NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of photodynamic therapy for early stage oesophageal cancer

Oesophageal cancer usually arises in the lining of the gullet. Photodynamic therapy firstly involves the administration of a medicine that has an affinity for cancerous cells, and is sensitive to special type of light. A source of light is then inserted in the gullet after the administration of the photosensitive medicine, to destroy cancer 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 May 2006

Procedure name

- Photodynamic therapy for early stage oesophageal cancer
- PDT for early stage oesophageal cancer

Specialty societies

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

Description

Indications

Oesophageal cancer or cancer of the gullet is a common cancer which is increasing in incidence, and is often discovered incidentally. The two most common histological types of oesophageal cancer are squamous cell carcinomas and adenocarcinomas. Adenocarcinoma is strongly associated with Barrett's oesophagus in which malignant changes occur in an unstable dysplastic mucosa. The cancer causes symptoms of difficulty in swallowing with subsequent weight loss, hoarseness or chronic cough, and retrosternal or posterior chest pain. The extent of depth of penetration of the tumour determines the tumour stage and tumours that are superficial or have only penetrated the submucosa can be defined as early stage cancer.

Current treatment and alternatives

As is the case for all cancers, treatments can have either a curative or palliative intent. Among patients treated with curative intent, oesophagectomy (surgical removal of the oesophagus) is the most radical treatment option for early stage oesophageal cancer. However, oesophagectomy is a major operation with the potential for morbidity and mortality. Some patients may also be unfit for oesophagectomy and others may be reluctant to accept this treatment.

Less invasive treatments include laser ablation, radiation therapy, chemotherapy and photodynamic therapy (PDT). All aim to ablate the specialised columnar epithelium which is affected by pre-malignant (dysplasia) and malignant change and to promote the regeneration of normal squamous epithelium.

What the procedure involves

Photodynamic therapy involves the administration of a photosensitising agent by intravenous injection. The agent is then activated by the application of light to the selected area, usually with a low-power laser. The agent absorbs the energy from the light, and this results in the formation of high-energy oxygen molecules. These molecules interact with the tissue leading to tumour necrosis through a photochemical effect. Treatment can be performed on an outpatient basis and is usually undertaken under intravenous sedation.

Skin photosensitivity, as a result of the uptake of the sensitiser to the skin, is quite long lasting and patients are recommended to avoid exposure to bright light from any source, especially direct sunlight. The labelling of the photosensitiser used in this procedure includes information on precautions that should be taken to avoid exposure of skin and eyes to bright light. A number of different photosensitising agents have been used in PDT for oesophageal cancer.

Efficacy

Tumour response

Some studies reported results for PDT as monotherapy and some in combination with other treatment modalities making comparison of outcomes difficult.

The definition of complete response/remission varies between the studies included, but it was most commonly defined as no evidence of tumour on endoscopy and negative findings on histological examination. Across case series complete response was achieved in 37% (23/62)[1], 75% (18/24)[2], 81% (43/53)[3], 97% (32/33)[4] and 100% (18/18)[5] of patients. However, the follow-up time varies between studies, and some patients received repeat PDT sessions. Where reported separately for subgroups, the response rate was 67% (22/33) in stage T1a tumours and 91% (20/22) among *in situ* squamous cell carcinomas[6].

Survival

In one case series 5-year disease-specific survival was 72% in 56 patients treated with PDT as monotherapy[3], and in another case series of 21 patients mean local progression-free survival was 60 months[1]. In a case series of 38 patients, nine of whom received repeat PDT sessions, mean disease-free survival was 32 months[6]. In another case series 54% (13/24) of patients were alive without recurrence at a mean follow-up of 21 months[2]. Finally, in a case series of 18 patients treated with PDT mean overall survival was 60.5 months[5].

Safety

Oesophageal stenosis or stricture following PDT occurred in 7% (3/41)[1], 8% (2/24)[7], 11% (2/18)[5], 13% (5/38)[6], 25% (6/24)[2] and 35% (43/123)[3] of patients, although the photosensitiser and light source varied between studies. In one case series chronic stenosis was reported to have occurred in 4% (5/123) of patients[3].

