NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of interstitial photodynamic therapy for malignant parotid tumours

The parotid glands are located in front of the ears and help to produce saliva. A tumour in a parotid gland usually causes a painless swelling on the side of the face where the affected gland is. Only a small number of these tumours are cancerous. In photodynamic therapy (usually abbreviated to PDT), a drug called a 'photosensitising agent' is injected into a vein. A few days later, needles are inserted into the tumour and a special light is shone through them. The light causes the photosensitising agent to destroy 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 October 2007

Procedure name

- Photodynamic therapy (PDT) for parotid tumours
- Interstitial PDT for malignant parotid tumours

Specialty societies

The following societies were approached to nominate Specialist Advisers:

- British Association of Head & Neck Oncologists
- British Association of Oral and Maxillofacial Surgeons
- British Association of Otorhinolaryngologists - Head and Neck Surgeons
- British Association of Surgical Oncology ~ the Association for Cancer Surgery
- British Medical Laser Association

Description

Indications

Tumours of the parotid glands (salivary glands located in front of the ears) are rare and are usually benign, although a small number are malignant. The tumours typically present with painless, localised swelling on one side of the face. Morbidity and mortality can vary greatly, depending on whether the tumour is benign or malignant, and in the case of malignant tumours, on the histological type and tumour grade.

Photodynamic therapy (PDT) is sometimes used for patients with locally persistent or recurrent parotid tumours after surgery or radiotherapy, when further surgery is deemed inappropriate.

Current treatment and alternatives

The main treatment for parotid tumours is surgical excision. Superficial parotidectomy with careful dissection and preservation of the facial nerve is the most common surgical treatment and, additionally, can be used to establish a definitive diagnosis of the tumour. If malignancy is diagnosed, more extensive surgery may be required.

Radiotherapy and chemotherapy may also be used in the treatment of malignant parotid tumours.

What the procedure involves

Photodynamic therapy involves initial administration of a photosensitising agent by intravenous injection. A few days later, a number of needles are inserted into the parotid tumour, either using a percutaneous approach or transorally. This may be done under local or general anaesthesia. Ultrasound, CT or MRI guidance are usually used to guide the needle placement. The required number and length of the needles depends on the size and exact position of the tumour. A beam splitter is used to split a primary laser beam of appropriate wavelength into a small number of optic fibres, which are passed through the needles to deliver laser light into the tumour. Light dosimetry calculations are made dependant upon the dose of light required and the primary output from the laser. A small number of optic fibres are positioned at a time and each fibre tip is in direct contact with the tissue. After the deepest portion of the tumour is treated, the needles and laser fibres are pulled back in 1-cm decrements, each withdrawal being followed by further illumination. As in all photodynamic treatments, the photosensitive agent is activated by the exposure to light, resulting in the formation of high-energy oxygen molecules that are cytotoxic. After administration of the photosensitising agent, patients need to follow a regimen of controlled re-exposure to ambient light over a period of 2 to 3 weeks.

Efficacy

One report described two patients with parotid tumours treated with photodynamic therapy.[1] One of these patients, a 42-year-old woman with a stage T4 adenoid cystic carcinoma of the parotid gland, had a complete response to photodynamic therapy at 4 weeks and was alive and well with no evidence of recurrence at 15-month follow-up. The other patient was described as responding to treatment; no additional information was provided.[1] A second report discussed a single patient, who appears to be the same 42-year-old woman described in the first report.[2] In this second report, the patient was still alive 3 years after treatment.

Safety

No complications attributable to PDT were described for the two patients with parotid tumours.[1, 2]

Literature review

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to PDT for parotid tumours. Searches were conducted via the following databases, covering the period from their commencement to 01/10/2007: 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 B 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 parotid 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.

List of studies included in the overview

This overview is based on two case series, including a total of two patients with parotid tumour[1, 2]. (It appears that the same patient has been described in both reports).

No other studies were identified that were considered to be relevant to the procedure.

Existing reviews on this procedure

There were no published systematic reviews with meta-analysis or evidence-based guidelines identified at the time of the literature search.

