NATIONAL INSTITUTE FOR CLINICAL EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedures overview of photodynamic therapy for bile duct cancer

Introduction

This overview has been prepared to assist members of the Interventional Procedures Advisory Committee (IPAC) in making recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and specialist opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This overview was prepared in October 2004.

Procedure name

- Photodynamic therapy (PDT) for biliary tract cancer.

Specialty societies

- British Society of Gastroenterology.
- Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland.
- British Association of Surgical Oncologists.

Description

Indications

Bile duct cancer (cholangiocarcinoma).

If cancer develops in the bile duct, it may prevent bile flowing from the liver to the intestine. Early cancers are often asymptomatic but as the disease advances patients may experience symptoms such as jaundice, itchy skin, abdominal discomfort, loss of appetite, weight loss and fever.

Current treatment and alternatives

Treatment options depend largely on the stage, size, position and type of the cancer. Bile duct cancer is not usually diagnosed before the symptoms of biliary obstruction occur, by which time the cancer may be too advanced for curative surgical resection. The standard options for palliative treatment include surgical bypass of the bile duct or the insertion of a stent using surgical, endoscopic or percutaneous techniques. The benefits of other palliative treatments such as radiotherapy, chemotherapy and brachytherapy are still being investigated.

What the procedure involves

Photodynamic therapy (PDT) produces localised tissue necrosis by applying a photosensitising agent and then exposing the area to laser light of an appropriate wavelength. A photosensitising agent is used that preferentially accumulates in the tumour tissue rather than normal tissue.

Photodynamic therapy is usually administered in conjunction with a biliary stenting procedure. The photosensitising agent is injected intravenously and photoactivation is performed approximately 48 hours later. This is done by inserting a laser through a translucent endoscopic catheter situated close to the tumour or by placing the laser directly across the tumour. Radiological control is used to ensure correct positioning of the laser fibre. Patients remain in the dark for about 3 days after injection and are then gradually readapted to light. The treatment can be repeated.

Efficacy

A randomised controlled study of 39 patients reported that those treated with PDT and stenting had a significantly longer median survival time than patients treated with biliary stenting alone (493 days versus 98 days, $p < 0.0001$). This study was terminated prematurely because PDT was so superior to stenting alone. Several quality of life scores were significantly improved after PDT, including global quality of life, fatigue, itching and weight loss. No significant improvements in quality of life scores were reported for the patients receiving biliary stenting alone. A non-randomised study of 44 patients reported that the mean survival after PDT and biliary stenting was 16 months, compared to 12.5 months after biliary stenting alone.

The Specialist Advisors agreed that there is not enough data to fully establish the effect of PDT on survival. One Specialist Advisor stated that this procedure is only effective for disease that is in visual proximity to the light source and would not be effective for disease more than a few millimetres deep into the bile duct wall.

Safety

Three studies reported 30-day mortality, which ranged from 0% (0/24) to 17% (1/6).

The most common complications were cholangitis, affecting between 15% (3/20) and 56% (13/23) of patients, and photosensitivity which was reported in 0% (0/8) to 33% (2/6) of patients. Other reported complications included bilioma, cholecystitis, stenosis, haemobilia and reversible paraesthesia of the hands.

The Specialist Advisors stated that potential adverse effects of the procedure include cholangitis, photosensitivity, stenosis of the biliary tree, biliary perforation, acute pancreatitis, bleeding and pain.

Literature review

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to photodynamic therapy for bile duct cancer. Searches were conducted via the following databases, covering the period from their commencement to October 2004: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and Science Citation Index. Trial registries and the Internet were also searched. No language restriction was applied to the searches.

The following selection criteria were applied to the abstracts identified by the literature search. Where these criteria could not be determined from the abstracts the full paper was retrieved.

Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies included. Emphasis was placed on identifying good quality studies. Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising methodology.
Patient	Patients with bile duct cancer.
Intervention/test	Photodynamic therapy.
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

List of studies included in the overview

This overview is based on five studies, which are summarised in Table 1. One randomised controlled trial and one non-randomised controlled study compared stenting and photodynamic therapy with photodynamic therapy alone.[1,2] Three case series are described, one of which was reported in two articles.[3,4,5,6]

Existing reviews on this procedure

No systematic reviews were identified.

