NATIONAL INSTITUTE FOR CLINICAL EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedures overview of photodynamic therapy for localised, inoperable endobronchial 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 November 2004.

Procedure name

- Photodynamic therapy (PDT).

Specialty societies

- British Thoracic Society.
- Society of Cardiothoracic surgeons of Great Britain and Ireland.
- Association of Cancer Physicians.

Description

Indications

Localised endobronchial (non-small-cell) lung cancer describes cases in which malignancy is confined within the bronchial wall, with no radiographic or endoscopic evidence of lymph node involvement. Improved diagnostic testing using methods such as flexible fibrebronchoscopy means more patients with early stage cancer can be identified.

For the purpose of this overview ‘inoperable cancer’ is defined as cancer in those patients who are unsuitable for lung resection because of bilateral lung cancer, who have impaired respiratory function because of chronic obstructive pulmonary disease, who have had previous resection for primary lung cancer, who are at high operative risk, or who refuse surgery.

Current treatments and alternatives

The range of treatment options for lung cancer is wide and varied, and depends on cancer type and stage, and the suitability for highly invasive procedures for the individual patient. Usual treatment options include endobronchial brachytherapy and external beam radiation. YAG laser ablation may be used for endobronchial obstructions, or wedge resection where appropriate. Photodynamic therapy (PDT) is an alternative for patients who are inoperable as described in the indications section above.

What the procedure involves

Photodynamic therapy is a minimally invasive treatment, involving injection of a photosensitising agent, followed a few days later by photo-radiation to the affected area through a bronchoscope. This is intended to reduce the bulk of the tumour, thus reducing symptoms caused by bronchial obstruction. PDT is performed endobronchially, with debridement of necrotic tumour within a few days of each treatment. The PDT process can be repeated following a washout period of the photosensitising agent.

Evidence was found that PDT causes skin photosensitivity and may cause pulmonary haemorrhage, stricture, or fistula formation.

Efficacy

There were no randomised controlled or comparative trials comparing the efficacy of PDT to other treatment modalities. There was considerable heterogeneity among the studies included in systematic reviews identified, both with regard to outcome measurements used and follow-up times reported. The lesion complete remission rates following PDT ranged from 62% (16/36)[1] through 83% (79/95)[2] to 85% (50/59)[3] of patients in different case series. There are some data from subgroup analyses that suggest that small lesions (in terms of diameter or surface area) respond to PDT better than larger lesions.

Where reported in case series, 5-year survival ranged from 43% (15/36) to 72% (15/21) depending on the severity of comorbidities of those undergoing therapy such as reduced cardiac and pulmonary function. Other studies reported PDT to have reduced airway obstruction and improve self-reported quality of life, from baseline levels.

Safety

In one systematic review, eight studies reported on adverse events. Photosensitivity was reported in all studies with mild to moderate symptoms. The incidence of these side effects was not extracted from the primary studies. Very severe toxicity occurred in a minority of patients undergoing PDT.

Fatal haemoptysis within 1 month of treatment was recorded in 8% (3/38) of patients in one case series.

Elsewhere hypercapnic respiratory failure (requiring mechanical ventilation) occurred in 5% (2/38) and 4% (1/24) of patients following PDT. In other case series patients suffered mild to moderate pulmonary events, two further studies found short-term productive cough following PDT, for both these outcomes incidence was not recorded.

According to the Specialist Advisors, PDT always causes skin photosensitivity, but most patients find this acceptable in practice. PDT may also cause bleeding and strictures, and increase bronchial obstruction as a result of exudate production.

Literature review

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to photodynamic therapy for early, inoperable endobronchial cancer. Searches were conducted via the databases of MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and Science Citation Index, covering the period from January 1996 to December 2004. Trial registries and the Internet were also searched. No language restriction was applied to the searches.

The following selection criteria (Table 1) 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

Table 1 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 localised endobronchial cancer as defined above.
Intervention/test	Photodynamic therapy, using any sensitiser and light delivery device.
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 two systematic reviews and three of the case series included within these. No more recently published case series in patients with early lung cancer were found.