One case series reported the complication of oesophago-tracheal fistula following PDT in 8% (2/24) of patients[7], and in another series this occurred in 8% (3/38) of patients[6].

The most widely reported complication reported in relation to PDT for early oesophageal cancer was skin photosensitivity, which was reported in 0% (no incidence in 24 patients)[2], 8% (5/62)[1] and 13% (16/123)[3] of patients. Where specifically reported second-degree sunburn occurred in 3% (1/38)[6], 5% (5/102)[5], and 13% (3/24)[7] of patients. However, the timing of adverse events due to skin photosensitivity following administration of the photosensitiser was not always recorded.

Literature review

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to PDT for early stage oesophageal cancer. Searches were conducted via the following databases, covering the period from their commencement to 2 May 2006. 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 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 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, laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising methodology.
Patient	Patients with early stage oesophageal 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 seven case series[5,1,7,3,6,4,2].

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[8].

Existing reviews on this procedure

An update to the Institute for Clinical Systems Improvement technology assessment report was published in 2002. This is included in appendix A.

Related NICE guidance

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

IP overview: Photodynamic therapy for early stage oesophageal cancer

Interventional procedures

- Photodynamic therapy for high-grade dysplasia in Barrett's oesophagus
- Thorocoscopy-assisted oesophagectomy.

Technology appraisals

- None

Clinical guidelines

- None

Public health

- None

Table 2 Summary of key efficacy and safety findings on photodynamic therapy for early stage oesophageal cancer

Abbreviations used: CT, computed tomography; PDT, photodynamic therapy; SE, standard error; UICC = International Union Against Cancer.

Study details	Key efficacy findings	Key safety findings	Comments
Sibille A (1995)[3] **Case series** France **n = 123 (n = 56 PDT monotherapy)** Study period: 1983–1991 Population: Mean age = 66 years, male = 88% Indications: Patients with 0.5–4 cm diameter oesophageal tumours with no extension beyond the muscular layer or adjacent organs invasion on CT scan. Japanese Society for Esophageal Diseases class 0 (superficial cancer) or 1 (protruding tumour presumed T1 or T2). n = 3 patients had previous surgical resection, n = 27 previous radiotherapy Technique: Photosensitiser – haematoporphyrin derivative (various preparations) intravenously, and dye laser irradiation at 48–72 hours, using a flexible quartz fibre for 6–20 minutes. PDT as monotherapy in 56 patients, or in combination with radiotherapy or chemotherapy in 67 patients. Repeat treatment for incomplete initial response in 16 patients **Follow-up = 24–36 months** Disclosure of interest: Not stated	**Tumour response** A complete response was defined as a normal or cicatricial mucosal endoscopic pattern with negative biopsies at tumour site and no evidence of tumour on CT or ultrasonography. Complete response achieved in 87% (99/114) of patients (9 patients were lost to follow up) . Local recurrence occurred in 36% (36/99) of patients at between 12 and 18 months. The complete response rate was similar among patients with squamous cell cancer (88% [84/96]) and those with adenocarcinoma (89% [16/18]). Among patients treated with PDT alone (as opposed to combination with another therapy) the complete response rate was 81% (43/53). There was no significant difference in complete response rates between patients treated for uT1 and uT2 stage oesophageal cancer (p > 0.05). **Survival** The 5-year survival rate was 25% (± 6% SE) among 123 patients, and disease-specific survival was 74% (± 5% SE). Overall survival among patients treated with PDT alone was 28% (± 8% SE) and the disease-specific survival was 72% (± 8%).	**Secondary cancer** A second tumour site was found in the oesophagus in 2% (2/104) of patients treated for squamous cell cancer. A metachronous cancer at a different body site was found during follow-up in 11% (11/104) of patients who were treated for squamous cell cancer. Metastases developed in 5% (1/19) of patients treated with PDT for adenocarcinoma. **Treatment complications** Complication — Rate Oesophageal stenosis requiring dilatation — 35% (43/123) Chronic oesophageal stenosis altering depth of oesophageal wall — 4% (5/123) Photosensitisation — 13% (16/123) Postoperative complications Chronic severe dysphagia/oesophagomediastinal/bronchial fistula — 6% (7/123) These symptoms were related to tumour progression and not a consequence of the initial PDT treatment, and were treated by stenting.	Retrospective study. Recurrences were treated by second PDT session (28 instances), laser therapy, chemotherapy or surgery. Rates of these interventions not stated. 2 patients had type III ulcerated cancer. Different classification system introduced during the study period. 9 patients lost to endoscopic follow-up to determine tumour response. Not clear whether period before recurrence is measured from time of treatment or time after first evaluation at 6 months. Not clear whether disease-specific survival in those who died of associated illness necessarily represents a cancer cure.

