

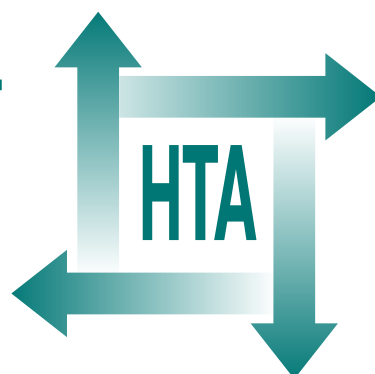
# **A systematic review of photodynamic therapy in the treatment of pre-cancerous skin conditions, Barrett's oesophagus and cancers of the biliary tract, brain, head and neck, lung, oesophagus and skin**

D Fayer, M Corbett, M Heirs, D Fox  
and A Eastwood



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# **A systematic review of photodynamic therapy in the treatment of pre-cancerous skin conditions, Barrett's oesophagus and cancers of the biliary tract, brain, head and neck, lung, oesophagus and skin**

**D Fayer,\* M Corbett, M Heirs, D Fox and A Eastwood**

Centre for Reviews and Dissemination (CRD), University of York,  
York, UK

\*Corresponding author

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## Abstract

# A systematic review of photodynamic therapy in the treatment of pre-cancerous skin conditions, Barrett's oesophagus and cancers of the biliary tract, brain, head and neck, lung, oesophagus and skin

D Fayer,\* M Corbett, M Heirs, D Fox and A Eastwood

Centre for Reviews and Dissemination (CRD), University of York, York, UK

\*Corresponding author

**Background:** Photodynamic therapy (PDT) is the use of a light-sensitive drug, in combination with light of a visible wavelength, to destroy target cells. PDT is used either as a primary treatment or as an adjunctive treatment. It is fairly well accepted in clinical practice for some types of skin cancer but has yet to be fully explored as a treatment for other forms of cancer.

**Objective:** To systematically review the clinical effectiveness and safety of PDT in the treatment of Barrett's oesophagus, pre-cancerous skin conditions and the following cancers: biliary tract, brain, head and neck, lung, oesophageal and skin.

**Data sources:** The search strategy included searching electronic databases (between August and October 2008), followed by update searches in May 2009, along with relevant bibliographies, existing reviews, conference abstracts and contact with experts in the field.

**Study designs:** Randomised controlled trials (RCTs) in skin conditions and Barrett's oesophagus, non-randomised trials for all other sites.

**Participants:** People with Barrett's oesophagus, pre-cancerous skin conditions or primary cancer in the following sites: biliary tract, brain, head and neck, lung, oesophageal and skin.

**Intervention:** Any type of PDT for either curative or palliative treatment.

**Comparators:** Any comparator including differing applications of PDT treatments (relevant comparators varied according to the condition).

**Main outcomes:** The outcomes measured were mortality, morbidity, quality of life, adverse events and resource use.

**Review methods:** A standardised data extraction form was used. The quality of RCTs and non-randomised controlled studies was assessed using standard checklists. Data extracted from the studies were tabulated and discussed in a narrative synthesis, and

the influence of study quality on results was discussed. Meta-analysis was used to estimate a summary measure of effect on relevant outcomes, with assessment of both clinical and statistical heterogeneity. Two reviewers independently screened all titles and abstracts, and data extracted and quality assessed the trials, with discrepancies resolved by discussion or referral to a third reviewer. A scoping review was also undertaken.

**Results:** Overall, 88 trials reported in 141 publications were included, with some trials covering more than one condition. For actinic keratosis (AK), the only clear evidence of effectiveness was that PDT appeared to be superior to placebo. For Bowen's disease, better outcomes with PDT were suggested when compared with cryotherapy or fluorouracil. For basal cell carcinoma (BCC), PDT may result in similar lesion response rates to surgery or cryotherapy but with better cosmetic outcomes. For nodular lesions, PDT appeared to be superior to placebo and less effective than surgery but suggestive of better cosmetic outcome. For Barrett's oesophagus, PDT in addition to omeprazole appeared to be more effective than omeprazole alone at long-term ablation of high-grade dysplasia and slowing/preventing progression to cancer. No firm conclusions could be drawn for PDT in oesophageal cancer. Further research into the role of PDT in lung cancer is needed. For cholangiocarcinoma, PDT may improve survival when compared with stenting alone. There was limited evidence on PDT for brain cancer and cancers of the head and neck. A wide variety of photosensitisers were used and, overall, no serious adverse effects were linked to PDT.

**Limitations:** There were few well-conducted, adequately powered RCTs, and quality of life (QoL) and resource outcomes were under-reported. Problems were identified with reporting of key study features and quality parameters, making the reliability of some

studies uncertain. Methodological limitations and gaps in the evidence base made it difficult to draw firm conclusions.

**Conclusions:** Evidence of effectiveness was found for PDT in the treatment of AK and nodular BCC in relation to placebo, and possibly for treating Barrett's oesophagus. However, the effectiveness of PDT in

relation to other treatments is not yet apparent. High-quality trials are needed to compare PDT with relevant comparators for all meaningful outcomes, including QoL and adverse effects. Further research is also needed on patient experience of PDT, as well as on the cost-effectiveness of PDT.



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## Glossary and list of abbreviations

### Glossary

**Actinic/solar keratosis** A form of pre-cancerous skin lesion, which, based on pathological evidence, is considered to be a precursor to squamous cell carcinoma.

**Adverse event** Any untoward medical occurrence in a patient who is administered a treatment, and which does not necessarily have a causal relationship with the treatment.

**Allocation concealment** When neither patients nor health-care professionals are aware of the randomisation schedule or allocation of treatment to any one individual.

**Barrett's oesophagus** A condition in which the injured lining of the oesophagus is replaced by a new abnormal lining (specialised intestinal metaplasia).

**Basal cell carcinoma** A skin cancer that may take a variety of clinical appearances, such as nodular, cystic, superficial, morpoeic, ulcerated or pigmented.

**Bowen's disease** A pre-invasive form of squamous cell skin cancer, also called squamous cell carcinoma (SCC) in situ.

**Brachytherapy** Form of radiotherapy where a radioactive source is placed inside or next to the area requiring treatment.

**Chi-squared ( $\chi^2$ ) test** A statistical test used to assess heterogeneity by testing the null hypothesis that the true treatment effects are the same in each study.

**Cholangiocarcinoma** Cancer of the bile ducts.

**Confidence interval** The range of uncertainty about an estimate of a treatment effect. It is the range of values above and below the point estimate that is likely to include the true value of

the treatment effect. A 95% confidence interval (CI) indicates that there is a 95% probability that the CI calculated from a particular study includes the true value of a treatment effect.

**Cryotherapy** The application of extreme cold to destroy abnormal or diseased tissue.

**DYE laser** A laser that uses an organic dye to obtain a desired wavelength.

**External validity** The extent to which the effects observed in a study can be expected to apply in routine clinical practice, i.e. to people who did not participate in the study.

**Fixed effect model** A statistical model that assumes only within-study variation as influencing the uncertainty of results [as reflected in the confidence interval (CI)] of a meta-analysis. Variation between the estimates of effect from each study (heterogeneity) does not affect the CI in a fixed effect model.

**Forest plot** A graphical display designed to illustrate the relative strength of treatment effects in multiple quantitative studies addressing the same question.

**Fluorouracil (5-FU)** A chemotherapy agent.

**Hazard ratio** The degree of increased or decreased risk of death or other clinical outcome over a period of time.

**Heterogeneity** Heterogeneity can be used as a statistical term: the differences/variability between the individual studies in the estimates of effects, or in terms of clinical variation between participants, interventions or settings.

**Homogeneity** The degree to which the results of studies are similar.

*continued*

**$I^2$  statistic** A measure to estimate how much of the total variation between the treatment estimates can be attributed to statistical heterogeneity rather than chance. It gives the proportion of the total variation that is due to heterogeneity between study results.

**Incidence** The number of new cases of a specific condition occurring during a certain period in a specified population.

**Incubation time** The period of time from drug application to light administration.

**Intention-to-treat analysis** An analysis based on the initial treatment intent, not on the treatment eventually administered.

**Internal validity** The degree to which a result (of a measurement or study) is likely to be true and free of bias.

**Karnofsky score** An attempt to categorise a patient's general well-being. It runs from 100 to 0, where 100 is 'perfect' health, 50% is 'requires help often', and 0 is 'death' (see Appendix 3).

**KTP laser** A laser that is directed through a potassium titanyl phosphate (KTP) crystal to produce a beam in the green visible spectrum.

**Meta-analysis** A method of combining studies to produce an overall summary of the treatment effect across studies (see also *Fixed effect model* and *Random effects model*).

**Odds ratio** A way of comparing whether the odds, or likelihood of a certain event is the same for two groups; the odds refers to the ratio of

the number of people having an event to the number not having an event.

**Per-protocol analysis** An analysis based on patients who complete/adhere to the course of treatment.

**Prevalence** The proportion of people in a population who have a given disease or attribute at a given point in time.

**Proton pump inhibitor** A drug used for treatment of erosion and ulceration of the oesophagus, caused by gastroesophageal reflux disease.

**Quality of life (health-related quality of life)** A concept incorporating all of the factors that might impact on an individual's life, including factors such as the absence of disease or infirmity, as well as other factors that might affect their physical, mental and social well-being.

**Random effects model** A statistical model, sometimes used in meta-analysis, in which both within-study sampling error (variance) and between-study variation are included in the assessment of the uncertainty (confidence interval) of the results of a meta-analysis.

**Serious adverse event** Any untoward medical occurrence that results in death, is life threatening, requires hospitalisation, or results in significant disability or incapacity.