Existing reviews on this procedure

The literature search identified two systematic reviews which are tabulated below. One was by the Agence d'Évaluation des Technologies et Des Modes d'Intervention en Santé for the Quebec government, which itself draws on the work of Comité d'Évaluation et de Diffusion des Innovations Technologiques (France) 1999, and the Institute for Clinical Systems Improvement (USA) 1997 and 2002. A second, more recent, systematic review was undertaken by the CancerCare Ontario Practice Guidelines Initiative Lung Cancer Disease Site Group, to direct management in the province.

Table 1 Summary of key efficacy and safety findings on PDT for localised, inoperable endobronchial cancer

Abbreviations used: PDT – photodynamic therapy			
Study details	**Key efficacy findings**	**Key safety findings**	**Comments**
Maziak DE et al (2004) Systematic review n = 9 studies, n = 444 cases Canadian review of international studies Studies included Edell (1987) Ono (1992) Furuse (1993) Imamura (1994) Cortese (1997) Kawahara (1997) abstract Kato (1998) Lam (1998) Patelli (1999) Searches up to October 2002 Treatment of non-small-cell lung cancer, with early-, mixed- and late-stage cancer reported separately All studies included combination with other therapy for the treatment of lung cancer, and number of PDT treatments varied across studies Most treated patients were considered medically inoperable or had refused surgery, these were not analysed separately Outcomes considered included: survival, response rate, toxicity (or symptoms of palliation for late stage).	**Response rate of treated lesions** The method and timing of response assessment varied across studies The response rate following PDT ranged from 31% (12/39) to 85% (50/59) of lesions Subgroup analysis of response as defined by tumour size was attempted in four studies. These found that response rates were higher where tumours lengths were less than 2 cm, equal to 1cm, or had surface area equal to $3cm^2$ **Survival** Five-year survival rates were reported in five of the included studies with early stage disease patients. Survival ranged from 43% (15/36) of patients with poor pulmonary or cardiac function, to 72% (15/21) of patients who were surgical candidates	Eight studies reported on adverse events **Toxicity** All reported reactions relating to photosensitivity, mostly mild to moderate symptoms. Very severe toxicities occurred in a small number of patients **Adverse events** One study reported fatal haemoptysis within 1 month of treatment in 8% (3/38) This was likely to be related to tumour necrosis and bleeding Hypercapnic respiratory failure requiring mechanical ventilation was required in 5% (2/38) and 4% (1/24) of patients in two case series Mild to moderate adverse pulmonary events were commonly reported Productive cough in the short term was reported in two studies	Predetermined inclusion and exclusion criteria used. RCTs or non-controlled prospective studies. Adequate searching strategy, and reference lists of selected items cross checked. Single selection and extraction of data. For many included studies trial methodology not described in detail. No study quality assessment undertaken.

Abbreviations used: PDT – photodynamic therapy

Study details	Key efficacy findings	Key safety findings	Comments
Follow-up times varied between studies Erickson L et al (2004) [5] Systematic review n = 6 studies, n = 355 cases Canadian review of international studies Studies included Diaz-Jimenez (1999) Pass (1997) Shikowitz (1998) Moskal (1998) Moghissi (1999) McCaughan (1999) Searches up to December 2003 Document considers PDT for oesophageal, bladder, and lung cancers, but data reported separately Data relating to inoperable advanced lung cancer is reported separately Concomitant treatment and length of follow-up are not always reported	**Overall conclusions** The use of PDT for endobronchial metastases has been shown to be beneficial in reducing obstructions and improving quality of life No survival outcomes are reported Further studies, especially controlled trials, must be conducted before the use of PDT can be justified for all lung cancer indications, or shown to have any comparative advantage over other available treatments	None reported	Limited search strategy, updating to existing reviews from 1997 onwards. However, conference abstracts hand searched, and references of selected studies were searched. Included studies were graded according to the Canadian guide to clinical preventative health care. No details given on single or duplicate study selection or data abstraction. No details of study quality assessment are given. Authors state that, owing to heterogeneity of study comparisons and outcomes, no quantitative analyses were attempted.