Abbreviations used: CT, computed tomography; PDT, photodynamic therapy; SE, standard error; UICC = International Union Against Cancer.

Study details	Key efficacy findings	Key safety findings	Comments
Corti L (2000)[1] **Case series** Italy **n = 62 (n = 21 PDT monotherapy)** Study period: not stated Population: Mean age n = 66 < 60 years; n = 36 > 60 years, male = 89% Indications: Patients with oesophageal tumours of up to 3 cm diameter who were medically inoperable or opted against operation for personal reasons. Stage Tis n = 18, T1 n = 30, T2 n = 7, recurrence post surgery n = 7. Squamous cell carcinoma n = 53, adenocarcinoma n = 9 Technique: Photosensitiser – haematoporphyrin derivative intravenously, and dye laser irradiation at 48–72 hours, using optical cylindrical fibres, at 300 J/cm. PDT as monotherapy in 21 patients, or in combination with radiotherapy in 41 patients. Repeat treatment was undertaken in patients with partial or non-response at 40 days follow-up. If 4-monthly follow-up identified recurrent disease, radiotherapy or surgery was undertaken. **Median follow-up = 32 months** Disclosure of interest: Not stated	**Tumour response** A complete response was defined as a no evidence of lesion on endoscopy and CT scan and a negative histological examination. Partial response was defined as a 50% shrinkage of the lesion, and non-response /minimal response as stable or progressive disease. Complete response achieved in 37% (23/62) of patients treated with PDT alone and in 82% (51/62) of patients treated with a combination of PDT and radiotherapy. The complete response rate was statistically higher in patients with Tis/T1 lesions (44% [21/48]) than stage T2 (28% [2/7]) and recurrent tumours (0% [0/7]) (p = 0.04). **Survival** Among the 23 patients who had complete response to PDT as monotherapy, median overall survival was 50 months, and local progression median free-survival was 60 months. There was no local tumour response in 52% (12/23) of patients treated with PDT alone to final follow-up.	**Treatment complications** There was no incidence of tissue necrosis or perforation during PDT therapy or subsequent radiotherapy. Complication — Rate Grade 1 photosensitivity — 8% (5/62) Oesophageal stenosis — 7% (3/41)* Tracheo-oesophageal fistula — 2% (1/41)* * Among patients who has both PDT and radiation therapy.	Considerable additional therapy employed in patients with recurrent disease. Survival outcomes for responders analysed separately. Treatment protocol makes evaluation of safety and efficacy of PDT as monotherapy difficult. No details provided of operator experience. Case accrual not described.

Abbreviations used: CT, computed tomography; PDT, photodynamic therapy; SE, standard error; UICC = International Union Against Cancer.