**Stricture** An abnormal contraction of any passage or duct of the body (e.g. due to scar tissue).

## List of abbreviations

|                  |  |         |   |
|------------------|--|---------|---|
| 5-FU             | fluorouracil   | HTA     | Health Technology Assessment                          |
| AE               | adverse event  | ICER    | incremental cost-effectiveness ratio                  |
| AK               | actinic keratosis  | ITT     | intention to treat                                    |
| ALA              | aminolevulinic acid                                      | LED     | light-emitting diode                                  |
| APC              | argon plasma coagulation                                 | LGD     | low-grade dysplasia                                   |
| BCC              | basal cell carcinoma                                     | MAL     | methyl aminolevulinate                                |
| CDSR             | Cochrane Database of Systematic Reviews                  | MeSH    | medical subject headings in the MEDLINE thesaurus     |
| CENTRAL          | Cochrane Central Register of Controlled Trials           | mTHPC   | meta-(tetrahydroxyphenyl) chlorine                    |
| CHE              | Centre for Health Economics                              | Nd:YAG  | neodymium-doped yttrium aluminium garnet (laser)      |
| CI               | confidence interval                                      | NHS     | National Health Service                               |
| CINAHL           | Cumulative Index to Nursing and Allied Health Literature | NICE    | National Institute for Health and Clinical Excellence |
| CR               | complete response  | NSCLC   | non-small cell lung carcinoma                         |
| CRD              | Centre for Reviews and Dissemination                     | OR      | odds ratio  |
| CRT              | chemoradiotherapy  | PDD     | photodynamic diagnosis                                |
| CT               | computerised tomography                                  | PDT     | photodynamic therapy                                  |
| DARE             | Database of Abstracts of Reviews of Effects              | PPI     | proton pump inhibitor                                 |
| DHE              | dihaematoporphyrin ether                                 | PpIX    | protoporphyrin IX                                     |
| MR               | endoscopic mucosal resection                             | PR      | partial response                                      |
| ERCP             | endoscopic retrograde cholangiopancreatography           | Ps      | porfimer sodium                                       |
| FEV <sub>1</sub> | forced expiratory volume in one second                   | PsD-007 | photocarcinorin                                       |
| FU               | follow-up  | QoL     | quality of life                                       |
| FVC              | forced vital capacity                                    | RCT     | randomised controlled trial                           |
| GORD             | gastroesophageal reflux disease                          | SAE     | serious adverse event                                 |
| Gy               | gray   | SCC     | squamous cell carcinoma                               |
| HGD              | high-grade dysplasia                                     | VAS     | visual analogue scale                                 |
| HpD              | haematoporphyrin derivative                              | VPL     | variable pulsed light                                 |

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices, in which case the abbreviation is defined in the figure legend or in the notes at the end of the table.





## Executive summary

### Background

Photodynamic therapy (PDT) is the use of a light-sensitive drug (a photosensitiser), in combination with light of a visible wavelength, to destroy target cells (e.g. cancerous or pre-cancerous cells). PDT is generally used either as a primary treatment (usually in skin conditions) or as an adjunctive treatment alongside surgery, radiotherapy or chemotherapy. Although PDT is a fairly well-accepted treatment in clinical practice for some types of skin lesion, as a treatment for other forms of cancer it has yet to be fully explored.

### Objectives

The aim of this project was to systematically review the clinical effectiveness and safety of PDT in the treatment of Barrett's oesophagus, pre-cancerous skin conditions and the following cancers: biliary tract, brain, head and neck, lung, oesophageal and skin. The findings will inform decisions about the role of PDT in clinical practice and also the need for further research.

### Methods

A comprehensive search strategy was developed to ensure that all relevant sources of data were located. The search strategy comprised the following main elements:

- Searching of electronic databases from their inception was undertaken between August and October 2008; update searches were carried out in a range of electronic databases in May 2009.
- Scrutiny of bibliographies of included studies and existing reviews.
- Hand searching of abstracts from recent relevant conferences.
- Contact with experts in the field and manufacturers of photosensitisers.

Published and unpublished studies from any country, and reported in any language, were eligible for inclusion, provided that they met the following inclusion criteria:

- Study designs: randomised controlled trials (RCTs) in skin conditions and Barrett's oesophagus, non-randomised trials for all other sites.
- Participants: people with Barrett's oesophagus, pre-cancerous skin conditions or primary cancer in the following sites: biliary tract, brain, head and neck, lung, oesophageal and skin.
- Intervention: any type of PDT for either curative or palliative treatment.
- Comparators: any comparator including differing applications of PDT treatments (relevant comparators varied according to the condition).
- Main outcomes: mortality, morbidity, quality of life, adverse events and resource use.

A standardised data extraction form was used. The quality of RCTs and non-randomised controlled studies was assessed using standard checklists adapted as necessary to incorporate topic-specific quality issues. Data extracted from the studies were tabulated and discussed in a narrative synthesis and the influence of study quality on the results of the studies and the findings of the review were discussed. Where appropriate, meta-analysis was used to estimate a summary measure of effect on relevant outcomes with assessment of both clinical and statistical heterogeneity.

Two reviewers independently screened all titles and abstracts, and data extracted and quality assessed the trials. Discrepancies were resolved by discussion or by referral to a third reviewer when necessary.

A scoping review was undertaken alongside the screening stage of the systematic review. The aim of this was to document the extent of the uncontrolled and observational research particularly in those areas for which we anticipated a paucity of controlled trials, thus providing as complete a picture of the evidence base as possible.

## Results

The search strategies identified 12,522 references. Full copies of 699 potentially relevant papers were obtained and assessed for inclusion in the systematic review. Duplicate publication of study results and multiple reports of partial data sets appeared to be common. Overall, we included 88 trials reported in 141 publications. Numbers of trials across the conditions studied were: actinic keratosis (AK) (28), Barrett's oesophagus (11), basal cell carcinoma (BCC) (13), biliary tract (5), Bowen's disease (7), brain (2), head and neck cancer (4), lung cancer (7) and oesophageal cancer (13). Some trials covered more than one condition.

There was generally a paucity of well-conducted, adequately powered RCTs. Quality of life and resource outcomes were under-reported. We also identified problems with reporting of key study features and quality parameters, which made the reliability of a number of studies uncertain. Methodological limitations and gaps in the evidence base made drawing of firm conclusions a challenge across the cancer sites and conditions that were investigated. What we were able to conclude was that, overall, PDT appeared to be a promising treatment in the majority of conditions we reviewed. However, the potential place of PDT amongst the range of other treatments available for each condition is not yet clearly defined. Optimal parameters for PDT were unclear in the majority of the areas under investigation.

In actinic keratosis, the only clear evidence of effectiveness was that PDT appeared to be superior to placebo. Uncertainties still exist around PDT's effectiveness compared with other topical treatments. For Bowen's disease there were suggestions of better outcomes with PDT when compared with cryotherapy or fluorouracil but these need further investigation. For superficial BCC, PDT may result in similar lesion response rates to surgery or cryotherapy with better cosmetic outcomes; however, these conclusions are tentative. PDT appeared to be superior to placebo for nodular lesions – less effective in lesion clearance than surgery although with suggestions of better cosmetic outcome. For the treatment of Barrett's oesophagus, PDT in addition to omeprazole appeared to be more effective than omeprazole alone at long-term ablation of high-grade dysplasia (HGD) and slowing or preventing progression to cancer. The priority for PDT research in the area of Barrett's oesophagus is to determine more clearly the role of PDT and its optimal delivery to patients

with HGD. Trials have been conducted with both curative and palliative intent in oesophageal cancer; however, firm conclusions in regard to effectiveness compared with other treatments cannot yet be drawn. No trials were located for early lung cancer, therefore all included trials related to PDT that was used with palliative intent. Further research is needed to determine the role of PDT in relation to current comparators in lung cancer and to identify particular subgroups that might benefit from PDT. In cholangiocarcinoma, PDT may improve survival when compared with stenting alone, and an ongoing trial should provide more definitive evidence. There was very limited evidence on PDT for brain cancer and no definitive statements can be made at present. There was a lack of good trial evidence for cancers of the head and neck, and so the value of PDT compared with other forms of treatment was not clear.

A wide variety of photosensitisers were used across the sites included in this review; these were administered topically or systemically, as appropriate. Overall, there were no serious AEs (SAEs), linked to PDT, reported in these trials. Where the photosensitiser was administered topically for the treatment of skin conditions, local AEs (including pain) ranging in severity were common but largely transient. Systemic administration of meta-(tetrahydroxyphenyl) chlorine (mTHPC) appeared to cause burning sensations at the site of injection, and oral administration of aminolevulinic acid (ALA) was linked to nausea and vomiting. Photosensitisation appeared to have been a problem only in patients receiving the photosensitiser systemically, who did not comply with the recommended precautions against light exposure. The reported data did not permit a comprehensive comparison of the AE profile for each photosensitiser.

## Conclusions

### Implications for practice

- Photodynamic therapy is currently most accepted in the treatment of malignant and pre-malignant non-melanoma skin lesions. In this review we found evidence of effectiveness for the treatment of AK and nodular BCC in relation to placebo. However, we do not yet fully know the effectiveness of PDT in relation to other treatments.
- The evidence suggested that PDT might be a useful option in the treatment of Barrett's

oesophagus but, again, its effectiveness in relation to other treatments is not yet apparent.

- The evidence for the other sites and conditions examined in this review was not sufficiently clear to draw firm conclusions.
- We did not find any clear evidence implying that PDT should definitely not be used for certain clinical conditions; rather there are a number of uncertainties that require further investigation.

### Research recommendations

- The optimal parameters of PDT need to be identified across the conditions studied.
- High-quality trials are needed to compare PDT with relevant comparators for all meaningful outcomes, including quality of life and AEs. Such trials should aim to establish the place of

PDT for the treatment of a given condition and should identify if subgroups of patients might respond differently to PDT.

- Good-quality research is needed on the patient experience of PDT across the conditions investigated.
- While the difficulties of conducting high-quality trials in rarer cancers – such as those of the brain and head and neck – are recognised, there is a need to establish where barriers are insurmountable. If RCTs cannot be conducted, other types of evidence may be considered.
- Photodynamic therapy is an active field of research and, as the results of ongoing trials become available, there will be a need to update this review.
- Future work should focus on the cost-effectiveness of PDT in those areas where effectiveness and safety have been established.





# Chapter I

## General background

### Basics of photodynamic therapy

Photodynamic therapy (PDT) is the use of a light-sensitive drug (a photosensitiser), in combination with light of a visible wavelength, to destroy target cells (e.g. cancerous or pre-cancerous cells). Photosensitisers can be administered systemically or topically, which targeted cells then preferentially absorb. A period of time is required to permit photosensitiser uptake (ranging from a few minutes up to several days), after which light is directed at the area to be treated. The photochemical reaction resulting from excitation of the photosensitiser produces singlet oxygen, which destroys cells (by reacting with, and damaging, cell organelles and biomolecules important to cell function).

Some of the light absorbed by photosensitisers is re-emitted at a different wavelength, a process known as fluorescence; this can be used as a means of detecting the presence and location of tumours. This technique, known as photodynamic diagnosis (PDD), may be used alongside PDT.

