NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of photodynamic therapy for brain tumours

Brain tumours may originate from brain tissue or spread from cancers in other parts of the body. Treatment usually consists of an operation to establish the nature of the tumour and, when possible, remove as much of it as seems safe. Photodynamic therapy (often abbreviated to PDT) has been developed as additional therapy (enhancing the effect of surgery) or as a treatment for tumours that are inoperable. It involves giving the patient a drug that makes the tissues sensitive to light. A laser light source is used during the operation and in some cases for a few days afterwards to activate the light-sensitive substance with the aim of destroying the tumour cells.

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 September 2008.

Procedure name

- Photodynamic therapy for brain tumours

Specialty societies

- Society of British Neurosurgeons
- Association of British Neurologists
- British Society of Neuroradiologists
- British Association of Head and Neck Oncologists
- British Neuro-Oncology Society.

Description

Indications and current treatment

Brain tumours may develop as a primary (intrinsic) tumour from glial, neuronal or meningeal cells, or metastases from tumours elsewhere in the body. Intrinsic brain tumours (such as astrocytoma, oligodendroglioma, glioblastoma, meningioma) are graded using a World Health Organization (WHO) classification from I (low grade and least aggressive) to IV (high grade and most aggressive). Prognosis with high-grade tumours is often poor, with survival measured in months, and worse with recurrent tumours.

The symptoms of a brain tumour depend on its location and size. Different locations can cause discrete disturbances such as limb weakness or language disturbance, while any brain swelling caused by the tumour can lead to raised intracranial pressure, headaches, vomiting and impaired consciousness.

Surgical resection is the mainstay of treatment removing tumour material. With the aim of reducing intracranial pressure without worsening neurological function. In most cases curative resection is not possible due to infiltrating growth of the tumour into normal brain parenchyma. Non surgical treatment options include chemotherapy and radiotherapy. A combination of these treatments may be given.

What the procedure involves

Photodynamic therapy (PDT) involves the administration of a photosensitising agent, usually by intravenous injection, although direct intraoperative injection into the tumour is possible. The agent is then activated by the application of light to the selected area, usually with a laser source. A number of different diffuser / applicator designs are available for this purpose. The agent absorbs this light and forms high-energy oxygen molecules which interact with the local tissue leading to tumour necrosis through a photochemical effect. PDT is usually undertaken following maximal surgical resection, during the same operation and under general anaesthesia. Occasionally repeated light applications following surgery are employed via access maintained through the skull.

A number of different photosensitising agents have been used in PDT for brain tumours. Skin photosensitivity is quite long-lasting and patients are recommended to avoid exposure to bright light from any source, especially direct sunlight, for a number of weeks.

List of studies included in the overview

This overview is based on approximately 380 patients in total, from one randomised controlled trial[1] and five case series[2,3,4,5,6].

Other studies that were considered to be relevant to the procedure but were not included in the main extraction table (table 2) have been listed in appendix A.

Efficacy

In a randomised controlled trial comparing PDT after surgery with surgical resection alone in 27 patients, mean survival in the PDT group (n=13) was significantly longer than in the surgical resection group (52.8 ± 26 weeks vs. 24.1 ± 11.5 weeks; p=0.001)[1]. In the same study, mean Karnofsky performance score improved from 60 points at baseline to 80 points at follow-up in the PDT group, and was unchanged at 70 in the control group ($p < 0.05$) (follow-up not stated). The Karnofsky score measures physical ability on a scale of 100% (normal health) to 10% (moribund) and 0% (death).

A case series of 126 patients treated by PDT following surgical resection reported that median survival from initial diagnosis was 76.5 months for patients with primary anaplastic astrocytoma and 14.3 months for patients with glioblastoma multiforme, with a minimum follow-up period of 3 years[2]. Survival length was not associated with location of the tumour in the brain (either 'frontal' or 'other').

Median survival in a case series of 112 patients treated by PDT following surgical resection was 30 weeks in patients with gliomas and 24 weeks in patients with metastatic carcinoma (follow-up not reported)[3]. In a case series of 28 patients who had a range of brain tumours the median overall survival following post surgical PDT was 14 months, and 11% (3/28) of patients were alive and disease-free at final follow-up (follow-up period not reported)[4].