Related NICE guidance

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

Interventional procedures:

Related procedure:

- Palliative photodynamic therapy for advanced oesophageal cancer. NICE interventional procedures guidance 206 (2007). Available from www.nice.org.uk/IPG206
- Photodynamic therapy for early-stage oesophageal cancer. NICE interventional procedures guidance 200 (2006). Available from www.nice.org.uk/IPG200
- Photodynamic therapy for non-melanoma skin tumours (including premalignant and primary non-metastatic skin lesions). NICE interventional procedures guidance 155 (2006). Available from www.nice.org.uk/IPG155
- Photodynamic therapy for bile duct cancer. NICE interventional procedures guidance 134 (2005). Available from www.nice.org.uk/IPG134
- Photodynamic therapy for localised inoperable endobronchial cancer. NICE interventional procedures guidance 137 (2005). Available from www.nice.org.uk/IPG137
- Photodynamic therapy for advanced bronchial carcinoma. NICE interventional procedures guidance 087 (2004). Available from www.nice.org.uk/IPG087
- Photodynamic therapy for high-grade dysplasia in Barrett's oesophagus. NICE interventional procedures guidance 082 (2004). Available from www.nice.org.uk/IPG082

Technology appraisals:

- None

Cancer service guidance:

- Service guidance on improving outcomes in head and neck cancers. NICE cancer service guidance (2004). Available from www.nice.org.uk/CSGHN

Clinical guidelines:

- None

Public health:

- None

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

Abbreviations used: MRI, magnetic resonance imaging, PDT, photodynamic therapy			
Study details	**Key efficacy findings**	**Key safety findings**	**Comments**
Lou PJ et al (2004)[1] Case series UK Study period: 1997–2002 n = 2 patients with malignant parotid tumours included in a case series of 45 patients with head and neck cancer Population: patients with recurrent or persistent cancers that had failed to respond to conventional therapy. The patients were all referred for 'last-hope' salvage treatment. One patient (42- year- old female) had adenoid cystic carcinoma, stage T4. She had previously been treated with surgery and radiotherapy. The other patient with parotid tumour is not described in detail. Technique: image-guided needle insertion was used for deep-seated tumours. Follow-up: 15 months for one patient Conflict of interest: none stated	Response definitions: Complete response: no evidence of disease Partial response: 50% decrease in tumour volume Both patients showed a response to treatment 4 weeks after PDT (one complete response and one partial response). The patient with a complete response at 4 weeks was alive and well with no evidence of recurrence at the last follow-up (15 months). No follow-up information was provided for the second patient.	Complications are not specified for the two patients with parotid tumours. The paper states that there was no treatment-related airway obstruction. The only major treatment-related complication was a carotid blow-out (rupture of carotid artery) 2 weeks after PDT in a woman with recurrent neck disease. On a scan 1 month prior to PDT, the tumour was judged to be close to, but not involving the carotid artery. Post-mortem examination showed malignant cells along the intima of the carotid artery implying tumour invasion. Skin photosensitivity was noted in one patient who failed to comply with the recommended regimen for ambient light exposure. No loss of function was detected in nerves encased by treated tumours.	Phase I-II study to assess safety and efficacy of interstitial PDT as a salvage treatment for recurrent head and neck cancers. Little information is provided on the two individual patients with parotid tumour. The authors state that PDT is probably not an appropriate treatment if there is any suspicion that tumours have invaded the carotid artery.

Abbreviations used: MRI, magnetic resonance imaging, PDT, photodynamic therapy			
Study details	**Key efficacy findings**	**Key safety findings**	**Comments**
Jäger HR et al. (2005)[2] Case series UK Study period: not stated n = 1 patient with parotid tumour included in a case series of 14 patients with head and neck cancers Population: patients with significant recurrent disease. The patient with a parotid tumour (adenoid cystic carcinoma) was 42 years old. PDT was done for pain relief and debulking. All patients had received previous treatment with surgery and irradiation. They were included in the study if they were deemed unsuitable for further surgery or if dose limits for radiation therapy and chemotherapy had been reached. Technique: MRI was used to guide needle insertion. Four of the 14 procedures were done under local anaesthesia. Follow-up: 158 weeks (for patient with parotid tumour) Conflict of interest: none stated	The patient with parotid tumour was alive 158 weeks after PDT. MRI showed areas of tumour necrosis 4–8 days after PDT. 'All patients experienced relief of symptoms.'	No complications were described.	It is likely that the one patient with parotid tumour included in this study is also described in Lou et al.[1] The paper states that survival in patients with adenoid cystic carcinoma can be prolonged.