### Development of photodynamic therapy

The photodynamic effect was discovered by chance over 100 years ago, followed shortly after by early pioneering work on PDT in Europe.<sup>1</sup> However, despite this early knowledge of the basic principles, it was not until the 1980s that PDT (which was then also often known as 'photoradiation therapy') developed to a level where it was used – to any significant extent – in both clinical research and practice. Randomised controlled trials (RCTs) of PDT in patients with malignant and pre-malignant conditions began in earnest in the 1990s. PDT has also been used to treat age-related macular degeneration, cardiovascular disease, psoriasis, acne vulgaris and viral warts.<sup>2</sup>

### Photosensitisers

Haemoglobin (which transports oxygen in the blood) and chlorophyll (an essential

component of photosynthesis) molecules contain heterocyclic ring structures, known as porphyrins. Many photosensitisers are derivatives of haematoporphyrin; the first photosensitiser used clinically in PDT was haematoporphyrin derivative (HpD). Its purified fraction is known as porfimer sodium (Ps). Ps and HpD are first-generation photosensitisers. There are two major drawbacks of using Ps or HpD. One is the time taken (typically 48 hours) for tissues to accumulate sufficient levels of photosensitiser to allow the next stage of the PDT process to occur (illumination). The second is the time taken for photosensitiser concentration to fall below clinically active levels. Persistent levels will typically last for many weeks, causing photosensitivity of the skin (sunburn-like effects), unless patients avoid bright light.<sup>3</sup>

An alternative approach to introducing the photosensitiser to the target tissue involves making use of biomolecules produced by the body. These can be exploited to naturally generate therapeutic levels of photosensitiser. An example is aminolevulinic acid (ALA), a naturally occurring intermediate in the haem biosynthetic pathway, and precursor of the photosensitising agent protoporphyrin IX (PpIX). Although ALA has no intrinsic photosensitising properties, it is metabolised to produce PpIX (the active agent in ALA-PDT). Administration of sufficient ALA results in a rapid elevation (for a few hours) of PpIX levels, meaning that illumination can take place.<sup>4</sup> Following this there is also rapid systemic clearance of ALA-induced PpIX, within 24 hours.

Aminolevulinic acid and its methylester, methyl aminolevulinate (MAL), are second-generation photosensitisers. Other types of photosensitiser have also been developed, including chlorins, bacteriochlorins, phthalocyanines, naphthalocyanines, pheophorbides and purpurins.<sup>3</sup> The mechanisms involved in the selective uptake and retention of photosensitisers by tumour cells are not yet fully understood. *Table 1* provides details of the photosensitisers studied in the trials included in this systematic review.

Topically active agents are preferred in the treatment of dermatological cancers and

**TABLE 1** Photosensitisers (and sites) included in this systematic review

| Photosensitiser (trade name)                            | Wavelength commonly used (nm) | Condition/site  |
|---|-------------------------------|---|
| Porfimer sodium (Photofrin <sup>®</sup> )               | 630                           | Barrett's oesophagus, biliary tract cancer, brain cancer, lung cancer, nasopharyngeal carcinoma, oesophageal cancer |
| Haematoporphyrin derivative (HpD)                       | ~630                          | Oesophageal cancer  |
| Dihaematoporphyrin ether (DHE) (Photosan <sup>®</sup> ) | ~630                          | Biliary tract cancer, lung cancer, oesophageal cancer   |
| Aminolevulinic acid (ALA) (Levulan <sup>®</sup> )       | ~630                          | Actinic keratosis, Barrett's oesophagus, basal cell carcinoma, Bowen's disease, brain cancer, lung cancer           |
| Methyl aminolevulinate (MAL) (Metvix <sup>®</sup> )     | ~630                          | Actinic keratosis, basal cell carcinoma, Bowen's disease  |
| PsD-007/photocarcinorin                                 | ~630                          | Oesophageal cancer  |
| mTHPC/temoporfin (Foscan <sup>®</sup> )                 | 652                           | Oesophageal cancer  |
| (Radachlorin <sup>®</sup> )                             | 662                           | Oral cancer   |
| Methylene blue  | 665                           | Laryngeal/pharyngeal cancer   |
| (Photosense <sup>®</sup> )                              | 670                           | Oral cancer   |
| Verteporfin (Visudyne <sup>®</sup> )                    | 688                           | Basal cell carcinoma, Bowen's disease   |

pre-cancerous conditions, as most systemic photosensitisers produce prolonged generalised photosensitivity. Ideally, the photosensitiser will be evenly distributed throughout the lesion and show a high lesion–normal tissue concentration ratio.<sup>5</sup>

## Light sources

When treating skin lesions, light is directed at the treatment area by straightforward means, such as a lamp or light-emitting diode (LED) light source (which can easily illuminate large areas). Laser light is used for treating internal sites, delivered via an endoscope, or a variety of other devices, including needles, optic fibres and balloons. Lasers enable the delivery of a more precise wavelength of light than lamps.

The wavelengths and intensity of light required in PDT vary, depending on the depth of light penetration needed and on the photosensitiser being used. The greater the wavelength of light, the deeper the penetration into tissue, which has implications for the type of tumour suitable for treatment with PDT; cancers occurring deep within tissues (where adequate illumination could be problematic) generally are currently not suitable for treatment with PDT. Red light is the most commonly used in PDT, as it has the longest wavelength in the visible spectrum, although for thin lesions [such as actinic keratoses (AKs)] blue light can also be used.

Light delivery systems for PDT have improved over time. Tuneable dye lasers – which allow flexibility of wavelength – have been used in research studies but are not ideal for clinical use because of their size and limited mobility. However, the licensing of specific photosensitisers (using a specific wavelength) has led to the development of small compact lasers, such as diode lasers and LED array lasers, which are more convenient for use in clinical settings.<sup>3</sup>

## The role of photodynamic therapy

Photodynamic therapy is generally used as either as a primary treatment (usually in skin conditions) or as an adjunctive treatment alongside surgery, radiotherapy or chemotherapy, as appropriate. Trials have tended to focus on patients who have not responded to usual treatment, but more recent research is now assessing the effectiveness of PDT as a first-line intervention. Some potential advantages of PDT may include the preservation of connective tissue within the treated area and limited side effects. PDT also offers the ability to treat large areas of diseased tissue, areas not reachable by surgery, and the option of re-treatment.

Although PDT is a fairly well-accepted treatment in clinical practice for some types of skin cancer, as a treatment for other forms of cancer it has yet to be

fully explored, although the National Institute for Health and Clinical Excellence (NICE) has issued a number of interventional procedure guidance documents, which make recommendations about whether the treatment is safe enough, and works well enough, for routine use.<sup>6-14</sup>

## Previous and ongoing reviews of photodynamic therapy

A number of existing reviews were identified in the initial stages of the systematic review. These were assessed by two independent reviewers using criteria developed by the Centre for Reviews and Dissemination (CRD) for the Database of Abstracts of Reviews of Effects (DARE).<sup>15</sup> As with the DARE database, reviews were required to meet all of the first three criteria and at least one of the last two in order to be accepted as a systematic review. As is usual practice, discrepancies were resolved by discussion, or by referral to a third reviewer when necessary. One of these reviews addressed lung cancer and PDT but only covered English-language research to 2002 and therefore did not fully answer our research questions.<sup>16</sup> The other reviews did not meet our criteria.

A research group from the Health Technology and Policy Unit, University of Alberta, has recently completed a scoping review of PDT for cancer in any site.<sup>17</sup> This review searched for English-language studies, including comparative and non-comparative designs published in the past 10

years. This scoping review was based on searches carried out in MEDLINE, the Cumulative Index to Nursing and Allied Health Literature (CINAHL), the Cochrane Library and Science Citation Index. Study classification and limited data extraction were carried out by only one reviewer. The project group were kind enough to supply us with draft results and the full database of references, which was cross-checked against our own searches. No further studies were identified as a result of this process.

The same research group has undertaken a full assessment of treatments for early-stage oesophageal cancer and Barrett's oesophagus, which includes PDT as one of the interventions. The evidence is drawn from the scoping review and additional searches for other interventions (searches were limited to English language, and the last 5 years). Results were unavailable for inclusion in this report but have recently been released.<sup>18,19</sup>

Two Cochrane reviews from the Cochrane Upper Gastrointestinal and Pancreatic Diseases Group were identified. One intended to compare surgery versus radical endotherapies, including PDT, in the treatment of Barrett's oesophagus, but no eligible trials were located and five retrospective studies were excluded.<sup>20</sup> The other review was at protocol stage at the time of writing, but has subsequently been published.<sup>21</sup> Having failed to locate any systematic reviews capable of answering our research questions, we therefore conducted the current review.



# Chapter 2

## Research questions

### Introduction

In its role as part of the CRD/ Centre for Health Economics (CHE) Technology Appraisal Review team, CRD was commissioned by the Health Technology Assessment (HTA) programme, on behalf of the National Cancer Director, to undertake a systematic review looking at PDT in five areas [Barrett's oesophagus, head and neck cancer, lung cancer, oesophageal cancer and skin cancer (including pre-cancerous conditions)]. The scope of the project was subsequently expanded to include an additional two cancer sites (bile duct, brain) at the request of the Scottish Government Health Directorates. No economic component was requested and so attention has been restricted to clinical effectiveness and safety.

### Research question

What is the clinical effectiveness and safety of PDT in the treatment of Barrett's oesophagus, pre-cancerous skin conditions and the following cancers: biliary tract, brain, head and neck, lung, oesophageal and skin?

### Aims and objectives

The aim of this project was to systematically identify, evaluate and summarise the findings of all relevant studies regarding clinical effectiveness and safety. The results of the review will be used to inform decisions about the role of PDT in clinical practice and also the need for further research.



## Chapter 3

# Methods for reviewing clinical effectiveness

A systematic review was undertaken following the principles recommended by CRD guidance and the QUOROM statement.<sup>22,23</sup>

### Search strategy

A comprehensive search strategy was developed to ensure that all relevant sources of data were located. Searches were not restricted by language, date of publication or study design. The search strategy comprised the following main elements:

- searching of electronic databases
- scrutiny of bibliographies of included studies and existing reviews
- hand searching of abstracts from recent relevant conferences
- contact with experts in the field including manufacturers of photosensitising agents.