A case series of 26 patients treated by PDT following surgical resection reported median time to disease progression was 6 months and median survival was 8.5 months[5]. Median survival in a case series of 11 patients with primary glioblastomas and 39 patients with recurrent glioblastomas was 19 months and 8 months, respectively, following post surgical PDT[6].

Safety

Two of the case series did not report safety outcomes[4,6].

Postoperative death occurred in 3% (3/112) of patients in the case series of 112 patients treated with PDT. One patient died of pulmonary embolism, and 2 of tumour cavity haemorrhage[3]. In the same study, 6% (7/112) of patients had increased neurological deficit following the procedure, which resolved within 1 month in 2 patients. Deep vein thrombosis occurred in 4% (4/112), infection in 4% (4/112), and spinal fluid leak in 1% (1/112) of patients (no further details provided).

A case series of 26 patients treated by PDT reported transient oedema of the treated area in 4% (1/26) of patients[5].

Across 3 case series, sunburn due to light exposure occurred at a rate of between 2% (2/112, 2/136)[2,3] and 8% (2/26)[5].

Literature review

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to photodynamic therapy for brain tumours. Searches were conducted of the following databases, covering the period from their commencement to 09/06/08 and updated to 04/12/09: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the Internet were also searched. No language restriction was applied to the searches (see appendix C for details of search strategy).

The following selection criteria (table 1) were applied to the abstracts identified by the literature search. Where selection criteria could not be determined from the abstracts the full paper was retrieved.

Table 1 Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies were 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, or a laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising study methodology, unless they reported specific adverse events that were not available in the published literature.
Patient	Patients with brain tumours (including unresectable brain tumours).
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.

Existing assessments of this procedure

There were no published assessments from other organisations identified at the time of the literature search.

Related NICE guidance

Below is a list of NICE guidance related to this procedure. Appendix B gives details of the recommendations made in each piece of guidance listed below.

Interventional procedures

None

Technology appraisals

- Brain cancer – temozolomide. NICE technology appraisal 23 (2001). Available from http://www.nice.org.uk/Guidance/TA23
- Glioma (newly diagnosed and high grade) - carmustine implants and temozolomide. NICE technology appraisal 121 (2007). Available from http://www.nice.org.uk/Guidance/TA121

Clinical guidelines

- Service guidance for improving outcomes for people with brain and other central nervous system tumours. NICE cancer service guidance (2006). Available from http://www.nice.org.uk/guidance/index.jsp?action=byID&o=10905

Public health guidance

None

Table 2 Summary of key efficacy and safety findings on photodynamic therapy for brain tumours

Abbreviations used: AA, anaplastic astrocytoma; CI, confidence interval; FGR, fluorescence-guided resection; GBM, glioblastoma multiforme; KTP, potassium titanyl phosphate;			
Study details	**Key efficacy findings**	**Key safety findings**	**Comments**
Eljamel M S (2007)[1] **Randomised controlled trial** Country: UK **n = 27** (13 PDT) Study period: not reported Indication: Patients with newly diagnosed GBM, who were considered for cytoreductive surgery, with Karnofsky performance score ≥ 60 points. Study population: Age: 60 years (median), Sex: 67% male, Karnofsky performance score = 70 points. Technique: Photosensitiser (photofrin) given at 2 mg/kg 48 hours prior to surgery. At surgery, maximal resection of the tumour was performed by neuro-navigation and then FGR, followed by a 100 J/m^2 light dose via a balloon diffuser generated by a diode laser. The light exposure was repeated on 4 subsequent days. Control group had craniotomy surgical resection. Both groups also received standard postoperative radiotherapy, **Follow-up: not reported** Conflict of interest: supported by a grant from a charitable trust.	**Survival** Patients followed up clinically and radiologically until death. One patient in the PDT arm (8% 1/13) had incomplete FGR and did not receive PDT due to the proximity of the tumour to the middle cerebral artery. This patient was included in an intention to treat analysis. The mean survival in the PDT group was significantly longer than in the surgical resection group (52.8 ± 26 weeks vs. 24.1 ± 11.5 weeks; p=0.001). The mean time to tumour recurrence in the PDT group was significantly longer than in the surgical resection group (8.6 ± 4.5 months vs. 4.8 ± 1.43 months; p < 0.01). **Clinical status / quality of life** The mean Karnofsky performance score improved from 60 to 80 points in the PDT group but remained the same at 70 points in the surgical resection group (p < 0.05). The mean length of stay was 7 days in both treatment groups.	**Complications** Deep vein thrombosis occurred in 15% (2/13) of the PDT group and 7% (1/14) of the surgical resection group (threshold of significance not reported). There were no infections or seizures in either study group.	Single-centre study. Randomisation method not described. Treatment allocation concealment by means of sealed opaque envelopes. This is the only study that uses a course of PDT light exposure over a number of days Postoperative scans evaluated by blinded radiologists. No details of blinding for clinical follow up. There were no significant differences in clinical or demographic characteristics of the two groups at baseline. Four patients received temozolomide, 3 patients PCV chemotherapy, and 7 further surgery during follow-up. There was no difference in additional therapy between groups. The Karnofsky score runs from 100 to 0, where 100 is "perfect" health and 0 is “death”.