Validity and generalisability of the studies

- It is likely that one patient has been described twice. Both reports were from the same study centre in the UK.

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.

Professor P Bradley, Mr K McKenzie, Mr C Milford (British Association of Otorhinolaryngologists - Head and Neck Surgeons)
Mr C Hopper (British Medical Laser Association),
Mr C Hartley, Mr G Putnam, Mr F Stafford (British Association of Head & Neck Oncologists)

- Four Specialist Advisers described the procedure as novel with uncertain safety and efficacy and two described it as a minor variation of an established procedure. One Specialist Adviser stated that PDT is a well established and safe technique but that this procedure is not currently standard practice.
- The indication is rare.
- Theoretical adverse events include photosensitisation that may result in burns to non-treated areas, pain, damage to nerves and blood vessels, prolonged healing, bleeding, ineffective tumour control and allergic reaction to photosensitising drug.
- Anecdotal adverse events include prolonged healing over exposed temporomandibular joint (healed spontaneously) and cutaneous fistula. One Specialist Adviser reported blow-out of major blood vessels if invaded by tumour and stated that nerves that have been invaded by tumour might suffer further damage. (He noted, however, that "these risks are less than with conventional therapy".)
- Key efficacy outcomes include local tumour control and functional assessment.
- Suggested measures of benefit for audit include local control, symptomatic relief, reduction in tumour size, quality of life, disease-free survival and functional outcomes. Several Specialist Advisers mentioned the DAHNO (Data for Head and Neck Oncology) audit dataset for malignant tumours.
- Adverse outcomes for audit include photosensitivity reactions, facial nerve paralysis, pain, bleeding and local tumour recurrence.
- Training in basic PDT and advanced interstitial techniques is required.
- Other photosensitising agents are in development that may allow PDT to be done as an adjunct to a surgical procedure. (The current agent requires a time lag of 4 days from administration to treatment.)
- The procedure should only be done in specialist units.

Issues for consideration by IPAC

- Should the title of the procedure be changed to ‘malignant’ tumours, or should it stay ‘for tumours’ (as scoped)? All the evidence (on three patients) is on malignant tumours – although it is perceived that the procedure is also used in benign tumours.
- A national audit service exists for head and neck oncology (DAHNO), sponsored by the Healthcare Commission and supported by the British Association of Head and Neck Oncologists (BAHNO). The database currently excludes cancers outside the larynx and oral cavity but it is proposed that the next phase will include carcinoma of the major salivary glands (parotid, submandibular and sublingual glands). The website states that phase II will begin in November 2007.

References

1. Lou PJ, Jäger HR, Jones L et al. (2004) Interstitial photodynamic therapy as salvage treatment for recurrent head and neck cancer. *British Journal of Cancer* 91: 441–6.
2. Jäger HR, Taylor MN, Theodossy T et al. (2005) MR imaging-guided interstitial photodynamic laser therapy for advanced head and neck tumours. *American Journal of Neuroradiology* 26: 1193–1200.

Appendix A: Related published NICE guidance for photodynamic therapy for malignant parotid tumours