The following electronic databases were searched from inception to August/October 2008:

- MEDLINE (including MEDLINE In-Process)
- EMBASE
- CINAHL
- PASCAL [database of INIST (Institut de l'Information Scientifique et Technique)]
- Latin American & Caribbean Health Sciences Literature (LILACS)
- Cochrane Database of Systematic Reviews (CDSR)
- DARE
- NHS Economic Evaluation Database (NHS EED)
- HTA Database
- Cochrane Central Register of Controlled Trials (CENTRAL)
- metaRegister of Current Controlled Trials (mRCT)
- ISI Conference Proceedings Citation Index
- Zetoc (British Library's Electronic Table of Contents)
- UK Clinical Research Network (UKCRN)

See Appendix 1 for full details of the search strategies used.

Where completed trials were identified from research registers without an associated full publication, or studies were indicated to be in progress, the principal investigator was contacted for further details and references. Reference lists from all identified reviews were checked for potentially relevant studies.

The original searches were undertaken between August and October 2008. Update searches were carried out in MEDLINE, EMBASE, CINAHL, DARE, CDSR, NHSEED, HTA and CENTRAL in May 2009.

Proceedings for two recent conferences that were not yet electronically indexed were obtained and hand searched: the 13th Congress of the European Medical Laser Association (EMLA), 23–24 August 2008 (published in *Photodiagnosis and Photodynamic Therapy*) and the 7th International Symposium on Photodynamic Therapy and Photodiagnosis in Clinical Practice, 7–10 October 2008.

As well as contact with the clinical advisors, the manufacturers of relevant photosensitising agents were also contacted. Where research bibliographies were kindly provided or available from websites, these were checked against the database of identified literature.

The results of all searches were imported in ENDNOTE XI bibliographic software and de-duplicated.<sup>24</sup>

### Inclusion criteria

Published and unpublished studies from any country and reported in any language were eligible for inclusion, provided that they met the following inclusion criteria.

### Population

The eligible populations included people with specified pre-cancerous conditions or primary cancer in the following sites:

- biliary tract
  - extrahepatic cholangiocarcinoma (usually adenocarcinoma)
  - perihilar cholangiocarcinoma
  - distal cholangiocarcinoma
  - gall bladder
  - ampulla
- brain
  - gliomas (astrocytoma, ependymoma, oligodendroglioma or mixed glioma)
  - any of the rarer brain cancer types, including invasive pituitary adenomas
- head and neck
  - laryngeal cancer
  - hypopharyngeal cancer
  - oropharyngeal cancer
  - oral cavity cancer
- lung
  - small cell, non-small cell lung cancer [squamous cell carcinoma (SCC), adenocarcinoma, large cell carcinoma]
  - tracheobronchial cancer was also classified as lung (based on advice from clinical advisors)
- oesophagus
  - Barrett’s oesophagus (a precursor to cancer)
  - squamous cell carcinoma, adenocarcinoma or undifferentiated cancer of the oesophagus
- skin
  - pre-cancerous conditions: actinic/solar keratosis, Bowen’s disease
  - non-melanoma skin cancers [basal cell carcinoma (BCC) (superficial and nodular), SCC, Merkel cell carcinoma, Kaposi’s sarcoma, T-cell lymphoma of skin or sarcoma].

We did not anticipate identifying any trials dealing with children as these cancers are extremely rare in such groups, but any data on children would have been included and considered separately where appropriate.

Where studies comprised populations covering more than one site of interest, these were included if the results were reported by diagnosis or where a minimum of 90% of patients was diagnosed with the same condition.

## Intervention

*Photodynamic therapy for either curative or palliative treatment* The specific interventional details varied according to cancer site. There are a number of variations possible in the application of PDT, for

example the type of photosensitising agent, the method of light delivery, wavelength and duration of light used. We have not restricted our review according to the details of the PDT treatment, but have extracted and reported data on agent, light source, wattage, light intensity, duration, number of treatment sessions and wavelength. Studies of prophylactic PDT alone were excluded; data relating to prophylactic PDT were not extracted when both treatment and prophylaxis were reported.

## Comparators

No restrictions were placed on the inclusion criteria for comparators. The relevant comparators varied according to the cancer site. Studies comparing differing application of PDT treatments (e.g. photosensitising agents; source, duration, or wavelength of light) were also included.

## Outcomes

Studies were included provided that they reported at least one relevant outcome. The primary outcomes the review focused on are listed below. These were addressed individually by site, where appropriate, due to differences in the specific outcome measures. Outcomes also reflected the curative or palliative nature of the intervention.

- mortality
- morbidity (symptom burden, symptom improvement, time to healing)
- quality of life (QoL) (patient-based outcomes, such as cosmetic appearance, QoL or depression scores)
- adverse events (AEs) (e.g. photosensitivity of skin in general, ulceration of the underlying tissues, haemoptysis, scarring, carcinogenicity, oesophageal strictures, cardiac complications, nausea, inflammation, pain, constipation)
- resource use (e.g. length of hospital stay)
- return to normal activities.

We also extracted data on recurrence and tumour response measures (such as tumour or lesion clearance or response), while bearing in mind the extent to which these outcomes relate to symptomatic morbidity and patient-perceived benefits.

## Study designs

In the evaluation of effectiveness and safety of clinical procedures, RCTs are normally seen as providing a ‘gold standard’ of evidence that is



less prone to bias.<sup>22</sup> However, such trials have not been conducted in large numbers for all of the conditions under investigation, so there was a need to consider other types of evidence. The particular study design inclusion criteria depended on the cancer site as shown below:

- *Skin* We anticipated sufficient RCTs and therefore restricted our attention to these.
- *Barrett's oesophagus* In a change to the protocol, we restricted our attention to RCTs, as the initial screening identified a significant number of RCTs in this area.
- *All other sites* Given the paucity of RCTs identified in our initial scoping searches, we considered prospective experimental studies with a control group, in addition to RCTs.

Animal models, pre-clinical and biological studies, narrative reviews, editorials, opinions and reports containing no outcome data were excluded from the reviews.

Alongside the systematic review we conducted a scoping review of studies, which met all of our inclusion criteria except the study design. The aim of this scoping review was to document the extent of the observational research in those areas in which we anticipated a paucity of controlled trials (see Chapter 3, Scoping review).

## Inclusion and exclusion strategies

Based on the volume of records within the ENDNOTE library, we adopted a three-stage screening process, as shown in *Figure 1*. Two reviewers independently

screened all titles and abstracts regardless of source at each stage. Discrepancies were resolved by discussion, or by referral to a third reviewer when necessary.

### Stage One

An initial sift of the records was carried out aiming to exclude any clearly irrelevant material. Records were excluded if they met any of the following criteria, i.e. the study:

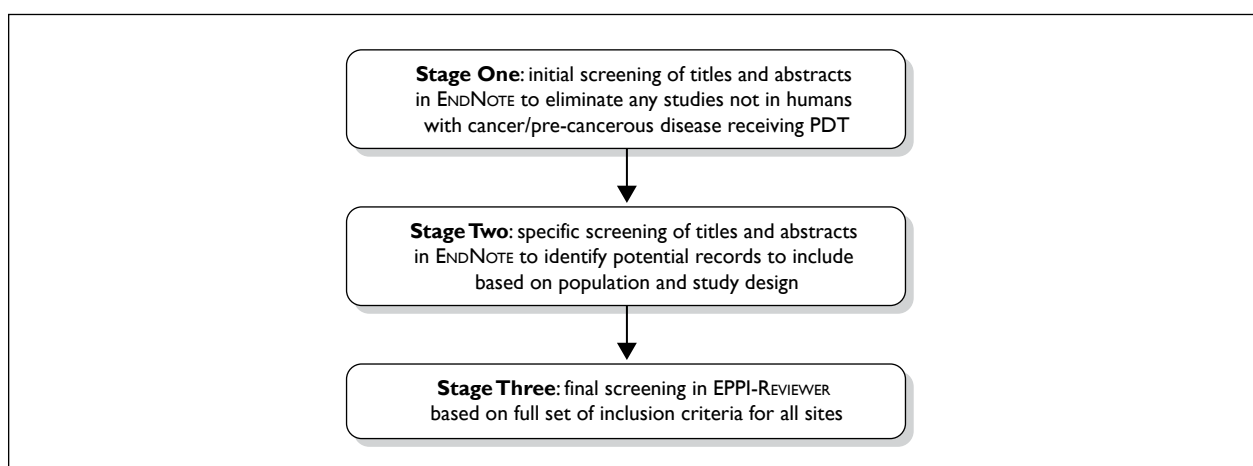
- was not in human patients (could be animals or in vitro, cell cultures, etc. only)
- was not of PDT (i.e. not the use of photosensitising agents in combination with a light source)
- was of PDD without any actual therapy
- did not include patients with the identified conditions.

### Stage Two

A more detailed assessment of the potentially relevant records identified in Stage One was carried out. An algorithm was used to determine which records were to be considered for inclusion (full paper obtained), which were considered for the scoping review (see Scoping review), and which should be rejected. The algorithm is described in *Figure 2*.

### Stage Three

All non-rejected records from Stage Two were then imported into EPPI-REVIEWER (systematic review software) for final assessment.<sup>25</sup> All references were screened and assessed, based on the complete set