Abbreviations used: AA, anaplastic astrocytoma; CI, confidence interval; FGR, fluorescence-guided resection; GBM, glioblastoma multiforme; KTP, potassium titanyl phosphate;			
Study details	**Key efficacy findings**	**Key safety findings**	**Comments**
Stylli SS (2005)[2] **Case series** Country: Australia **n = 136** (145 treatment sessions) Study period: 1986–2000 Indication: Patients with GBM (n=78) or AA (n=58) treated with adjuvant PDT following surgical resection of the tumour. Study population: Age: 40 years (median), Sex: 62% male, 55% recurrent tumour. Technique: Photosensitiser (HpD) given intravenously at 5 mg/kg 24 hours prior to surgery. At surgery maximal resection of the tumour was performed, followed by a 70–240 J/m^2 light dose via a quartz fibre generated by an argon-dye pumped laser, a gold metal vapour laser or a KTP laser. All patients with primary tumour had standard postoperative radiotherapy, and those with recurrent tumor had previously received it; 29% of the patients also received chemotherapy. **Follow-up: 3 years minimum.** Conflict of interest: not stated.	**Survival** *Primary tumours* Median survival from initial diagnosis was significantly longer with AA than with GBM (76.5 vs. 14.3 months; p = 0.001). Five-year survival was 63% (95% CI 44–78%), and 22% (95% CI 10–38%) respectively. *Recurrent tumours* Median survival from repeat surgery was 66.6 months in patients with AA tumours and 14.9 months in patients with GBM. Five-year survival was 50% (95% CI 31–67%), and 34% (95% CI 21–48%) respectively. Older age at diagnosis was associated with worse prognosis (hazard ratio 1.25, 95% CI 1.05–1.49; p = 0.010). This was independent of tumour grade, and whether primary or secondary tumour. Among patients with primary tumours, light dose ≥ 230 J/m^2 was associated with better prognosis (hazard ratio 0.502, 95% CI 0.27–0.94; p=0.033). For recurrent tumours there was no statistically significant association. Tumour location ('frontal' or 'other') was not associated with survival (p = 0.540). Neither was there any significant association with survival with regard to gender, or use of concomitant chemotherapy.	**Complications** 2% (2/136) of patients reported excessive sunburn related to photo sensitisation. In both cases they had failed to adhere to written instructions regarding exposure.	Photosensitiser was manufactured in local hospital pharmacies. Survival time data were censored at 1st January 2004. All deaths otherwise unexplained were assumed to have been caused by the brain tumour. Survival analysis for primary tumours was based on date of radiological diagnosis and not surgery. Primary and recurrent tumour groups were analysed separately for survival. Median age at diagnosis was significantly younger for patients with AA than with GBM (35 vs. 44 years; p < 0.001). Patient accrual method not described. Experience of surgeons not described. Retrospective database analysis.