Table 1 Summary of key efficacy and safety findings on photodynamic therapy for bile duct cancer

Abbreviations used: PDT = photodynamic therapy, ERCP = endoscopic retrograde cholangiopancreaticography, CI = confidence interval

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>Ortner M (2003)[1]

Randomised controlled trial

Germany

1996–2000

39 patients
• 51% (20/39) stenting and subsequent PDT
• 49% (19/39) stenting alone

Median age:
• stenting and PDT = 64 years
• stenting alone = 68 years

Inclusion criteria: age ≥ 18 years, nonresectable bile duct tumour, tumour size > 3 cm diameter, clearly visible tumour on computed tomography and endoscopic retrograde cholangiopancreaticography (ERCP), unequivocal positive histology, no evidence of cancer of another organ

Exclusion criteria: porphyria, previous chemotherapy or radiation therapy, previous technically successful stenting, insertion of a metal stent, partial resection of cholangiocarcinoma, diagnostic ERCP more than 1 month previously, a Karnofsky index of < 30%, refusal of informed consent

Photosensitising agent: Sodium porfimer (Photofrin; Axcan Pharma Inc, Canada)</td>
<td>Primary outcome = survival

Median survival (days):
• stenting and PDT = 493 (95% CI, 276 to 710)
• stenting alone = 98 (95% CI, 87 to 107)
p < 0.0001
Relative risk = 0.21 (95% CI, 0.12 to 0.35)

After PDT, serum bilirubin reached lower levels relative to baseline and stenting (p < 0.01).

Quality of life (QLQ-C30) – Functioning scales (scores range from 0 to 100, with a higher score representing a higher level of functioning)
<table>
<tr><th rowspan="2">Functioning scales</th><th colspan="2">Stenting & PDT</th><th colspan="2">Stenting alone</th></tr>
<tr><th>Before</th><th>After</th><th>Before</th><th>After</th></tr>
<tr><td>Physical</td><td>63.0</td><td>77.0**</td><td>64.2</td><td>55.8</td></tr>
<tr><td>Role</td><td>50.0</td><td>65.0</td><td>52.6</td><td>44.7</td></tr>
<tr><td>Cognitive</td><td>64.0</td><td>71.1</td><td>62.3</td><td>59.6</td></tr>
<tr><td>Emotional</td><td>62.1</td><td>71.2*</td><td>60.1</td><td>60.9</td></tr>
<tr><td>Social</td><td>68.4</td><td>77.5</td><td>60.1</td><td>58.3</td></tr>
<tr><td>Global quality of life</td><td>56.2</td><td>74.2**</td><td>62.3</td><td>54.8</td></tr>
</table>
* p < 0.05, ** p < 0.01

Quality of life (QLQ-C30) – Symptom scales (scores range from 0 to 100, with a higher score representing a greater degree of symptoms)
<table>
<tr><th rowspan="2">Symptom scales</th><th colspan="2">Stenting & PDT</th><th colspan="2">Stenting alone</th></tr>
<tr><th>Before</th><th>After</th><th>Before</th><th>After</th></tr>
<tr><td>Fatigue</td><td>55.1</td><td>41.1*</td><td>48.2</td><td>57.0</td></tr>
<tr><td>Nausea and vomiting</td><td>10.8</td><td>9.2</td><td>14.0</td><td>22.8</td></tr>
<tr><td>Pain</td><td>27.2</td><td>26.7</td><td>30.7</td><td>30.7</td></tr>
<tr><td>Sleep disturbance</td><td>26.6</td><td>13.3</td><td>19.3</td><td>29.8</td></tr>
<tr><td>Itching</td><td>43.8</td><td>5.0**</td><td>44.7</td><td>34.2</td></tr>
<tr><td>Weight loss</td><td>77.5</td><td>25.4**</td><td>64.5</td><td>53.9</td></tr>
<tr><td>Fever</td><td>14.9</td><td>9.9</td><td>15.8</td><td>33.3*</td></tr>
</table>
* p < 0.05, ** p < 0.01</td>
<td>Mortality
• stenting and PDT = 90% (18/20)
• stenting alone = 100% (19/19)

Nonfatal adverse events
Cholangitis:
• stenting and PDT = 15% (3/20)
• stenting alone = 37% (7/19)

Stenosis:
• stenting and PDT = 10% (2/20)
• stenting alone = 0% (0/19)

Photosensitivity:
• stenting and PDT = 10% (2/20)
• stenting alone = 0% (0/19)</td>
<td>Randomisation process described.

Of 70 patients with nonresectable cholangiocarcinoma, 7 refused randomisation and 24 had at least 1 other exclusion criterion.

No patients were lost to follow-up.

Plastic stents were used.

The study was terminated prematurely after 39 patients because PDT proved to be so superior to stenting alone. Further randomisation was deemed unethical.

If any follow-up examination showed evidence of tumour in the bile duct, PDT was repeated.