**FIGURE 1** Three-stage screening process.

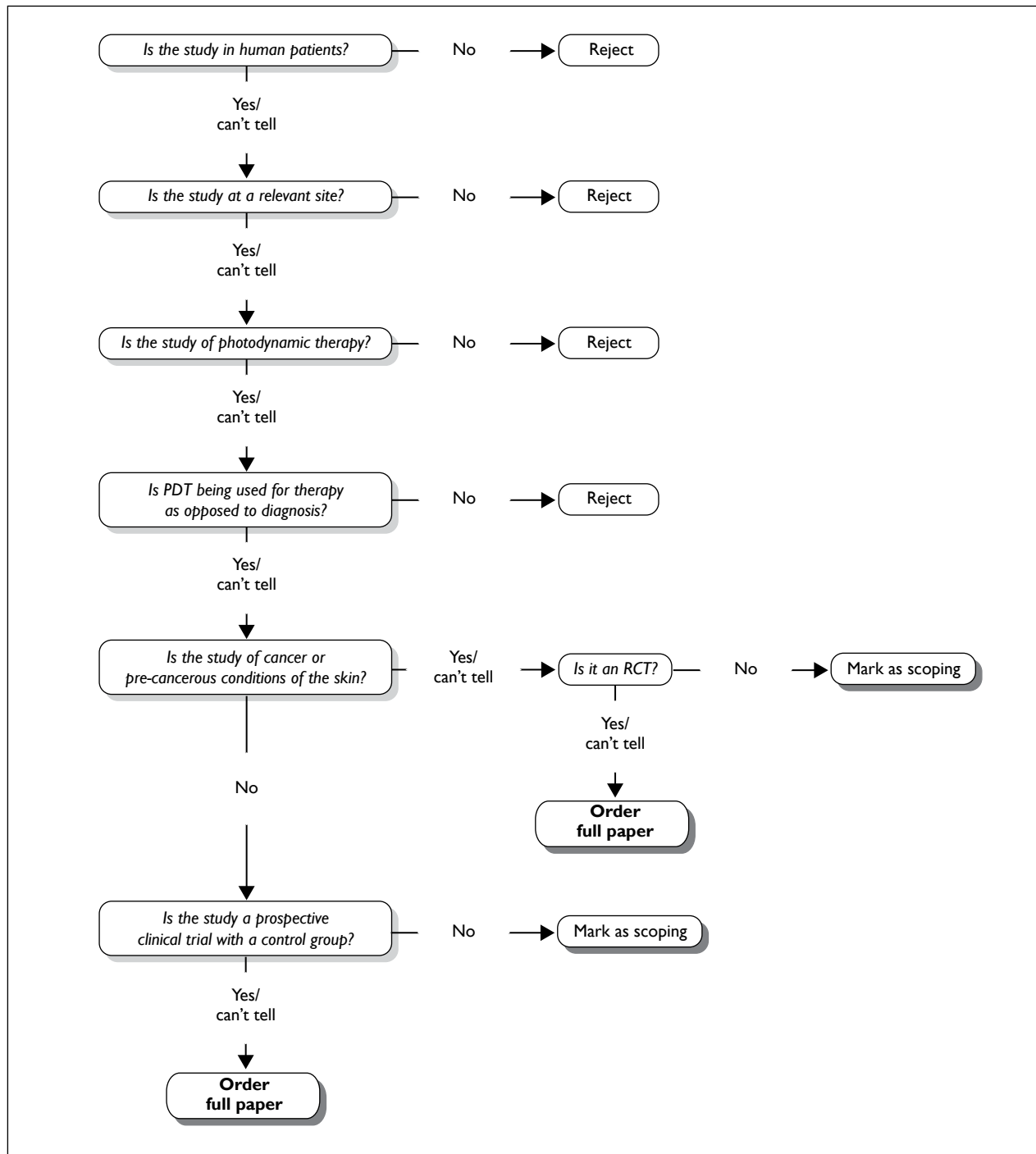


FIGURE 2 Decision algorithm.

of inclusion criteria reported above (see Inclusion criteria). Foreign language papers were assessed by either a single reviewer who was competent in that language or an appointed external reviewer under guidance, but not checked by a second reviewer. Studies that did not fulfil all of the criteria were excluded, with documented reasons.

## Data extraction and quality assessment

Data extraction and quality assessment was undertaken by one reviewer, and independently checked by a second reviewer. Any disagreements were resolved by discussion and if necessary a third reviewer was consulted. Foreign language papers

were extracted by either a single reviewer who was competent in that language or an appointed external reviewer under guidance, but not checked by a second reviewer.

## Data extraction

A standardised data extraction form was developed within EPPI-REVIEWER (see Appendix 2). It was piloted by all reviewers on a selection of studies and refined to ensure consistency of data extraction between reviewers and across sites. Guidelines on its use were produced to enhance consistency.

Data from multiple publications of the same study were extracted and reported as a single study. Within the data extraction tables the term 'linked publications' refers to abstracts or full papers that report related information about the same patient group (see Appendices 13–21). Where publications appeared to be duplicates or linked, these were assessed independently by two reviewers.

Extraction included data on: study details (e.g. study identifier, author, year, country, setting, number of participants, and duration of follow-up), patient characteristics (e.g. age, gender, cancer site and stage), intervention (full details of photosensitising agent with dosage, light source, wavelength spectrum and method of delivery), comparator treatment (type of comparison with full details of delivery methods), and outcomes relating to effectiveness and safety as specified under Inclusion criteria, above. Attempts were made to contact authors for missing data.

## Quality assessment

The quality of RCTs and non-RCTs was assessed using standard checklists, which were adapted, as necessary, to incorporate topic-specific quality issues (see Appendix 2). Quality assessment data were extracted directly into an EXCEL spreadsheet.

## Methods of analysis/synthesis

Data extracted from the studies were tabulated and discussed in a narrative synthesis. The results of the quality assessment were tabulated and graphs created, where appropriate. The influence of quality on the results of the studies and the findings of the review was discussed. Where appropriate, meta-analysis was undertaken using REVMAN software to estimate a summary measure of effect on relevant outcomes based on intention-

to-treat (ITT) populations.<sup>26</sup> Random effects meta-analyses were used throughout. Where ITT results were not explicitly reported, the relevant data were extracted based on data reported in the text, graphs and tables of the publications if possible. Heterogeneity was explored through consideration of the study populations, methods and interventions, by visualisation of results and, in statistical terms, by the chi-squared test for heterogeneity and the  $I^2$  statistic.

## Scoping review

Given the likely paucity of RCTs in some of the cancer sites, a scoping review was undertaken alongside the screening stage of the systematic review. The aim was to document the extent of the observational research in those areas where we anticipated relatively few controlled trials. This was intended to provide as complete a picture of the evidence base as possible, while bearing in mind the inherent bias and limitations of such studies.

All records that met the population, intervention, comparator and outcome criteria reported above, but were excluded on study design, were considered in the scoping review.

For all sites, records that appeared to be uncontrolled trials, observational studies with a control group, case series or case reports were included. In addition, non-RCTs in skin and Barrett's oesophagus were also included. These decisions were made as part of the screening process detailed above (see *Figure 2*). Where the decision to include in the scoping review could be made based on the title and abstract, the full paper was not ordered.

No formal data extraction or quality assessment was undertaken due to the limited time available. For four sites (biliary, brain, head and neck, lung) for which few included studies were identified in the systematic review, the scoping publications were categorised into broad study design groups as follows:

- observational comparative studies
- non-comparative experimental trials
- case series (with 10 or more patients)
- case reports (individual case reports of reports with fewer than 10 patients).

This was done by extracting the cancer site, number of patients and study design, along with

study identifier, author and year of publication into an EXCEL spreadsheet (details available on request). It should be noted that this brief categorisation might not be accurate. It was undertaken by one reviewer and based on the authors' terminology as reported in the publication; however, many publications, often in abstract form, did not provide sufficient details to be clear.

For the remaining sites (pre-cancerous skin, skin, Barrett's oesophagus and oesophageal) no such categorisation was undertaken and all identified references are listed together.

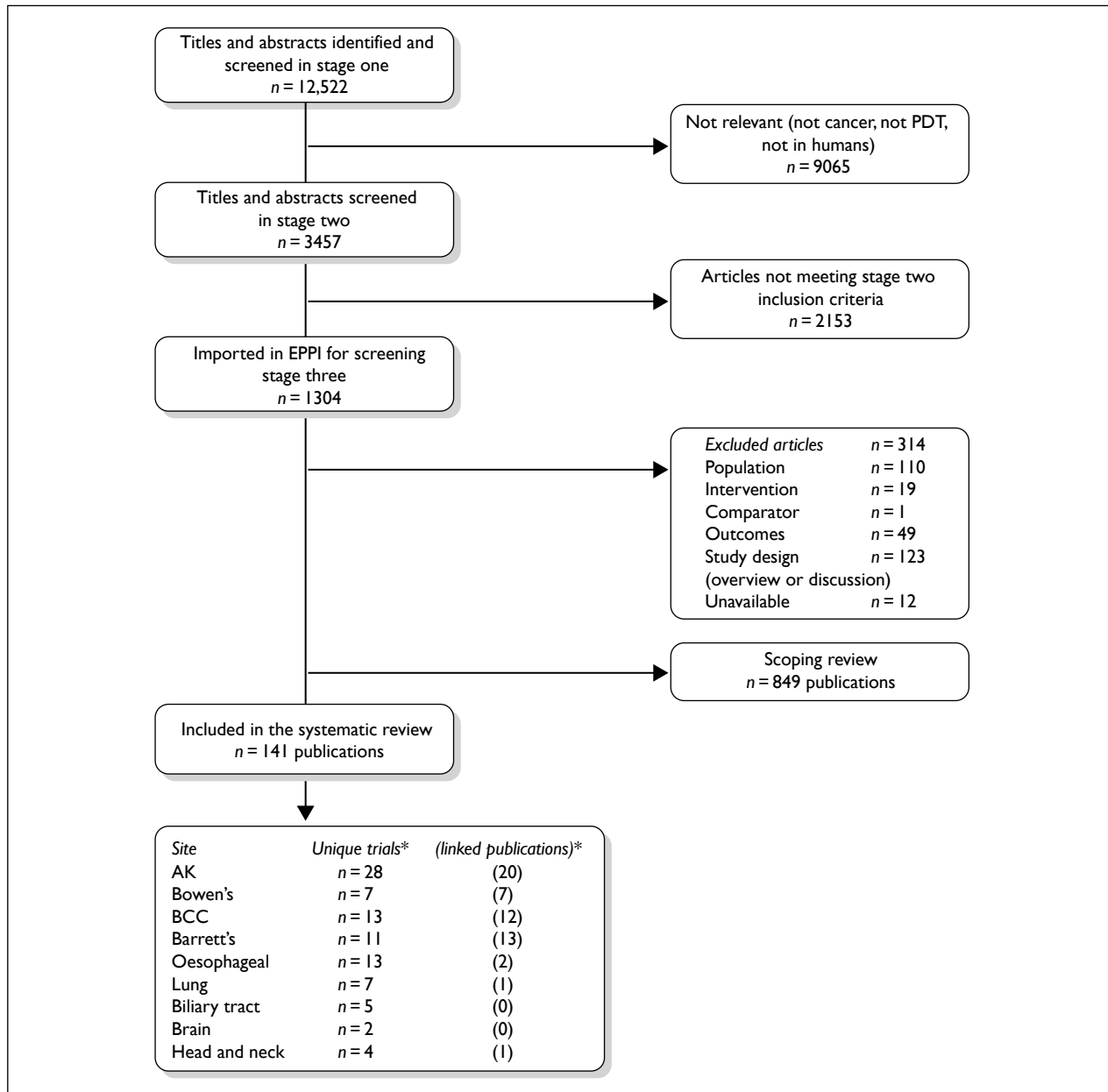
For further details of the findings of the scoping review, see Chapter 5.