Study details	Key efficacy findings	Key safety findings	Comments
Radu A (2005)[6] **Case series** Switzerland **n = 38 (55 tumours)** Study period: Not stated Population: Not stated Indications: Patients with squamous cell carcinoma lesions (1–6 cm length and 60° to 200° radial extension). Stage Tis n = 22, T1a n = 33, secondary malignancies to head or neck n = 38 Technique: Photosensitiser – Photofrin or Foscan given intravenously, and dye laser irradiation using circumferential cylindrical light distributors (windowed in later cases), at 100–180 J/cm^2. Repeat PDT was used in 9 patients **Follow-up = Not stated** Disclosure of interest: Not stated	**Tumour response** Endoscopy, biopsies and abrasive cytology were performed at 3 months follow-up and then twice yearly. No definition given for complete response. A complete response with no recurrence was achieved in 76% (42/55) of tumours. The complete response rate was 91% (20/22) for in situ squamous cell carcinoma and 67% (22/33) for stage T1a lesions. Complete response rates did not vary between the different photosensitisers used. **Survival** The mean disease-free follow-up was 32 months. Overall survival not reported.	**Secondary treatment** Oesophagectomy was performed in 5 cases where PDT failed to cure the tumours. **Treatment complications** Oesophago-tracheal fistula (requiring surgery) 8% (3/38) Oesophageal stenosis (requiring dilatation) 5% (2/38) High-grade fever 3% (1/38) Pleural effusion 3% (1/38) The above two complication responded to antibiotics Skin reaction 8% (3/38) Second degree sunburn 3% (1/38)	No details of case accrual given. Patient demographic characteristics are not described. Length of follow-up (mean or range) was not given. Case selection was not described. Outcomes of patients treated with repeat therapy are not reported separately. Authors state that selectivity of photosensitisers is controversial, and the light delivery method may affect complication rates.

Abbreviations used: CT, computed tomography; PDT, photodynamic therapy; SE, standard error; UICC = International Union Against Cancer.			
Study details	**Key efficacy findings**	**Key safety findings**	**Comments**
Hayata Y (1996)[4] **Case series** Japan – 5 participating centres **n = 33** Study period: 1980–1995 Population: Not stated Indications: Patients with superficial oesophageal cancer who were inoperable or refused surgery in the first phase of the study, or subsequently those with histologically confirmed cancer with superficial appearance on endoscopy with tumour size < 4 cm^2 Technique: Photosensitiser – various preparations and dye laser irradiation at 48–72 hours, at a dose of between 60 J/cm^2 and 600 J/cm^2 All cases received PDT monotherapy **Mean follow-up = Not stated** Disclosure of interest: Study part supported by a grant from government and academic institutions.	**Tumour response** A complete remission was defined as no evidence of lesion on endoscopy and negative histological examination for at least 4 months. Complete remission was achieved in 97% (32/33) of patients. Recurrence occurred in one patient 27 months following PDT. **Survival** 24 patients alive at time of last follow-up, 5 survived to 5 years or more. Of the 6 patients treated who had tumour size greater than 3 cm in diameter 3 died of disseminated disease.	No safety outcomes reported.	Study describes use of PDT in lung and oesophageal cancer but results reported separately. No details of case accrual given. Patient demographic characteristics are not described. Length of follow-up (mean or range) was not given. Case selection criteria changed during phases of the study. Baseline demographic or clinical characteristics of patients are not provided. Authors state that maximum diameter of lesions that should be treated by PDT is 3 cm.

Abbreviations used: CT, computed tomography; PDT, photodynamic therapy; SE, standard error; UICC = International Union Against Cancer.

Study details	Key efficacy findings	Key safety findings	Comments
Savary J-F (1998)[7] **Case series** Switzerland **n = 24 (31 tumours)** Study period: 1984 –1995 Population: Male = 92%, age = 56 years Indications: Patients with squamous cell carcinoma lesions, mean diameter 2.8 cm Stage Tis n = 11, T1a n = 20 Technique: Photosensitiser – various preparations given intravenously, and dye laser irradiation using a variety of lasers via circumferential cylindrical light distributors at 72–96 hours PDT as monotherapy **Mean follow-up = 2 years** Disclosure of interest: Not stated	**Tumour response** A complete response was defined as no macroscopic and microscopic evidence of carcinoma, partial response was described as no visible tumour on endoscopy but positive histological evaluation, and no response was described as tumour visible on endoscopy and positive histological evaluation. Complete response was achieved in 94% (29/31) of the tumours. Tumour recurrence occurred in 10% (3/31) of tumours treated, at between 7 and 9 months follow-up. There was no recurrence in 84% (26/31) tumours at a mean follow-up of 2 years.	**Secondary treatment** Oesophagectomy was performed in 2 patients in whom PDT failed to cure the tumours and 1 patient in whom an oesophago-tracheal fistula occurred. **Treatment complications** Oesophago-tracheal fistula 8% (2/24) Oesophageal stenosis (requiring dilatation) 8% (2/24) Second degree sunburn 13% (3/24)	Overlap with patient population included in Radu (2005); more details given in this report on a small number of patients. 8 patients were lost to follow-up after the 6-month follow-up, due to death n = 4 (progression of primary ENT cancer or cardiac arrest), subsequent oesophagectomy n = 3, or refusal n = 1. Some outcomes relate to tumours treated as and some to patients treated. Significant variation in technique (both photosensitiser and laser used) within the series. No details given of methods used to stage the tumours. Authors state that some cases where recurrence occurred may have been understaged.