Mean number of PDT sessions = 2.4 (range 1 to 5).

Technically successful insertion of stents was followed by successful drainage (decrease of bilirubin levels > 50% within 1 week) in only 21% of patients in both groups.</td>
</tr>
</table>

Abbreviations used: PDT = photodynamic therapy, ERCP = endoscopic retrograde cholangiopancreaticography, CI = confidence interval

Study details	Key efficacy findings	Key safety findings	Comments
Dumoulin F (2003)[2] Non randomised controlled study Germany 1999–2002 44 patients • 54% (24/44) PDT and biliary drainage • 45% (20/44) biliary drainage only Mean age at diagnosis: • PDT and biliary drainage = 69.5 years • Biliary drainage only = 70.9 years Inclusion criteria: obstructive jaundice, hilar cholangiocarcinoma, nonresectable tumour or significant comorbidity precluding curative tumour resection, histopathological or cytologic confirmation Exclusion criteria: severe comorbidity with a prognosis of < 6 weeks survival, Karnofsky score < 50%, impaired renal or liver function, leukocyte count < 2 g/l, platelet count < 50 g/l, radiotherapy or chemotherapy within the previous 4 weeks, porphyria or known intolerance to porphyrins Photosensitising agent: Sodium porfimer (Photofrin; Axcan Pharma Inc, Canada) Median follow-up: • PDT and biliary drainage = 10.2 months (range 3.6 to 38.4) • stenting alone = 10.7 months (range 1.5 to 40)	**Primary outcome = mean and median survival** **Patients treated with PDT and biliary drainage** Mean survival after PDT = 15.9 months Median survival after PDT = 9.9 months (95% CI, 6.4 to 13.4) At the end of the study, 79% (19/24) of patients treated with PDT had died because of tumour progression, 6 of whom had signs of cholangitis "Quality of life was preserved for most patients" (assessed using EORTC-QLQ-C30 questionnaire) **Patients treated with biliary drainage only** Mean survival = 12.5 months Median survival = 5.6 months (95% CI, 3.7 to 7.6) p = 0.09 At the end of the observation period, 90% (18/20) of patients had died	30-day mortality: • PDT and biliary drainage = 0% (0/24) • Biliary drainage only = 0% (0/20) 60-day mortality: • PDT and biliary drainage = 0% (0/24) • Biliary drainage only = 5% (1/20) Bilioma (symptomatic): • PDT and biliary drainage = 4% (1/24) • Biliary drainage only = 0% (0/20) Skin phototoxicity: • PDT and biliary drainage = 8% (2/24) • Biliary drainage only = 0% (0/20) Median number of episodes of cholangitis: • PDT and biliary drainage = 2 per patient (range 0 to 5) • Biliary drainage only = 0 per patient (range 0 to 2)	Consecutive patients. Historical controls were treated from 1993 to 1998. In this group, biliary drainage was achieved by metal stent insertion (n = 6), plastic stent insertion (n = 13), drainage catheter (n = 1). A plastic stent was inserted immediately after PDT and replaced by a metal stent 4 weeks later. PDT was restricted to a single sensitisation. Plastic stents were exchanged prophylactically every 3 months. Three patients requested chemotherapy and were censored upon beginning this treatment. The low number of episodes of cholangitis in the control group is probably due to the fact that full outpatient data were not available.