## Chapter 4

### Studies included in the systematic review

The search strategies identified 12,522 references, of which 38 were located from hand searches, reference checking and contact with individuals. These were screened as described in the methods chapter, and full copies of 699 papers were obtained and assessed for inclusion in the main review. *Figure 3* shows the flow of studies through the review process and the numbers excluded at each stage.

Duplicate publication of study results and multiple reports of partial data sets appeared to be common. A total of 54 papers were designated as 'linked' publications. Overall, we included 88 trials reported in 141 publications; one publication reported two separate trials, and two publications reported on two sites and were extracted into both relevant groups in this systematic review.



**FIGURE 3** Flow chart of study selection. \*Numbers do not total as one publication reported two separate trials, and two trials included multiple distinct patient groups, thus were extracted more than once. Some publications were linked to more than one study.

## Chapter 5

### Studies excluded from the systematic review

As described previously in Chapter 3, articles that met all of the agreed inclusion criteria apart from study design were included in the scoping review (Figure 4). For all sites, records that appeared to be uncontrolled trials, observational studies with a control group, case series or case reports were included. In addition, non-RCTs on skin and Barrett's oesophagus were also included in the scoping review.

We made the decision to include non-RCTs in the scoping review rather than the systematic review for Barrett's oesophagus because initially our screening indicated there were over 20 RCTs in this area. Subsequent examination revealed that there were only 11 unique trials due to multiple publications.

A total of 849 articles were included in the scoping review; however, this figure is likely to contain a number of linked and duplicate publications. The totals per group do not sum to 849, as some publications appeared to report data for multiple sites and have been included in each accordingly. For each of the sites we have generated a list of scoping records – please see the relevant appendices (Appendices 5–12). For four sites (biliary, brain, head and neck, lung), for which few included studies were identified in the systematic review, the records have been classified in terms of study design according to the authors' terminology and are identified as such in the scoping lists. For all other sites an alphabetical list has been prepared.

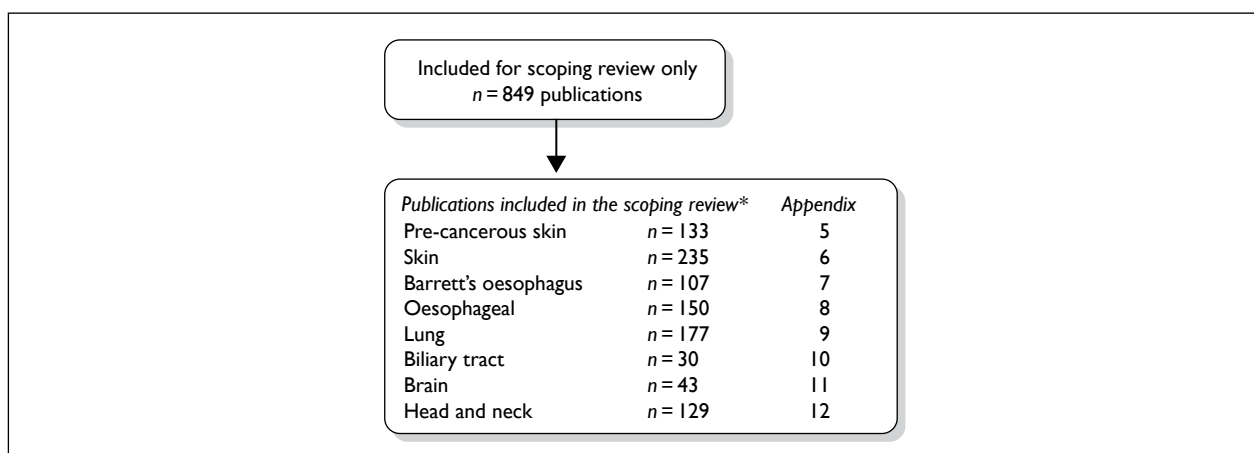


FIGURE 4 Flow chart of scoping review. \*Numbers do not total as some publications report on more than one site.





## Chapter 6

# Skin cancers and pre-cancerous skin conditions

## ACTINIC KERATOSIS

### Background

Actinic (or solar) keratosis is a form of pre-cancerous skin lesion which, based on pathological evidence, is considered to be a precursor to SCC. AK is usually diagnosed clinically rather than histologically, with criteria including parakeratosis, epidermal atrophy or thickening, and atypia.

Actinic keratoses most commonly affect areas that are prone to chronic sun exposure (the face, scalp, backs of hands and forearms) in older populations, especially in men. Most people will have multiple AKs, although single lesions do occur. AK lesions are usually small (less than 1 cm in diameter), erythematous and scaly, and they may become enlarged or bleed. The lifetime risk of developing AK is greater than 50% in parts of Australia and the USA; this rises to 90% in people who are over 80 years old.<sup>27,28</sup> In England the data suggest that prevalence in people over 70 years is around 15% for men and 6% for women.<sup>29</sup>

The exact conversion rate varies but estimates suggest that between 0.25% and 25% may progress to SCC,<sup>30</sup> 3–4% of which will metastasise;<sup>27</sup> early treatment is therefore recommended. Evidence suggests the yearly progression of AK to invasive SCC is between 8 and 24 per 10,000 in an average-risk Australian, while around 2% of these resultant SCCs metastasise, leading to significant morbidity or death.<sup>31</sup> To date no studies have accurately predicted which AKs will progress to invasive SCC. Overall AK incidence is estimated as around 10 times the usual SCC rates.<sup>30</sup>

Data suggest that there is a continuum from AK to SCC in situ (Bowen's disease) to invasive SCC.<sup>31</sup> There is still some debate as to whether AKs should be classed as pre-cancerous or as early stages of actual cancer. AKs are usually graded according to Olsen's criteria, which divide lesions according to thickness: grade I = thin, grade II = moderate and grade III = thick.<sup>32</sup>

Treatment options for AK include destruction (e.g. cryotherapy), topical therapies [such as

fluorouracil (5-FU), imiquimod, diclofenac and retinoids], resurfacing (chemical peels), excision or combinations of these. Choices may be based on location and size of the lesion, as well as cosmetic considerations. The AHRQ (Agency for Healthcare Research and Quality) report on AK states that there is a general consensus that all AKs on the lip, ear, eyelid or in immunocompromised patients should be treated because of the high rate of metastases in these areas.<sup>31</sup>

Photosensitisers that are used to treat AK include ALA and MAL, both of which are usually applied topically as a cream, and left on the skin for an appropriate incubation period. Lesions may be prepared using abrasion or curettage (without local anaesthetic) to scrape away any excess tissue, as in the treatment of BCC.<sup>33</sup> An experimental photosensitiser ATX-S10(Na) has recently been developed but has not yet been trialled in humans.<sup>34</sup>

Illumination is commonly provided by a non-coherent red light source, including an illuminant and a reflector. These can be used to treat large areas and the long wavelength light penetrates relatively deeply into the tissues. Green and blue light may be used but the depth of penetration is reduced – below 1 mm for blue and between 0.5 and 2 mm for green, compared with 1–6 mm for red – making their use suitable only for superficial lesions.<sup>5</sup> Lasers are also being increasingly used as light sources.

### Study characteristics

Twenty-eight RCTs investigated the use of PDT for treating AK, all reporting results between 1998 and 2009 (including 10 studies in 2008) (*Table 2*). Seven trials were reported only as abstracts<sup>35–41</sup> and 20 as published papers<sup>42–61</sup> (see *Table 2*). In total, the studies randomised 2611 participants. One publication reported results for two different trials.<sup>60</sup>

Four RCTs compared PDT with cryotherapy<sup>46,48,51,59</sup> and seven trials compared PDT with placebo PDT (cream).<sup>41,42,44,49,56,58,60</sup> Two three-armed trials

TABLE 2 Actinic keratosis study characteristics

| Authors   | No. patients | Trial treatments   |
|---|--------------|--|
| <b>PDT vs cryotherapy</b>                                   |              |  |
| Kaufmann <i>et al.</i> (2008) <sup>46</sup>                 | 121          | MAL-PDT vs cryotherapy (within-participant comparison)   |
| Morton <i>et al.</i> (2006) <sup>48</sup>                   | 119          | MAL-PDT vs cryotherapy (within-participant comparison)   |
| Szeimies <i>et al.</i> (2002) <sup>51</sup>                 | 202          | MAL-PDT vs cryotherapy   |
| Wennberg <i>et al.</i> (2008) <sup>59</sup>                 | 81           | MAL-PDT vs investigator's choice of treatment, mostly cryotherapy (organ transplant recipients, within-participant comparison)   |
| <b>PDT vs placebo PDT</b>                                   |              |  |
| Fowler and Zax (2002) <sup>44</sup>                         | 243          | ALA-PDT vs placebo PDT   |
| Hauschild <i>et al.</i> (2009), <sup>60</sup> trial AK03    | 103          | ALA-PDT vs placebo PDT   |
| Jeffes <i>et al.</i> (1998) <sup>41</sup> (abstract only)   | 36           | ALA-PDT vs placebo PDT (within-participant comparison)   |
| Dragieva <i>et al.</i> (2004) <sup>42</sup>                 | 17           | MAL-PDT vs placebo PDT; organ transplant recipients (within-participant comparison)  |
| Pariser <i>et al.</i> (2008) <sup>56</sup>                  | 100          | MAL-PDT vs placebo PDT   |
| Pariser <i>et al.</i> (2003) <sup>49</sup>                  | 80           | MAL-PDT vs placebo PDT   |
| Szeimies <i>et al.</i> (2009) <sup>58</sup>                 | 131          | MAL-PDT vs placebo PDT   |
| <b>PDT vs placebo PDT vs cryotherapy</b>                    |              |  |
| Freeman <i>et al.</i> (2003) <sup>45</sup>                  | 204          | MAL-PDT vs placebo PDT vs cryotherapy  |
| Hauschild <i>et al.</i> (2009), <sup>60</sup> trial AK04    | 346          | ALA-PDT vs placebo PDT vs cryotherapy  |
| <b>PDT parameter comparisons</b>                            |              |  |
| Braathen <i>et al.</i> (2009) <sup>54</sup>                 | 119          | MAL-PDT comparing incubation times (1 hour or 3 hours) and doses (160 mg/g or 80 mg/g)   |
| Ericson <i>et al.</i> (2004) <sup>43</sup>                  | 40           | ALA-PDT 50 mW/cm <sup>2</sup> vs ALA-PDT 75 mW/cm <sup>2</sup> vs ALA-PDT 30 mW/cm <sup>2</sup> vs ALA-PDT 45 mW/cm <sup>2</sup> ; total dose 100 J/cm <sup>2</sup> (all treatments) |
| Hauschild <i>et al.</i> (2009) <sup>55</sup>                | 149          | Patch containing ALA (PD P 506 A) applied to lesions for 0.5, 1, 2, or 4 hours, followed by illumination with red light  |
| Legat <i>et al.</i> (2006) <sup>36</sup> (abstract only)    | 22           | MAL-PDT with fractionated illumination vs MAL-PDT with unfractionated illumination (within-participant comparison)   |
| Puizina-Ivic <i>et al.</i> (2008) <sup>57</sup>             | 36           | ALA-PDT with 16-hour incubation and 2 light fractions vs ALA-PDT with 5-hour incubation and a single illumination  |
| Szeimies <i>et al.</i> (2007) <sup>38</sup> (abstract only) | 25           | MAL-PDT with VPL vs MAL-PDT with LED light (within-participant comparison)   |
| Tarstedt <i>et al.</i> (2005) <sup>52</sup>                 | 211          | MAL-PDT single session vs MAL-PDT 2 sessions (1 week apart)  |
| Touma <i>et al.</i> (2003) <sup>39</sup> (abstract only)    | 18           | ALA-PDT 1-hour incubation vs 2-hour incubation vs 3-hour incubation  |
| Wiegell <i>et al.</i> (2008) <sup>53</sup>                  | 30           | MAL-PDT with daylight vs MAL-PDT with red LED (within-participant comparison)  |
| Wiegell <i>et al.</i> (2008) <sup>40</sup> (abstract only)  | 29           | PDT with 8% MAL vs PDT with 16% MAL (within-participant comparison)  |