Abbreviations used: PDT – photodynamic therapy

Study details	Key efficacy findings	Key safety findings	Comments
Kato H (1996)[2] Case series Japan n = 75 cases, with 95 lesions All cases bar one were squamous cell carcinoma. Each patient had a measurable lesion in two dimensions Patients included because of refusal of surgery, tumour inoperability due to poor organic function, serious concomitant disease, or age of patient Age = 66yrs, male = 99%, tumour size 0.88 cm (mean) Endoscopic appearance, superficial 75% (71/95), nodular 17% (16/95), polypoid 8%(8/95) 2.0 mg/kg of photofrin administered and 48 hours later excimer dye laser used Evaluation by endoscope, roentgenograph, cytology, and histology at 1 month Complete remission determined as no tumour found by biopsy of brushing cytology for a minimum 4 weeks Partial remission defined as a reduction of tumour volume > 50% Follow-up to mean 60 months	**Tumour destruction** Complete remission 83.2% (79/95 lesions) Partial remission 16.8% (16/95) **Survival** Recurrence of tumour occurred in 6.3% lesions (6/95) 68% of patients (51/75) were disease free from 5 to 176 months Survival was 68.4% at 60 months **Subgroup analysis** Complete remission was seen in 94.2% of lesions < 1 cm, but only in 53.8% of lesions > 1 cm (p = 0.00001) Distal margin visibility was not significantly related to remission	None reported	Long experience using the technology at the study centre. Patient selection method not stated. Patients who were resected or autopsy cases had tumour assessed histologically.

Abbreviations used: PDT – photodynamic therapy

Study details	Key efficacy findings	Key safety findings	Comments
Furuse K (1993)[3] Case series Japan n = 51 with 61 lesions. 2 cases broke protocol and were not included in analysis Age = 69 years, male = 95%, TisN0M0 = 33%, T1N0M0 = 67% Patients inoperable due to synchronous double lung cancer, refusal, COPD or other respiratory comorbidity, or previous resection of primary lung cancer Histologically proven lung cancer with superficial thickening or protrusion as assessed by endoscope All lesions in the subsegmental or larger bronchi Photofrin II at 2 mg/kg and argon or excimer dye laser used at 48 hours after dye injection Follow–up evaluation by endoscope, roentgenograph, cytology, and histology Follow-up for 2 years	**Tumour destruction** Complete remission 84.8% (50/59 lesions) Partial remission 10.1% (6/59) No change 5.0% (3/59) **Survival** Of the tumours with complete remission 10% (5/50) had local recurrence outside of the photo-radiated field Survival was 88.2 % at 20.2 months Complete remission determined as no tumour found by biopsy of brushing cytology for a minimum 4 weeks Partial remission defined as a reduction of tumour volume > 50%	**Toxicity** WHO grade 2 toxicity were generally transient Pulmonary toxicity WHO grade 1 73.1% (38/51), WHO grade 2 7.7% (4/51) **Adverse events** Cases were reported of allergic reaction, and sunburn following photofrin II injection	Potentially some of the same cases as Kato. Subgroup analysis showed no difference in remission rates between lasers used. Local recurrence of tumours may have been because the distal tumour margin was not clearly visible and these lesions were not completely irradiated. Method of laser energy delivery and dose rate not yet defined.

Abbreviations used: PDT – photodynamic therapy

Study details	Key efficacy findings	Key safety findings	Comments
Patelli M (1999)[1] Case series Italy n = 23 with 26 lesions Early-stage central type squamous cancers, confirmed by bronchoscopy, with negative CT scans Lesion diameter ranged from 5 to 20 mm 87% (20/23) of the cases inoperable due to age or poor pulmonary or cardiac function. 13% (3/23) patients had refused surgical resection 5 mg/kg body weight of haematoporphyrin injected, photo-radiation after 2 to 3 days with either an argon laser-pumped dye laser or a gold vapour laser Tumour response evaluated at 1 month following PDT Follow-up ranged from 3 months to 10 years	**Tumour destruction** Complete remission (no evidence of tumour endoscopically or histologically) 62% (16/36 lesions) Partial remission (significant reduction in tumour size) 38% (10/26) No change 0% No differences were found between the results using the two different laser types **Survival** During follow-up to data, one case with complete remission at 1 month hate a late relapse at 10 years with neoplastic infiltration of the tracheal carina with nodal involvement.	None reported	No detail of median follow-up. Three cases were treated with brachytherapy following PDT because of remaining tumours, and not explicitly excluded from analysis. Different laser systems used during the series. No analysis of effect of tumour size.