Abbreviations used: CT, computed tomography; PDT, photodynamic therapy; SE, standard error; UICC = International Union Against Cancer.

Study details	Key efficacy findings	Key safety findings	Comments
Maunoury V (2005)[2] **Case series** France **n = 24** Study period: 2004 –2004 Population: Male = 96%, age = 60 years Indications: Patients with oesophageal cancer considered superficial on endoscopic ultrasonography, unsuitable for other treatment on multidisciplinary team agreement. Stage T1 n = 20, T2 n = 4, all patients staged N0. Recurrent/residual/second metachronous cancer after previous treatment n = 13, Squamous cell carcinoma n = 19, adenocarcinoma n = 4 Technique: Photosensitiser – Photofrin given intravenously, and diode laser irradiation using diffusing quartz fibre, at 250–300 J/cm. Under general anaesthetic **Mean follow-up = 21 months** Disclosure of interest: None declared	**Tumour response** No tumour was visible on endoscopic assessment following PDT in 75% (18/24) of patients. Treatment failures occurred in 13% (3/24) of patients. Oesophageal recurrences occurred in 13% (3/24) of patients at up to 36 months follow-up. **Survival** 54% (13/24) of patients were alive without recurrence at a mean follow up of 21 months.	**Treatment complications** There was no incidence of skin photosensitisation during PDT. Complication — Rate Fibrous stenosis requiring dilatation — 25% (6/24) Persistent severe dysplasia — 4% (1/24) Delayed discharge due to thoracic pain and fever — 8% (2/24) There was 1 death from oesophageal necrosis and perforation of the main left bronchus 8 weeks following PDT.	The light dose administered did not significantly affect outcomes. Case selection not well defined. Not clear whether repeat PDT was given in any patient. Assumed PDT monotherapy, but this is not explicitly stated. T2 stage defined as no invasion of tumour beyond the muscularis propria. Operator experience not described.

Abbreviations used: CT, computed tomography; PDT, photodynamic therapy; SE, standard error; UICC = International Union Against Cancer.

Study details	Key efficacy findings	Key safety findings	Comments
Moghissi K (2003)[5] **Case series** UK **n = 18** Study period: Not stated Population: Male = 67%, age = 74 years. Indications: Patients with superficial squamous cell or adenocarcinoma cancers up to 0.5 cm presenting no obstruction to endoscope. Stage Tis or TI.. 4 patients had previous treatment with dilatation or resection Technique: Photosensitiser – Photofrin given intravenously followed at 24–72 hours by laser illumination via flexible fibreoptic instrument with surface/intraluminal application, under general anaesthetic. A mean of 1.4 treatments per patient (across both early and advance disease patients) **Mean follow-up = not stated** Disclosure of interest: Not stated	**Tumour response** A complete response was defined as absence of the tumour macroscopically at endoscopy and a negative histological examination. Partial response was defined as a 50% shrinkage of the lesion. Complete remission was recorded in 100% (18/18) patients, 1 patient having repeat PDT. **Survival** 3 patients died at between 3 and 36 months of follow-up, 2 from unrelated causes. Mean overall survival 60.5 months (± 8.7 months). 5-year survival in a series of patients with stage T1 cancer treated by surgical resection by the same author was 72%. **Other** All patients stated that they were satisfied with their treatment. Dysphagia was evaluated at 6–8 weeks after PDT therapy Dysphagia grade (n = 18) / Pre PDT / Post PDT 0–I / 17 / 16 II / 0 / 2 III / 1 / 0 IV / 0 / 0	**Treatment complications** There was no procedure-related mortality. Most complication rates relate to patients treated for both early and advanced stage oesophageal cancer. Complication / Rate n = 102 Skin photosensitivity - sunburn / 5% (5/102) Chest pain due to oesophagitis / 10% (10/102) Esophageal stricture requiring dilation / 8% (8/102) Esophageal stricture requiring dilation Among early stage oesophageal cancer patients / 11% (2/18)	Baseline clinical and demographic data not compared between PDT group and surgical resection group. Consecutive patients treated with PDT. Staging using UICC criteria. Not all patients treated by one surgeon.