Abbreviations used: PDT = photodynamic therapy, ERCP = endoscopic retrograde cholangiopancreaticography, CI = confidence interval			
Study details	**Key efficacy findings**	**Key safety findings**	**Comments**
Wiedmann M (2004)[3], Berr F(2000)[4] Prospective case series Germany 1996–1998 23 patients (4 patients had metastases at study enrolment) Median age = 68 years (range 22 to 87) Inclusion criteria: unresectable hilar cholangiocarcinoma, Karnofsky performance status > 30% Exclusion criteria: age < 18 years, pregnancy, acute porphyria, renal or hepatic insufficiency, leukopaenia, thrombocytopaenia, chemotherapy within the prior 4 weeks Photosensitising agent: Sodium porfimer (Photofrin; QLT Pharmaceuticals, Canada)	**Primary outcome = survival at 6 months** Survival at 6 months after diagnosis = 91% (21/23) Survival at 6 months after PDT = 74% (17/23) Mean survival after enrolment: All patients = 14.7 months Patients without metastases = 17.0 months Median survival after enrolment All patients = 9.3 months (95% CI, 6.5 to 12.1) Patients without metastases = 11.2 months (95% CI, 6.8 to 15.6) Survival rate estimates for all patients: 1-year = 39% 2-year = 17% 3-year = 9% 4-year = 4% Survival rate estimates for patients without metastases at enrolment: 1-year = 47% 2-year = 21% 3-year = 11% 4-year = 5% 74% (17/23) patients died of tumour progression, 17% (4/23) of cholangitis, 4% (1/23) of septic shock and 4% (1/23) of appendicitis/peritonitis For all patients, there was an improvement in Karnofsky performance status (65% versus 55.4%, $p < 0.05$) and quality of life index (6.8 versus 4.8, $p = 0.017$)	• Cholangitis during follow-up = 56.5% (13/23) (9 patients recovered and 4 died) • Sun-induced erythema = 13% (3/23) • Reversible paraesthesia of the hands = 4% (1/23) • Recurrent haemobilia = 4% (1/23) • Migration of the biliary stent into the appendix = 4% (1/23)	Consecutive patients. The first study (Berr et al, 2000) reported the results after a median follow-up time of 10 months after diagnosis and 8.5 months after first PDT. The second study (Wiedmann et al, 2004) presented 5-year follow-up data for the same patients. Median number of PDT sessions = 3 (range 1 to 6) After PDT, 1 or 2 plastic stents were inserted to drain both liver lobes.

Abbreviations used: PDT = photodynamic therapy, ERCP = endoscopic retrograde cholangiopancreaticography, CI = confidence interval			
Study details	**Key efficacy findings**	**Key safety findings**	**Comments**
Zoepf T (2001)[5] Case series Germany 1998 – 1999 8 patients Median age = 67 years (range 56 to 79) Inclusion criteria: histologically proven nonresectable bile duct cancer Photosensitising agent: Photosan-3 (SeeLab, Germany) Follow-up = 1 to 15 months	**Primary outcome = radiologically proven reduction of the bile duct stenosis and reduction of cholestasis as measured by serum bilirubin concentration** Elimination of the bile duct stenosis at 4 weeks = 100% (8/8) Median serum bilirubin declined from 5.8 mg/dl (range 2.0–10.1) to 1.0 mg/dl (range 0.8–4.4) Median survival from time of 1st PDT treatment = 119 days (range 52–443) 3 patients received a 2nd PDT session after 3, 4 and 9 months respectively Quality of life, measured using the Karnofsky index, did not change significantly after PDT In 4 patients, transpapillary stent insertion was not possible initially so they were given percutaneous endoprostheses. In all 4 patients, the percutaneous drain could be replaced with a transpapillary one after the first PDT treatment At end of study, 3 patients had died of tumour-related causes and 5 were still alive	• 30-day mortality = 0% (0/8) • Infected bilioma with prolonged cholangitis = 12.5% (1/8) • Cholecystitis = 12.5% (1/8) • Skin phototoxicity = 0% (0/8)	Pilot study. Unclear whether patients were consecutive. Small patient numbers. Short term follow-up. All patients were given at least one plastic stent during the follow-up period. Survival data looked at time from 1st treatment rather than diagnosis. Both patients with infectious complications were provided with only one stent. The authors note that it may be important to provide 2 stents for each patient.

Abbreviations used: PDT = photodynamic therapy, ERCP = endoscopic retrograde cholangiopancreaticography, CI = confidence interval

Study details	Key efficacy findings	Key safety findings	Comments
Rumalla A (2001)[6] Case series USA Date of study not reported 6 patients Age range = 38 to 79 years Inclusion criteria: unresectable cholangiocarcinoma Photosensitising agent: Sodium porfimer (Photofrin II; Axcan Pharma Inc, Canada) Median follow-up = 199 days	**Primary outcome = serum bilirubin concentration.** Median bilirubin value at start of study = 2.7 mg/dl (range 1.5–3.7) Median bilirubin value at 6 months = 1.3 mg/dl (range 0.9–2.3) Biliary stent occlusion developed on 4 occasions in 3 patients, at a median time of 78 days (range 44–81) At 9 month follow-up, 50% (3/6) patients had died	• 30-day mortality = 16.7% (1/6) • Cholangitis = 33.3% (2/6) • Skin phototoxicity = 33.3% (2/6)	Patient selection not described. Small patient numbers. Short term follow-up. Five patients had metastasis to regional lymph nodes. One patient had prior combination radiochemotherapy. All patients had undergone prior endoscopic or percutaneous biliary stent insertion. Five patients had an adequate response to biliary stent insertion and one patient already had a low serum bilirubin level. Patients were offered further sessions of PDT at intervals of every 3 months if there was no significant worsening in bilirubin values and the Karnofsky score was 60 (patient able to care for most personal needs) or higher.