Abbreviations used: AA, anaplastic astrocytoma; CI, confidence interval; FGR, fluorescence-guided resection; GBM, glioblastoma multiforme; KTP, potassium titanyl phosphate;

Study details	Key efficacy findings	Key safety findings	Comments
Muller P J (2006)[3] **Case series** Country: Canada **n=112** Study period: not stated. Indication: Patients with primary or recurrent brain tumours undergoing PDT. Supratentotial gliomas (n=96), metastatic carcinoma (n=11) or malignant meningioma (n=3) treated with adjuvant PDT following surgical resection of the tumour. Study population: Age: 45 years (mean), Sex: 66% male, Karnofsky performance score 80 points (mean). Technique: Photofrin given intravenously at 2 mg/kg 13–36 hours prior to surgery. At surgery maximal resection of the tumour was performed, followed by a cavity illumination (sometimes supplemented with interstitial fibres) generated by an argon-dye pumped laser or a KTP laser. All patients with primary tumours had standard postoperative radiotherapy, and 'many' also received chemotherapy. The recurrent cases had failed radiotherapy. **Follow-up: not reported.** Conflict of interest: Supported by a grant from a national governmental agency.	**Survival** *Gliomas* The median survival was 30 weeks; 1- and 2-year actuarial survival was 22% and 2%, respectively. Patients with primary tumours were older (55 years) and had a lower performance score (78 points) than those with recurrent tumours (41 years, 80 points), but had similar median survival (44 and 40 weeks, respectively). *Metastatic carcinoma* Median survival post PDT treatment was 24 weeks; however, 3 patients who had previously failed radiotherapy survived 1–2.5 years. *Meningioma* Three patients were treated with PDT for palliation of large recurrent malignant meningiomas. They survived 1.1, 1.3 and 6.25 years, respectively.	**Complications** Postoperative death occurred in 3% (3/112) of patients receiving PDT for brain tumours. One patient died following pulmonary embolism, and 2 patients following tumour cavity haemorrhage. Additionally, 1% (1/112) patients had a haematoma that required surgery, with a good result. 9% (1/11) of patients with metastatic carcinoma developed facial erythema (no other details provided). 6% (7/112) of patients had increase in neurological deficit following the resection and PDT procedure; in 2 cases this resolved within 1 month. **Complication** — **Rate** Deep vein thrombosis (required anticoagulants but did not affect lungs) — 4% (4/112) Hand burns — 2% (2/112) Facial pruritus — 1% (1/112) Infection — 4% (4/112) Spinal fluid leak (not further defined) — 1% (1/112)	Patient cohort is those treated before the onset of ongoing phase III trials or those ineligible for the trials. Follow-up recorded from date of PDT treatment. Study population demographics are based on patients with gliomas only. Survival data for whole study population not presented together. Light intensity for treatment varied depending on tumour type and from patient to patient. It is not clear if any patients received multiple treatments or not.

Abbreviations used: AA, anaplastic astrocytoma; CI, confidence interval; FGR, fluorescence-guided resection; GBM, glioblastoma multiforme; KTP, potassium titanyl phosphate;			
Study details	**Key efficacy findings**	**Key safety findings**	**Comments**
Rosenthal MA (2003)[4] **Case series** Country: Australia **n = 28** Study period: not stated. Indication: Patients with primary or recurrent GBM (n=16) or AA (n=11), or anaplastic oligodendroglioma (n=1) treated with adjuvant PDT following surgical resection of the tumour. Study population: Age: 51 years (median), Sex: 68% male. Technique: Photosensitiser (boronted porphyrin) given intravenously following a previous dose escalation study at 4.0 mg/kg 24 hours prior to surgery. At surgery maximal resection / debulking of the tumour was performed, followed by a 630 nm laser light via an optical fibre at 25–100 J/cm^2 to the residual tumour bed. **Follow-up: not reported.** Conflict of interest: not reported.	**Survival** Median overall survival was 14 months (range 2–48 months). At final follow-up, 11% (3/28) of patients were alive and disease-free, 4% (1/28) had recurrent disease, 79% (22/28) of patients had died from disease progression, and 7% (2/28) of patients were lost to follow up with known disease progression. The median overall survival among 16 patients with GBM was 8 months (range 2–38 months), and for the 11 patients with AA 18 months (range 5–48 months)	No safety outcomes were reported on.	From the same institution as Stylli (2005) study; however these are different patients as they were treated using a different photosensitiser. Single-centre, open-label trial. Authors state that PDT is encouraging but still experimental and that larger phase II studies are required to confirm findings, and, if appropriate, randomised controlled trials established.