**TABLE 2** Actinic keratosis study characteristics (continued)

| Authors  | No. patients | Trial treatments  |
|--|--------------|---|
| <b>MAL-PDT vs ALA-PDT</b>                                |              |   |
| Moloney and Collins (2007) <sup>37</sup> (abstract only) | 16           | MAL-PDT vs ALA-PDT  |
| <b>PDT vs 5-FU</b>                                       |              |   |
| Gupta (2004) <sup>35</sup> (abstract only)               | 50           | ALA-PDT vs 5-FU   |
| Kurwa <i>et al.</i> (1999) <sup>47</sup>                 | 17           | ALA-PDT vs 5-FU (within-participant comparison)             |
| <b>Other comparisons</b>                                 |              |   |
| Smith <i>et al.</i> (2003) <sup>50</sup>                 | 36           | ALA-PDT with blue light vs ALA-PDT with laser light vs 5-FU |
| Sotiriou <i>et al.</i> (2009) <sup>61</sup>              | 30           | ALA-PDT vs imiquimod (within-participant comparison)        |

J, joule; mW, milliwatt; VPL, variable pulsed light.

compared PDT with both cryotherapy and with placebo PDT.<sup>45,60</sup> Eleven trials compared PDT using different parameters,<sup>36–40,43,52–55,57</sup> and two compared PDT to 5-FU;<sup>35,47</sup> one three-armed trial compared two different PDT light parameters with 5-FU.<sup>50</sup> One trial compared PDT with imiquimod.<sup>61</sup>

Where studies provided participant information, it was evident that the majority of participants were male, with multiple AKs on the face or scalp. Two studies were of organ transplant recipients.<sup>42,59</sup>

For PDT treatments, MAL and ALA were used as photosensitisers, at doses of 160 mg/g of MAL with red light, and 20% ALA with blue light, in most studies. The drug–light interval (incubation time) was around 3 hours in nearly all of the MAL populations being treated, but varied greatly in the ALA studies (between 45 minutes and 18 hours).

## Study quality

Sample sizes varied widely between 16 and 346 participants, with just over one-third of the studies reporting use of calculations to generate an appropriate sample size. Most participants had more than one lesion treated; even in studies reporting use of a power calculation it was often unclear whether the calculations had accounted for the likely existence of a correlation between lesion responses within patients. The number of independent observations per group may therefore not have been large enough for many studies. Eleven studies did however make use of a within-participant comparison design, removing the possibility of there being baseline differences between treatment groups.

Randomisation and allocation concealment procedures were generally poorly reported, although 46% of trials did report some use of blinding (generally of outcome assessors). Most trials reported incidence of AEs. A graph illustrating study quality is presented overleaf (*Figure 5*).

## Results of effectiveness

The results are presented in a narrative synthesis, and for two comparisons we were able to conduct meta-analyses.

Mortality was not assessed in the AK RCTs as this outcome is less relevant for a non-invasive cancer. Resource use was not evaluated in any of the trials.

### PDT vs cryotherapy

Six trials compared PDT with cryotherapy, with five using MAL<sup>45,46,48,51,59</sup> (one of which was in organ transplant recipients<sup>59</sup>), and one using ALA.<sup>60</sup>

#### Morbidity

Four RCTs of MAL-PDT versus cryotherapy, in patients (other than organ transplant recipients) with mild or moderate lesions, reported lesion complete response (CR) data for the ITT populations (two at 12 weeks<sup>45,51</sup> and two at 24 weeks<sup>46,48</sup>). Although only one study directly reported results for the ITT population, the necessary ITT data could be extracted from the other three studies. Morton *et al.*<sup>48</sup> reported CR at both 12 and 24 weeks, with the 24-week response rates being only marginally the better; this provided the basis of our justification for

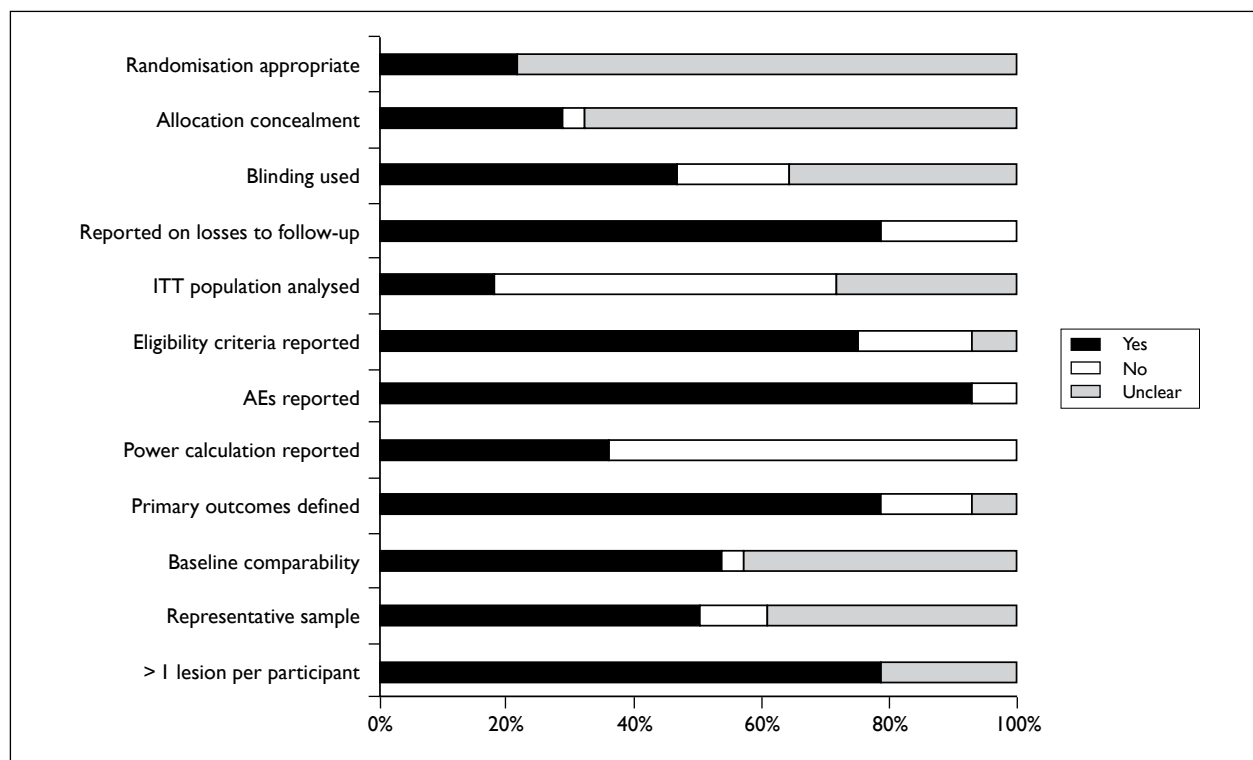


FIGURE 5 Actinic keratosis study quality.

pooling the 12- and 24-week data. All four studies defined a complete lesion response as complete disappearance of a lesion. The individual study results have been combined into a pooled estimate and the results presented in a forest plot (Figure 6).

Although the pooled result [odds ratio (OR) = 0.97; 95% confidence interval (CI) 0.64 to 1.46] indicates that there is no difference in effectiveness

between the treatments, the substantial statistical heterogeneity ( $I^2 = 88\%$ ), coupled with the discernible polarity of individual study results, suggest this result may be unreliable. Two factors in particular may possibly explain the root of this variation. Firstly, the study quality of the trials was variable, with only one trial reporting the use of blinding (of outcome assessors) and reporting appropriate methods for randomisation and

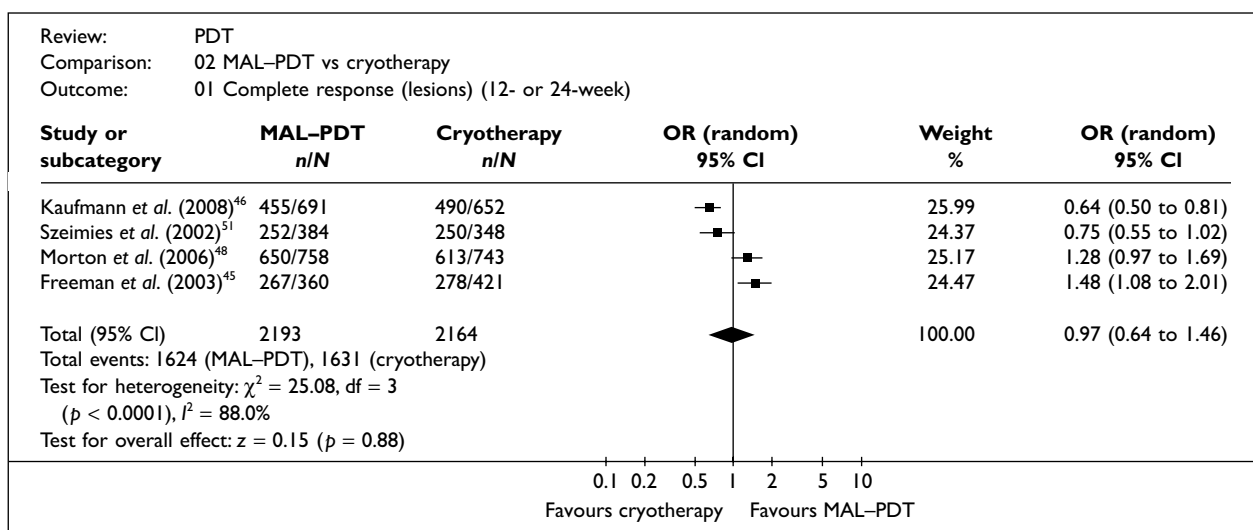


FIGURE 6 Methyl aminolevulinat–photodynamic therapy versus cryotherapy.