Validity and generalisability of the studies

- The randomised controlled study excluded patients who had previously had a successful stenting procedure.[1] The results may not be generalisable to the use of PDT in patients responding to conventional biliary stenting procedures.
- The number of PDT sessions offered to patients varied between studies.
- All of the studies were small. The randomised controlled study was terminated prematurely because the superior results from PDT made further randomisation unethical.
- The number and type of stents varied between studies. This may have affected safety and efficacy outcomes.
- In studies without control groups, it is impossible to know how much of the improvement in symptoms can be attributed to PDT rather than the stenting procedure.

Specialist Advisors' opinions

Specialist advice was sought from consultants who have been nominated or ratified by their Specialist Society or Royal College.

- Photodynamic therapy for locally advanced biliary tree cancer is novel and of uncertain safety and efficacy.
- The key efficacy outcomes are survival, disease progression, recurrence of jaundice/stent failure and quality of life.
- The appropriate comparator would be endoscopic or percutaneous stenting alone plus best supportive care or chemotherapy.
- Most of the Specialist Advisors considered that this procedure will have a moderate impact on the NHS in terms of numbers of patients eligible for treatment and use of resources.
- Photodynamic therapy can be repeated as necessary.
- There are a number of photosensitisers that require shorter drug light intervals currently under investigation.

Issues for consideration by IPAC

Recruitment for a UK phase II study was completed in August 2004 (PHOTOSTENT). A phase III study is due to start in Spring 2005 (PHOTOSTENT II).

References

1 Ortner M, Caca K, Berr F, et al. Successful photodynamic therapy for nonresectable cholangiocarcinoma: a randomized prospective study. *Gastroenterology* 2003; 125: 1355–63.

2 Dumoulin F, Gerhardt T, Fuchs S, et al. Phase II study of photodynamic therapy and metal stent as palliative treatment for nonresectable hilar cholangiocarcinoma. *Gastrointestinal Endoscopy* 2003; 57: 860–7.

3 Wiedmann M, Berr F, Schiefka I, et al. Photodynamic therapy in patients with non-resectable hilar cholangiocarcinoma: 5-year follow-up of a prospective phase II study. *Gastrointestinal Endoscopy* 2004; 60: 68–75.

4 Berr F, Wiedmann M, Tannapfel A, et al. Photodynamic therapy for advanced bile duct cancer: evidence for improved palliation and extended survival. *Hepatology* 2000; 31: 291–8.

5 Zoepf T, Jakobs R, Arnold J, et al. Photodynamic therapy for palliation of nonresectable bile duct cancer – preliminary results with a new diode laser system. *American Journal of Gastroenterology* 2001; 96: 2093–7.

6 Rumalla A, Baron T, Wang K, et al. Endoscopic application of photodynamic therapy for cholangiocarcinoma. *Gastrointestinal Endoscopy* 2001; 53, 500–4.

Appendix A: Additional papers on photodynamic therapy for bile duct cancer not included in the summary tables

Article title	Number of patients	Comments	Direction of conclusions
Berr F, Tannapfel A, Lamesch P, et al. Neoadjuvant photodynamic therapy before curative resection of proximal bile duct carcinoma. *Journal of Hepatology* 2000; 32: 352–7.	1 patient.	Case report	PDT was confined to the superficial layer of bile duct cancer.
McCaughan J, Mertens B, Cho C, et al. Photodynamic therapy to treat tumours of the extrahepatic biliary ducts. A case report. *Archives of Surgery* 1991; 126: 111–3.	1 patient.	Case report.	7 PDT treatments. Patient still alive after 4 years.
Suzuki S, Inaba K, Yokoi Y, et al. Photodynamic therapy for malignant biliary obstruction: a case series. *Endoscopy* 2004; 36: 83–7.	4 patients.	Case series	Patients could not be treated surgically because of cardiopulmonary disease. No cholangitis. Performance levels were improved in 3 patients.

Appendix B: Literature search for photodynamic therapy for bile duct cancer

The following search strategy was used to identify papers in Medline. A similar strategy was used to identify papers in EMBASE, Current Contents, PreMedline and all EMB databases.

For all other databases a simple search strategy using the key words in the title was employed.

1. photodynamic therapy.mp. or exp Photochemotherapy/
2. biliary.mp.
3. GALLBLADDER/
4. 2 or 3
5. CHOLANGIOCARCINOMA/
6. (cancer or carcinoma).mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
7. 4 and 6
8. 5 or 7
9. 1 and 8