Validity and generalisability of the studies

- Lack of standardisation in staging and different inclusion criteria across studies makes comparisons of outcomes difficult.
- Some studies analysed results by patients and some by number of tumours treated.
- Some studies reported results on PDT as monotherapy, and some used PDT in combination with a range of other treatments.
- A proportion of patients in most studies were treated with repeat PDT.
- No controlled or randomised controlled trials are available comparing PDT with other treatment modalities.

Specialist advisors' opinions

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

Dr L Lovat, Mr G Fullerton, Prof. H Barr, Prof. K Moghissi, Mr P McCulloch, Mr R Ackroyd

- The proposed advantages of PDT are long-term survival with cancer cure, improvements in dysphagia if present, and good quality-of-life outcomes.
- Advisors were split (three each) in their opinions whether this procedure is established practice or novel and of uncertain safety and efficacy.
- Reported and anecdotal adverse events include death (two cases in treatment of Barrett's oesophagus), photosensitivity, stricturing, acute neuropathy, chest pain, low-grade fever, oesophageal or lung perforation, nausea, atrial fibrillation, congestive heart failure, skin reaction and recurrence of cancer/progression.
- Additional theoretical adverse events may include pleural effusions, hypotension, pneumonia, oesophagitis and haemorrhage.
- Some advisors suggest that adverse events may be photosensitiser-dependent.
- Randomised controlled trials against other treatments would be useful, but one advisor suggested these are unlikely to be forthcoming.
- PDT is one of a range of treatment options, and it may be used as a combination therapy, for example with mucosal resection.
- If the disease is localised, a local treatment method may be effective.
- PDT may be particularly useful for patients unsuitable for surgical resection.
- Training is required in laser safety and the wavelengths required for different photosensitisers, and treatment is likely to be provided by specialist units with relevant experience.
- Patients should be carefully counselled with regard to photosensitivity.
- The Yorkshire laser centre is establishing a national registry of PDT procedures in major specialties.
- Advisors suggested the following audit criteria may be useful: survival; development of locally advanced or metastatic disease; recurrence rates,

swallowing ability; quality-of-life criteria (EORTC QLQ-C30) and patient satisfaction; complications including hypotension, pneumonia, nausea, constipation, gastrointestinal bleeding, atrial fibrillation, heart failure, pain; rates of photosensitivity and stricture (medium to long term); and time to re-intervention.

Issues for consideration by IPAC

- Prognosis is poor for patients with secondary oesophageal cancer even if superficial.

References

1 Corti L, Skarlatos J, Boso C et al. (1-5-2000) Outcome of patients receiving photodynamic therapy for early esophageal cancer. *International Journal of Radiation Oncology, Biology, Physics* 47: 419-424.

2 Maunoury V, Mordon S, Bulois P et al. (2005) Photodynamic therapy for early oesophageal cancer. *Digestive & Liver Disease* 37: 491-495.

3 Sibille A, Lambert R, Souquet JC et al. (1995) Long-term survival after photodynamic therapy for esophageal cancer.[see comment]. *Gastroenterology* 108: 337-344.

4 Hayata Y, Kato H, Furuse K et al. (1996) Photodynamic therapy of 168 early stage cancers of the lung and oesophagus: A Japanese multi-centre study. *Lasers in Medical Science* Vol. 11: 259.