Abbreviations used: AA, anaplastic astrocytoma; CI, confidence interval; FGR, fluorescence-guided resection; GBM, glioblastoma multiforme; KTP, potassium titanyl phosphate;

Study details	Key efficacy findings	Key safety findings	Comments
Kostron H (2006)[5] **Case series** Country: Austria **n = 26** Study period: not stated. Indication: patients with recurrent glioblastoma (WHO grade IV) given adjuvant PDT following fluorescence guided surgical resection of the tumour. Study population: not reported. Technique: Photosensitiser (not stated) given (route not stated). Fluorescence-guided maximal resection of the tumour was performed, followed by KTP or diode laser light via a diffuser or distributor at 20 J/cm^2 to the residual tumour bed. **Follow-up: not reported.** Conflict of interest: not stated.	**Survival** Patients followed up every 3 months. Median time to disease progression was 6 months and median survival was 8.5 months. There was no significant difference in survival between patients with superficial light exposure or interstitial light exposure. Median survival for a matched-pair control group was 3.5 months.	**Complications** Transient oedema of the treated area 4% (1/26) not otherwise described. Sunburn due to light exposure 8% (2/26).	Results describe outcomes for matched-pair controls; however, it was not described how these were generated, nor what treatment they received. Experience of surgeons not stated. Patient selection and accrual method not described. Patient demographic details are not provided.

Abbreviations used: AA, anaplastic astrocytoma; CI, confidence interval; FGR, fluorescence-guided resection; GBM, glioblastoma multiforme; KTP, potassium titanyl phosphate;			
Study details	**Key efficacy findings**	**Key safety findings**	**Comments**
Kostron H (1995)[6] **Case series** Country: Austria **n = 58** Study period: 1984 onwards. Indication: patients with primary (n=11) or recurrent (n=39) gliomas, melanomas (n=3), malignant meningioma (n=3) or metastases (n=2). Study population: not stated. Technique: Photosensitiser (various) applied intravenously, 1–2 days prior to surgery, dose dependent on agent used and body mass. Administration of light immediately following maximal resection of the tumour using a conventional light source or argon-dye laser at up to 250 J/cm^2. All patients also received radiotherapy. **Follow-up: not reported.** Conflict of interest: not reported.	**Survival** *Primary glioblastomas* Median survival was 19 months (range 0.5–27 moths) in these 11 patients. Median recurrence was at 13 months. *Recurrent glioblastomas* Median survival was 8 months in these 39 patients. Median recurrence was at 7 months (range not reported). *Other histologies* Three patients who presented with a recurrence of malignant meningioma had a median survival of 12 months (range 6–23 months) after PDT therapy. Of the three patients treated for cerebral metastases of melanoma, median survival was 12 months.	No safety outcomes were reported on.	The treatment protocol varied across this series, depending on tumour type and availability of photosensitiser. Unlikely to be the same patients as Kolstron (2006), as those patients received concomitant FGR. Total overall follow-up was not reported. Experience of clinicians not reported.

Validity and generalisability of the studies

- There is a divergence in patient population between the studies, with some including patients with primary tumours, some with recurrent tumours or metastases, and some with a mixed cohort.
- The intervention varied considerably between the studies. PDT was used as an adjuvant therapy in all studies. In addition, photoreactive / fluorescent agents have been used as a guide to resection in some series. Studies where this has been used as a stand-alone treatment with no PDT have been excluded from this overview. In two studies, fluoroscopy was used to assist in tumour removal prior to PDT.
- It is difficult to distinguish which adverse events related to PDT and which to surgical resection.
- Two of the studies used Intralipid, an intravesical light diffusion medium, to improve diffusion of PDT; the others did not.
- Some patients received concomitant radiotherapy or chemotherapy in addition to PDT.
- In the majority of studies, absolute (median, mean or range) follow-up period for the whole patient cohort is not defined; however, the average survival period is described
- A number of different photosensitising products are available, and these are given to the patients either intravenously or, less commonly, via direct intratumoral injection during concomitant surgical resection.
- There is a limited quantity of controlled data, which means that survival following maximal resection without PDT is difficult to assess. Some of the studies make informal comparisons to normal / expected survival but no quantitative evaluations are made.