Guidance	Recommendation
Interventional procedures	**Palliative photodynamic therapy for advanced oesophageal cancer. NICE interventional procedures guidance 206 (2007)** 1.1 Current evidence on the safety and efficacy of palliative photodynamic therapy (PDT) for advanced oesophageal cancer is of poor quality but appears adequate to support the use of this procedure to relieve symptoms in patients with a poor prognosis. Clinicians wishing to use this procedure should ensure that normal arrangements are in place for consent, audit and clinical governance. 1.2 Palliative PDT for advanced oesophageal cancer should only be performed in specialist centres with regular experience in surgery for oesophageal cancer. **Photodynamic therapy for early-stage oesophageal cancer. NICE interventional procedures guidance 200 (2006)** 1.1 Current evidence on the safety of photodynamic therapy (PDT) for early-stage oesophageal cancer appears adequate. PDT appears efficacious in reducing tumour bulk in carefully selected patients with small early-stage tumours. However, the current evidence is of poor quality and relates only to short-term outcomes; it is therefore not adequate to support the use of this procedure without special arrangements for consent, audit and clinical governance. 1.2 Clinicians wishing to undertake PDT for early-stage oesophageal cancer should take the following actions. • Inform the clinical governance leads in their Trusts. • Ensure that patients understand the uncertainty about the procedure's efficacy and provide them with clear written information. Use of the Institute's information for patients ('Understanding NICE guidance') is recommended (available from www.nice.org.uk/IPG200publicinfo). • Audit and review clinical outcomes of all patients having PDT for early-stage oesophageal cancer (see section 3.1). 1.3 Further research will be useful, and clinicians are encouraged to enter patients into well-designed trials and to collect longer-term follow-up data. The Institute may review the procedure upon publication of further evidence.

	Photodynamic therapy for non-melanoma skin tumours (including premalignant and primary non-metastatic skin lesions). NICE interventional procedures guidance 155 (2006) 1.1 Current evidence suggests that there are no major safety concerns associated with photodynamic therapy for non-melanoma skin tumours (including premalignant and primary nonmetastatic skin lesions). 1.2 Evidence of efficacy of this procedure for the treatment of basal cell carcinoma, Bowen's disease and actinic (solar) keratosis is adequate to support its use for these conditions, provided that the normal arrangements are in place for consent, audit and clinical governance. 1.3 Evidence is limited on the efficacy of this procedure for the treatment of invasive squamous cell carcinoma. Recurrence rates are high and there is a risk of metastasis. Clinicians should ensure that patients understand these risks and that retreatment may be necessary. In addition, use of the Institute's *Information for the public* is recommended. **Photodynamic therapy for bile duct cancer. NICE interventional procedures guidance 134 (2005)** 1.1 Current evidence on the safety and efficacy of photodynamic therapy (PDT) for bile duct cancer does not appear adequate for this procedure to be used without special arrangements for consent and for audit or research. 1.2 Clinicians wishing to undertake PDT for bile duct cancer should take the following actions. • Inform the clinical governance leads in their Trusts. • Ensure that patients understand the uncertainty about the procedure's safety and efficacy 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 PDT for bile duct cancer. 1.3 Publication of safety and efficacy outcomes will be useful. A randomised trial (PHOTOSTENT 2) is in progress and clinicians are encouraged to enter patients in this trial (www.ncrn.org.uk/portfolio/data.asp?ID=1461). The Institute may review the procedure upon publication of further evidence. **Photodynamic therapy for localised inoperable endobronchial cancer. NICE interventional procedures guidance 137 (2005)** 1.1 Current evidence on the safety and efficacy of photodynamic therapy for localised inoperable endobronchial cancer appears adequate to support the use of this procedure provided that the normal