5 Moghissi K and Dixon K. (2003) Photodynamic therapy (PDT) in esophageal cancer: a surgical view of its indications based on 14 years experience. *Technology in Cancer Research & Treatment* 2: 319-326.

6 Radu A, Grosjean P, Jaquet Y et al. (2005) Photodynamic therapy and endoscopic mucosal resection as minimally invasive approaches for the treatment of early esophageal tumors: Pre-clinical and clinical experience in Lausanne. *Photodiagnosis & Photodynamic Therapy* Vol. 2: 43.

7 Savary JF, Grosjean P, Monnier P et al. (1998) Photodynamic therapy of early squamous cell carcinomas of the esophagus: a review of 31 cases. *Endoscopy* 30: 258-265.

8 Institute for Clinical Systems Improvement. (2002) Photodynamic therapy for head and neck, tracheobronchial, and esophageal cancer.

Appendix A: Additional papers on photodynamic therapy for early stage oesophageal cancer not included in summary table 2

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 title	Number of patients/ follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Institute for Clinical Systems Improvement (2002) Photodynamic therapy for head and neck, tracheobronchial, and esophageal cancer. Bloomington, MN: Institute for Clinical Systems Improvement (ICSI).	Systematic review. n = 150 (early oesophageal cancer). Follow-up = ?	Early stage oesophageal cancer has been shown to respond to PDT. Complete response rates range from 40% to 81%.	Search to 2002 only.
Messmann H, Szeimies RM, Baumler W, et al. (1997) Enhanced effectiveness of photodynamic therapy with laser light fractionation in patients with esophageal cancer. *Endoscopy* 29: 275–80.	Case series. n = 4. Follow-up = to 32 months.	Complete remission following continuous light PDT in 2/3 cases, and 3/3 cases following fractionated PDT (some repeated treatments).	Have larger case series in table 2.
Mitton D, Ackroyd R (2004) Photodynamic therapy in oesophageal carcinoma: an overview. *Photochemical & Photobiological Sciences* 3: 839–50.	Review. n = 399 in 24 case series. Follow-up = ?	An established role in the management of precancerous and malignant conditions.	Non-systematic review. Some overlap in cases with those included in table 2.
Okunaka T, Kato H, Conaka C, et al. (1990) Photodynamic therapy of esophageal carcinoma. *Surgical Endoscopy* 4: 150–3.	Case series. n = 6. Follow-up = ?	Complete remission in 4 of 6 cases.	Have larger case series in table 2. Come cases in combination .
Spinelli P, Dal Fante M, Mancini A (1992) Current role of laser and photodynamic therapy in gastrointestinal tumors and analysis of a 10-year experience. *Seminars in Surgical Oncology* 8: 204–13	Case series. n = 12 (early oesophageal cancer). Follow-up = 27 months.	Results for early stage oesophageal cancer not reported separately.	Have larger case series in table 2.

Appendix B: Related published NICE guidance for photodynamic therapy for early stage oesophageal cancer

Guidance	Recommendation
Interventional procedures	**IPG082 Photodynamic therapy for high-grade dysplasia in Barrett's oesophagus** Current evidence on the safety of photodynamic therapy for high-grade dysplasia in Barrett's oesophagus appears adequate to support the use of this procedure. Photodynamic therapy appears efficacious in downgrading dysplasia in Barrett's oesophagus, when used for the treatment of high-grade dysplasia (a premalignant lesion). However, its efficacy in preventing the progression of Barrett's oesophagus to invasive cancer is not clear. Clinicians wishing to undertake photodynamic therapy for high-grade dysplasia in Barrett's oesophagus should take the following actions: • Inform the clinical governance leads in their trusts. • Inform patients, as part of the consent process, about the uncertainty of influencing their long-term prognosis and provide them with clear written information. Use of the Institute's Information for the Public is recommended. • Audit and review clinical outcomes of all patients having photodynamic therapy for high-grade dysplasia in Barrett's oesophagus. Publication of long-term efficacy outcomes will be useful in reducing the current uncertainty. Randomised trials are in progress and clinicians are encouraged to consider entering patients into these (www.cancerhelp.org.uk/trials/trials/default.asp). The Institute may review the procedure on publication of further evidence. This guidance is limited to the procedure using pharmaceuticals licensed for photodynamic therapy of oesophageal dysplasia.
Technology appraisals	None applicable.
Clinical guidelines	None applicable.
Public health	None applicable.