Specialist Advisers' opinions

Specialist advice was sought from consultants who have been nominated or ratified by their Specialist Society or Royal College. The advice received is their individual opinion and does not represent the view of the society.

Dr Eljamel (British Neuro-Oncology Society), Dr T Hodgson (British Society of Neuroradiologists), Mr N Hoggard (British Society of Neuroradiologists), Dr D Jellinek (British Neuro-Oncology Society), Dr N Hoggard (British Society of Neuroradiologists), Dr C Romanowski (British Society of Neuroradiologists), Mr S Thomson (Society of British Neurological Surgeons), Mr I Whittle (Society of British Neurological Surgeons).

- Three of the Specialist Advisers classified the procedure as novel and of uncertain safety and efficacy, two that it is established and no longer new, and two did not comment.
- The key efficacy outcomes for this procedure are overall and progression-free survival, completeness of resection and quality of life

- Adverse events known by the Advisers or reported in the literature include; cerebral oedema, raised intracranial pressure, hypersensitivity reaction, skin photosensitisation.
- Additional, theoretical adverse events may include impairment of consciousness, damage to the normal brain and cerebral blood vessels, stroke, and compromising other secondary therapies by increasing their brain toxicity.
- The procedure has been used by enthusiasts for almost 25 years. It has been well publicised in the neurosurgical literature but it has failed to catch on.
- Only about 25% of malignant gliomas are unresectable. There would probably be a maximum of 500 treatments a year in the NHS and likely a lot fewer.
- Any work using PDT in brain tumours should be done within a clinical trial setting.
- The optimal light exposure dose is still being studied. The technique is constantly evolving with new photodynamic agents and light delivery systems.
- Uncertainty about efficacy needs to be overcome by a properly structured controlled trial.
- Surgeons need to be trained to use the technology, including light sources.
- If it was found to be safe and efficacious, three of the Specialist Advisers thought that it would be offered at <10 specialist centres, and two thought that it would be available at a minority of hospitals but at least 10.

Issues for consideration by IPAC

- Non-English-language studies were excluded from the overview as sufficient papers written in English were available.
- Only one study relating to pituitary tumours was identified in the literature search (Appendix A).

References

1 Eljamel MS, Goodman C and Moseley H. (2007) ALA and Photofrin® Fluorescence-guided resection and repetitive PDT in glioblastoma multiforme: a single centre Phase III randomised controlled trial. Lasers Med Sci.

2 Stylli SS, Kaye AH, MacGregor L et al. (2005) Photodynamic therapy of high grade glioma – long term survival. Journal of Clinical Neuroscience 12:389-398.

3 Muller PJ and Wilson BC. (2006) Photodynamic therapy of brain tumors – a work in progress. Lasers in Surgery & Medicine 38:384-389.

4 Rosenthal MA, Kavar B, Uren S et al. (2003) Promising survival in patients with high-grade gliomas following therapy with a novel boronated porphyrin. Journal of Clinical Neuroscience 10:425-427.

5 Kostron H, Fiegele T and Akatuna E. (2006) Combination of 'FOSCAN' mediated fluorescence guided resection and photodynamic treatment as new therapeutic concept for malignant brain tumors. Medical Laser Application 21:285-290.

6 Kostron H, Hochleitner BW, Obwegeser A et al. (1995) Clinical and experimental results of photodynamic therapy in neurosurgery. SPIE 2371:126-128.

Appendix A: Additional papers on photodynamic therapy for brain tumours

The following table outlines the studies that are considered potentially relevant to the overview but were not included in the main data extraction table (table 2). It is by no means an exhaustive list of potentially relevant studies.