	arrangements are in place for audit and clinical governance. 1.2 This procedure is a treatment option for patients with localised endobronchial cancer that is unsuitable for surgical resection. Clinicians should ensure that patients understand the aim of the treatment, especially when its purpose is palliation. Patients should also be informed of the alternative treatment options available. Clinicians should provide them with clear written information and, in addition, use of the Institute's *Information for the public* is recommended. 1.3 Further research and audit will be useful in clarifying the indications and benefits of this procedure. **Photodynamic therapy for advanced bronchial carcinoma. NICE interventional procedures guidance 087 (2004)** 1.1 Current evidence on the safety and efficacy of photodynamic therapy for advanced bronchial carcinoma appears adequate to support the use of this procedure provided that the normal arrangements are in place for consent, audit and clinical governance. 1.2 These recommendations apply only to the use of this technique to treat advanced bronchial carcinoma. The Institute will consider photodynamic therapy for early bronchial carcinoma separately. **Photodynamic therapy for high-grade dysplasia in Barrett's oesophagus. NICE interventional procedures guidance 082 (2004)** 1.1 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. 1.2 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. 1.3 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 upon publication of further evidence. 1.4 This guidance is limited to the procedure using pharmaceuticals licensed for photodynamic therapy of oesophageal dysplasia.
Technology appraisals	None applicable
Cancer service guidance	**Improving outcomes in head and neck cancers. NICE cancer service guidance (CSG) (2004)** Multi-disciplinary teams (MDTs) with a wide range of specialists will be central to the service, each managing at least 100 new cases of upper aerodigestive tract cancer per annum. They will be responsible for assessment, treatment planning and management of every patient. Specialised teams will deal with patients with thyroid cancer, and with those with rare or particularly challenging conditions such as salivary gland and skull base tumours. *Management of patients with recurrent disease* Treatment for recurrent disease may involve surgery and/or radiotherapy (sometimes brachytherapy) and palliative care. Chemotherapy or chemoradiation is increasingly used, but reliable evidence of effectiveness is lacking and there is uncertainty about the overall impact on quality of life. Other forms of therapy such as photodynamic therapy and monoclonal antibody treatment should only be offered in the context of multi-centre clinical trials, unless there is reliable evidence of effectiveness. Research is urgently needed, especially to evaluate newer therapeutic agents.
Clinical guidelines	None applicable
Public health	None applicable

Appendix B: Literature search for photodynamic therapy for malignant parotid tumours

Database	Date searched	Version searched
Cochrane Library	01/10/2007	Issue 3, 2007
CRD databases (DARE & HTA)	01/10/2007	Issue 3, 2007
EMBASE	01/10/2007	1980 to 2007 Week 38
MEDLINE	01/10/2007	1950 to September Week 3 2007
PREMEDLINE	01/10/2007	September 28, 2007
CINAHL	01/10/2007	1982 to September Week 3 2007
British Library Inside Conferences	01/10/2007	-
NRR	01/10/2007	2007, Issue 3
Controlled Trials Registry	01/10/2007	-

Search strategy used in MEDLINE

The search strategy was adapted for use in the databases above

1	((photodynamic adj3 therap$) or (photo-dynamic adj3 therap$) or PDT).tw.
2	(phototherap$ or photo-therap$).tw.
3	Phototherapy/
4	(photochemotherap$ or photo-chemotherap$).tw.
5	Photochemotherapy/
6	(photoradiation or photo-radiation).tw.
7	(photosensitis$ or photosensitiz$).tw.
8	Photosensitizing Agents/
9	(haematoporphyrin$ or hematoporphyrin$ or HPD).tw.
10	Hematoporphyrin Derivative/
11	Hematoporphyrin Photoradiation/
12	Dihematoporphyrin Ether/
13	(foscan or temoporfin).tw.
14	((mesotetrahydroxyphenyl adj3 chlorin) or

	(m-tetrahydroxyphenyl adj3 chlorin) or m-THPC).tw.
15	(porfimer adj3 sodium).tw.
16	photofrin.tw.
17	((aminolevulinic adj3 acid) or ALA).tw.
18	Lasers/
19	or/1-18
20	Parotid Gland/
21	Parotid Neoplasms/
22	(parotid adj3 mass$).tw.
23	(parotid adj3 gland adj3 (neoplasm$ or cancer$ or carcinoma$ or adenocarcinom$ or tumour$ or tumor$ or malignan$)).tw.
24	(parotid adj3 (neoplasm$ or cancer$ or carcinoma$ or adenocarcinom$ or tumour$ or tumor$ or malignan$)).tw.
25	(salivary adj3 gland$ adj3 (neoplasm$ or cancer$ or carcinoma$ or adenocarcinom$ or tumour$ or tumor$ or malignan$)).tw.
26	(warthin$ adj3 (neoplasm$ or cancer$ or carcinoma$ or adenocarcinom$ or tumour$ or tumor$ or malignan$)).tw.
27	"Head and Neck Neoplasms"/
28	((head or neck) adj3 (neoplasm$ or cancer$ or carcinoma$ or adenocarcinom$ or tumour$ or tumor$ or malignan$)).tw.
29	or/20-28
30	19 and 29
31	Animals/
32	Humans/
33	31 not (31 and 32)
34	30 not 33