Appendix C: Literature search for photodynamic therapy for early stage oesophageal cancer

Action	Comments	Version searched (if applicable)	Date searched
Search for similar NICE topics	IP 82 Photodynamic therapy for high-grade dysplasia in Barrett's oesophagus. IP 134 Photodynamic therapy for bile duct cancer	N/A	11/10/2005
Consult notification and specialist advisors questionnaires for additional papers	A number of references have been provided by specialist advisors.	N/A	4/10/2005
Conduct general internet search for background	American Cancer society information on photodynamic therapy. National Cancer Institute: photodynamic therapy for cancer. CancerBACUP: photodynamic therapy information Types of photosensitisers: information provided by University of Leeds.	N/A	4/10/2005
Search for Cochrane systematic review	Cochrane protocol: Interventions for dysphagia in oesophageal cancer	2005 Issue 3	4/10/2005
ASERNIP website	No procedures found.	N/A	4/10/2005
FDA website	FDA oncology tools approval summary for porfimer sodium for oesophageal cancer	N/A	4/10/2005
Search conferences websites	Abstracts from the association of upper gastrointestinal surgeons 2005 scientific meeting	N/A	11/10/2005
Search databases			
The Cochrane Library	24 hits	2005 Issue 3	11/10/2005
CRD databases	6 hits	September 2005	11/10/2005
EMBASE	217 hits	1980 to 2005 Week 41	11/10/2005
Medline	239 hits	1966 to September Week 4 2005	11/10/2005
Premedline	13 hits	October 10, 2005	11/10/2005
CINAHL	21 hits	1982 to September Week 5 2005>	11/10/2005
BLIC (limit to current year only)	0 hit	1993 to date	11/10/2005
National Research Register	6 hits	2005 Issue 3	11/10/2005
Controlled Trials Registry	0 hit	N/A	11/10/2005

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

Database: Medline 1966 to September Week 4 2005	**Date searched: 11/10/2005**
1 (photodynamic therap$ or photo-dynamic therap$ or PDT).tw. (5093) 2 (phototherap$ or photo-therap$).tw. (3343) 3 (photochemotherap$ or photo-chemotherap$).tw. (1488) 4 (photoradiation or photo-radiation).tw. (284) 5 Photochemotherapy/mt [methods] (1357) 6 *Photochemotherapy/ (5147) 7 photosensitis$.tw. (354) 8 photosensitiz$.tw. (5495) 9 (haematoporphyrin$ or hematoporphyrin$ or HPD).tw. (2092) 10 *hematoporphyrin photoradiation/ (477) 11 photofrin.af. (778) 12 porfimer sodium.af. (74) 13 *Photosensitizing Agents/tu [therapeutic use] (781) 14 *Dihematoporphyrin Ether/tu [therapeutic use] (113) 15 aminolevulinic acid.af. (4097) 16 or/1-15 (18835) 17 (oesophag$ adj3 (cancer$ or neoplasm$ or carcinoma$ or adenocarcinoma$ or tumo?r$ or malignant)).tw. (3760) 18 (esophag$ adj3 (cancer$ or neoplasm$ or carcinoma$ or adenocarcinoma$ or tumo?r$ or malignant)).tw. (16209) 19 Esophageal Neoplasms/dt [drug therapy] (1979) 20 or/17-19 (20065) 21 16 and 20 (335) 22 *Barrett Esophagus/ (2576) 23 Esophageal Neoplasms/ (23246) 24 22 not (22 and 23) (1148) 25 21 not 24 (311) 26 Animals/ (3805732) 27 Humans/ (8990279) 28 26 not (26 and 27) (2912659) 29 25 not 28 (302) 30 limit 29 to yr="1990 - 2005" (270) 31 limit 30 to english language (239)	