Validity and generalisability of the studies

- Most studies don't define early-stage cancer, and others include a range of endobronchial cancer patients without separate analysis of early-stage patients.
- Most studies represent a carefully selected patient cohort rather than a consecutive sample.
- Some studies include patients who were suited to surgery but chose PDT instead.
- All studies include the use of additional treatment modalities at some point, which may impact on the efficacy profile of the PDT intervention.

Specialist advisors' opinions

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

.

- There may be a difference in support for PDT when used in endobronchial carcinoma in situ, compared with use where there is visible disease and micro-invasive histology, at which point the question becomes where PDT fits amongst other possible treatment modalities.
- The effective dosage has yet to be confirmed.
- There are no comparative trials with long-term outcomes.
- Common adverse events have been reported to include skin photosensitivity and tissue necrosis leading to bleeding or fistula formation.
- There are few other effective treatments for early stage lung cancer, and PDT may be used as a first option because it does not preclude other modalities as subsequent treatment.
- The likely impact of the procedure is low - few patients will require treatment because identifying early cases is difficult.
- Training requirement was not very important but competence with the equipment involved is required.

Issues for consideration by IPAC

Both systematic reviews are Canadian based. Photofrin is licensed for use in non-small-cell lung cancer. NICE has previously issued guidance on the use of PDT in advanced bronchial carncinoma (IPG 087).

References

(1) Patelli M, Lazzari AL, Poletti V, et al. Photodynamic laser therapy for the treatment of early-stage bronchogenic carcinoma. *Monaldi Archives for Chest Disease* 1999; 54(4):315-8.

(2) Kato H, Okunaka T, Shimatani H. Photodynamic therapy for early stage bronchogenic carcinoma. J*ournal of Clinical Laser Medicine & Surgery* 1996; Vol. 14(5):-238.

(3) Furuse K, Fukuoka M, Kato H, et al. A prospective phase II study on photodynamic therapy with photofrin II for centrally located early-stage lung cancer. The Japan Lung Cancer Photodynamic Therapy Study Group. J *Clin Oncol* 1993; 11(10):1852-1857.

(4) Maziak DE, Markman BR, MacKay JA, et al. Cancer Care Ontario Practice Guidelines Initiative Lung Cancer Disease Site Group. Photodynamic therapy in nonsmall cell lung cancer: a systematic review. [Review] [21 refs]. *Annals of Thoracic Surgery* 2004; 77(4):1484-91.

(5) Erickson L. *Assessment of photodynamic therapy using porfimer sodium for esophageal, bladder and lung cancers.* (2004). Agence d'Evaluation des Technologies et des Modes d'Intervention en Sante (AETMIS).

Appendix A Literature search for photodynamic therapy for localised, inoperable endobronchial cancer

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

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

1. photochemotherapy/
2. photochemotherapy.tw.
3. photodynamic therapy.tw.
4. pdt.tw.
5. argon-dye laser system$.tw.
6. argon-dye lazer system$.tw.
7. $dye laser system.tw.
8. photosensiti?er$.tw.
9. dihematoporphyrin ether/
10. dihematoporphyrin ether.tw.
11. porfimer sodium.tw.
12. photofrin.tw.
13. dhe.tw.
14. exp hematoporphyrin derivative/
15. hematoporphyrin derivative.tw.
16. hpd.tw.
17. fiber optic endoscop$.tw.
18. fibre optic endoscop$.tw.
19. micro?lens fiber.tw.
20. micro?lens fibre.tw.
21. cylindrical diffuser.tw.
22. exp lung neoplasms/
23. lung cancer$.tw.
24. lung neoplasm$.tw.
25. lung tumo?r$.tw.
26. (hilar adj5 lung carcinoma$).tw.
27. endobronchial cancer$.tw.
28. bronchial neoplasms/
29. *LASERS/du, tu [Diagnostic Use, Therapeutic Use]
30. fiber?optic endoscop$.tw.
31. fibre?optic endoscop$.tw.
32. or/1-21,29,30-31
33. or/22-28
34. 32 and 33
35. limit 34 to human
36. carcinoma, squamous cell/
37. lung.tw.
38. 36 and 37
39. 33 or 38
40. 32 and 39
41. limit 40 to human
42. *Carcinoma, Non-Small-Cell Lung/
43. 39 or 42
44. 32 and 43
45. limit 44 to human