmann H, Pauer M, *et al*. Distribution and photodynamic effects of meso-tetrahydroxyphenylchlorin (mTHPC) in the pancreas and adjacent tissues in Syrian golden hamster. Br J Cancer 1996; 73:1473-1479
11. Grant WE, Buonaccorsi G, Spheight PM, *et al*. The effect of photodynamic therapy on the mechanichal integrity of normal rabbit carotid arteries. Laryngoscope 1995; 105: 867-871
12. Schroder T, Chen IW, Sperling M, *et al*. Hematoporphyrin derivative uptake and photodynamic therapy in pancreatic carcinoma. J Surg Oncol 1988; 38: 4-9
13. Chatlani PT, Nuutinen PJO, Toda N, *et al*. Selective necrosis in hamster pancreatic tumours using photodynamic therapy with phthalocyanine photosensitization. Br J Surg 1992; 79: 786-790
14. Regula J, Ravi B, Bedwell J, *et al*. Photodynamic therapy using 5-aminolevulinic acid for experimental pancreatic-cancer – prolonged animal survival. Br J Cancer 1994; 70: 248-254
15. Milkvy P, Messman H, MacRobert AJ, *et al*. Photodynamic therapy of a transplanted pancreatic cancer model using meta-tetrahydroxyphenylchlorin (mTHPC). Br J Cancer 1997; 76: 713-8
16. Bown SG, Rogowska AZ, Whitelaw DE, *et al*. Photodynamic therapy for cancer of the pancreas. Gut 2002; 50: 549-557