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Beck TJ, Kreth FW, Beyer W et al. (2007) Interstitial photodynamic therapy of nonresectable malignant glioma recurrences using 5-aminolevulinic acid induced protoporphyrin IX. Lasers in Surgery & Medicine 3:386-393	Case series n=10 Follow-up: up to 24 months	PDT in combination with 3D treatment planning is a safe and feasible treatment modality. The clinical impact of these findings deserves further prospective evaluation.	Larger studies are included in table 2
Kaye AH, Morstyn G, Brownbill D (1987). Adjuvant high-dose photoradiation therapy in the treatment of cerebral glioma: a phase 1-2 study. Journal of Neurosurgery 67:500-505.	Case series n=23 Follow-up: not reported	There was no evidence of cerebral oedema and no other toxicity from therapy; 15 patients had no recurrence and were alive at 7 months follow up.	Larger studies are included in table 2
Krishnamurthy S, Powers SK, Witmer P. (2000) Optimal light dose for interstitial photodynamic therapy in treatment for malignant brain tumors. Lasers in Surgery & Medicine 27:224-234	Case series n=18 Follow-up: not reported	Increasing the light dose delivered to the tumour increases the odds of permanent neurological deficit but does not increase survival or time to progression	Larger studies are included in table 2
Laws ER, Jr., Cortese DA, Kinsey JH et al. (1981) Photoradiation therapy in the treatment of malignant brain tumors: a phase I (feasibility) study. Neurosurgery 9:672-678	Case series n=5 Follow-up: not reported	No significant adverse reactions have occurred and further development and research are planned.	Larger studies are included in table 2
Marks PV, Belchetz PE, Saxena A et al. (2000) Effect of photodynamic therapy on recurrent pituitary adenomas: clinical phase I/II trial – an early report. British Journal of Neurosurgery 1:317-325	Case series n=12 Follow-up: up to 2 years	3 patients showed complete recovery of the visual field. Tumour volume was 46% of baseline at 24-month follow-up. No treatment-related mortality or morbidity.	Larger studies are included in table 2

Origitano TC, Reichman OH. (1993) Photodynamic therapy for intracranial neoplasms: development of an image-based computer-assisted protocol for photodynamic therapy of intracranial neoplasms. Neurosurgery 32:587-595	Case series n=15 Follow-up: not reported	Recurrence occurred outside of treated area. No surgical mortality at 3-month follow-up. 2 patients experienced minor skin photosensitisation.	Larger studies are included in table 2
Perria C, Carai M, Falzoi A et al. (1988) Photodynamic therapy of malignant brain tumors: clinical results of, difficulties with, questions about, and future prospects for the neurosurgical applications. Neurosurgery 23:557-563	Case series n=8 Follow-up: up to 10 months	The longer survival of some patients with glial tumours treated by PDT may make this treatment suitable when traditional therapies fail.	Larger studies are included in table 2
Powers SK, Cush SS, Walstad DL. (1991) Stereotactic intratumoral photodynamic therapy for recurrent malignant brain tumors. Neurosurgery 29:688-695	Case series n=7 Follow-up: not reported	Two patients suffered permanent neurological sequelae: monocular blindness and partial visual field deficit.	Larger studies are included in table 2
Schmidt MH, Meyer GA, Reichert KW et al. (2004) Evaluation of photodynamic therapy near functional brain tissue in patients with recurrent brain tumors. Journal of Neuro-Oncology 67:201-207	Case series n=20 Follow-up: not reported	PDT with balloon adapters has acceptable toxicity in brain tumour patients. More effective photosensitisers could improve local recurrence control.	Larger studies are included in table 2

Appendix B: Related NICE guidance for photodynamic therapy for brain tumours

Guidance	Recommendations
Interventional procedures	There is currently no NICE guidance related to this procedure.
Technology appraisals	**Brain cancer - temozolomide. NICE technology appraisal 23 (2001)** 1. Guidance 1.1 Patients with recurrent malignant glioma (brain cancer) who have failed first-line chemotherapy treatment with other agents (either because of lack of efficacy or because of side effects) may be considered for treatment with temozolomide. Such patients must have a histologically proven malignant glioma (WHO grades III and IV, or transformed grade II) at first relapse, recurrence or progression (as assessed by imaging), Karnofsky performance status greater than or equal to 70 and a projected life expectancy of 12 weeks or more, at initiation of temozolomide treatment. (See Appendix D for definition of Karnofsky status and Appendix E for definition of WHO tumour grading). 1.2 Temozolomide is not recommended for first-line chemotherapy treatment for patients with malignant glioma who have failed primary therapy (surgery and/or radiotherapy), except in the context of a randomised controlled trial against a standard-treatment comparator. 1.3 As temozolomide is not currently licensed for adjuvant chemotherapy treatment of malignant glioma, its use in this indication has not been considered in this appraisal.
Clinical guidelines	**Service guidance for improving outcomes for people with brain and other central nervous system tumours. NICE Cancer service guidance (2006)** Treatment A wide variety of treatments is available for these tumours. Choice between the various options crucially depends on the diagnosis made, either by histopathological evaluation of specimens from biopsy or resection, or by review of the radiological imaging.
Public health guidance	There is currently no NICE guidance related to this procedure.

Appendix C: Literature search for photodynamic therapy for brain tumours

Database	Date searched	Version/files	No. retrieved
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	10/06/2008	Issue 2, 2008	0
Database of Abstracts of Reviews of Effects – DARE (CRD website)	10/06/2008	-	0
HTA database (CRD website)	10/06/2008	-	0
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	10/06/2008	Issue 2, 2008	16
MEDLINE (Ovid)	09/06/2008	1950 to May Week 4 2008	339
MEDLINE In-Process (Ovid)	10/06/2008	June 06, 2008	23
EMBASE (Ovid)	10/06/2008	1980 to 2008 Week 23	538
CINAHL (Dialog DataStar)	10/08/2008	-	10
BLIC (Dialog DataStar)	10/08/2008	-	1
National Research Register (NRR) Archive	10/08/2008	-	-
UK Clinical Research Network (UKCRN) Portfolio Database	10/08/2008	-	-
Current Controlled Trials *meta*Register of Controlled Trials - *m*RCT	10/08/2008	-	-
Clinicaltrials.gov	10/08/2008		4

The following search strategy was used to identify papers in MEDLINE. A similar strategy was used to identify papers in other databases.

1 exp Brain Neoplasms/
2 ((Brain$ or Intracran$ or Pituitar$ or Cerebell$ or Infratentor$ or Supratentor$) adj3 (Neoplas$ or cancer$ or carcinom$ or adencarcinom$ or tumor$ or tumour$ malignan$ or gliom$)).tw
3 exp Glioma/
4 Gliom$.tw.
5 exp Meningioma/
6 Meningiom$.tw.
7 exp Astrocytoma/
8 Astrocytom$.tw.
9 Ependymoma/
10 Ependymom$.tw.
11 exp Pituitary Neoplasms/
12 exp Oligodendroglioma/

13	Oligodendrogliom$.tw.
14	Glioblastoma/
15	Glioblastom$.tw.
16	or/1-15
17	Photochemotherapy/
18	exp Phototherapy/
19	(Photo$ adj3 (dynamic$ or chemotherap$ or radiat$ or therap$)).tw.
20	(photochemotherap$ or phototherap$ or (photodynamic$ adj3 therap$)).tw.
21	PDT.tw.
22	photofrin$.tw.
23	porfimer$.tw.
24	Photosensitizing Agents/
25	((Photosensitiz$ or photosensitis$) adj3 agent$).tw.
26	Porphyrins/
27	Hematoporphyrins/
28	(haematoporphyrin$ or hematoporphyrin$ or HPD).tw.
29	Hematoporphyrin Photoradiation/
30	Hematoporphyrin Derivative/
31	Aminolevulinic Acid/
32	(aminolevulinic adj3 acid).tw.
33	Dihematoporphyrin Ether/
34	(Dihematoporph$ adj3 ether$).tw.
35	or/17-34
36	16 and 35
37	Animals/
38	Humans/
39	37 not (37 and 38)
40	36 not 39
41	from 40 keep 1-339