allocation concealment;<sup>45</sup> the other three trials may therefore have been subject to bias. Secondly, there was variation in the cryotherapy regimens used, both within and between studies (mean freeze times ranged from 16 to 24 seconds between studies); two studies explicitly stated that individual centres could use their own preferred regimens (relevant details to clarify this information were not provided in the other two studies).<sup>45,46</sup> The effects of this are likely to have been exacerbated by the large numbers of recruiting sites for each trial (ranging from 9 to 25 centres). The large reported variances of freezing time means (which suggested the populations were not normally distributed) made it difficult to adequately assess the possible effect of differing freezing times (between studies). None of the studies reported median times, which could have been useful for this purpose.

Other factors may also have affected the individual study results. Although the number of lesions studied was large, the numbers of patients recruited were more modest (ranging from 119 to 202 participants), raising doubts as to whether the number of independent observations per treatment group was large enough for some trials. Additionally, trials recruiting across a large number of sites sometimes results in small numbers of participants recruited at many of the individual sites, a factor which appears to indicate reduced site performance, for example in terms of correct recruitment, or lower event rates.<sup>62,63</sup>

The only study of PDT versus cryotherapy which used ALA as the photosensitiser utilised a standardised cryotherapy protocol (a freeze time of between 5 and 10 seconds) and reported complete clinical clearance rates at 12 weeks to be significantly better for patients treated with ALA-PDT than with cryotherapy (89% vs 77%,  $p = 0.007$ ).<sup>60</sup> However, it should be noted that the cryotherapy freeze times used were considerably lower than for the trials comparing MAL-PDT with cryotherapy.

One RCT studied the use of MAL-PDT in organ transplant recipients. Wennberg *et al.*<sup>59</sup> evaluated MAL-PDT against investigators' choice of other treatment, which was cryotherapy in 83% of cases. The lesion CR rate in the PDT group at 3 months was 77% compared with 74% in the control group, and recurrence rates were also similar with no statistically significant difference. The lesion response rate at 15 months was 88% in the PDT group versus 89% in the control group. Although the MAL-PDT group had more favourable

outcomes for hypopigmentation, they also had more AEs, such as erythema, pain and crusting (reported by 75% of patients) compared with the control group (reported by 48% of patients).

### Quality of life

Five RCTs presented cosmetic outcomes, as either investigator ratings or preferences, with all reporting PDT achieving significantly better results than cryotherapy.<sup>45,46,48,51,60</sup> However, in only one trial<sup>45</sup> were the outcomes assessed by blinded investigators; the other four studies may have been subject to bias, casting doubt on the reliability of their results.

#### Evidence summary

The evidence is unclear whether MAL-PDT (in five trials) or ALA-PDT (in one trial) is more effective, less effective, or equivalent to cryotherapy for treating AKs. Although PDT appears to produce a better cosmetic outcome than cryotherapy, the lack of blinding in most studies means that there is uncertainty regarding the reliability of this conclusion.

### PDT vs chemotherapy creams (5-FU and imiquimod)

Three trials evaluated the use of ALA-PDT compared with 5-FU,<sup>35,47,50</sup> although one reported just AEs as an outcome,<sup>35</sup> and one was a three-armed trial comparing treatment with 5-FU with PDT using a blue light illuminator, and PDT using a laser.<sup>50</sup> Kurwa *et al.*<sup>47</sup> studied patients with a long history of AK affecting forearms and hands, and randomised (left or right) both treatments to be received in each patient. One trial was of ALA-PDT compared with imiquimod in patients with AK on the hands and forearms.<sup>61</sup>

#### Morbidity

For the 5-FU studies, Kurwa *et al.*<sup>47</sup> found no statistically significant difference after 6 months in the reduction of lesional area between the treatment areas and found that no patients were completely cleared of AKs with either treatment. In a small three-armed trial, Smith *et al.*<sup>50</sup> found PDT with a laser to be somewhat less effective than PDT with blue light or 5-FU.

In the imiquimod study, at 6 months there were no statistically significant differences in overall CR (65% PDT vs 56% imiquimod), or for grade I lesions (72% for both treatments), but PDT resulted in a significantly higher rate of CR for grade II lesions (58% vs 37%,  $p < 0.05$ ).<sup>61</sup>

**Quality of life**

Only Smith *et al.*<sup>50</sup> evaluated QoL outcomes in the 5-FU studies, with results of skin photoageing assessments suggesting the 5-FU and PDT with blue light groups had more benefit in terms of tactile roughness, and the 5-FU and PDT laser groups had more benefit in terms of pigmentation.

Sotiriou *et al.*'s imiquimod study<sup>61</sup> reported no significant differences between treatments in investigator-assessed cosmetic outcome but did find that 69% of patients preferred PDT to imiquimod.<sup>61</sup>

**Evidence summary**

The two trials reporting effectiveness results for PDT versus 5-FU were of uncertain quality, and had small sample sizes, but they suggest there is no difference in effectiveness between the treatments. Results of the imiquimod study suggest that ALA-PDT may be superior to imiquimod for treating grade II lesions.

**PDT vs PDT with placebo cream**

Nine RCTs compared PDT to PDT with placebo cream, with five using MAL<sup>42,45,49,56,58</sup> and four using ALA<sup>41,44,60</sup> as a photosensitiser (two trials were reported in one paper).<sup>60</sup> One study was of organ transplant recipients.<sup>42</sup>

**Morbidity**

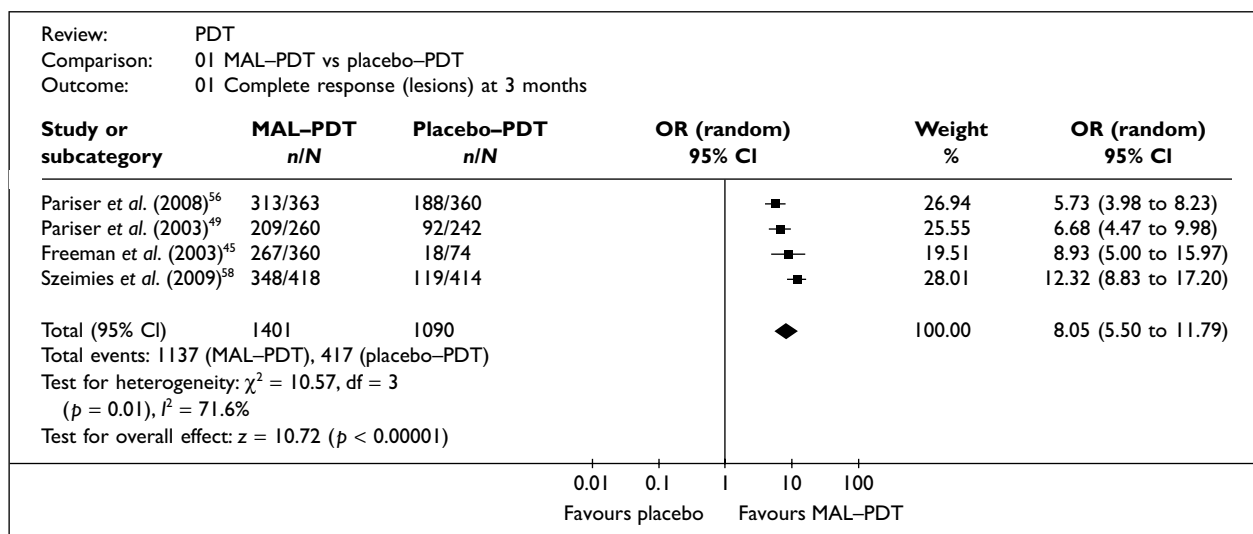
Four RCTs of MAL-PDT versus placebo PDT, in patients (other than organ transplant recipients) with mild or moderate lesions, reported CR data (complete disappearance of the lesion) at 3 months.<sup>45,49,56,58</sup> Where ITT results were not explicitly reported the relevant data were extracted

and the results from the individual studies have been combined and presented in a forest plot (Figure 7).

The pooled result (OR = 8.05; 95% CI 5.50 to 11.79) clearly indicates that MAL-PDT is more effective than treatment with placebo cream. However, the magnitude of effect is more uncertain as there was significant heterogeneity between studies ( $I^2 = 72\%$ ). There appears to be no obvious explanation for this variation (all studies appeared to be generally well conducted, with study investigators blinded in all four trials), other than the fact that all were multicentre trials (with between 5 and 10 sites) with quite small numbers of participants (between 80 and 204), increasing the possibility that institutional differences (e.g. experience of clinicians), protocol deviations, and data from sites with few participants, could have affected the reliability of results.

The one other RCT comparing MAL-PDT with placebo was also generally well conducted, and was of organ transplant recipients with mild to moderate AK.<sup>42</sup> The authors reported overall lesion CR rates of 56/62 for the MAL-PDT group versus 0/67 in the placebo group ( $p = 0.0003$ ).

Of the four RCTs comparing ALA-PDT with placebo PDT one did not report methods and results adequately.<sup>41</sup> Two of the other three trials were reported in one paper and used an incubation time of 4 hours; both reported significantly better lesion CR rates with ALA-PDT (89% vs 29%, and 82% vs 19%).<sup>60</sup> Fowler and Zax<sup>44</sup> also reported lesion CR results strongly favouring ALA-PDT – in



**FIGURE 7** Methyl aminolevulinat–photodynamic therapy versus placebo PDT.

two trials with identical protocols – although the incubation times used were not stated.

### Quality of life

None of the MAL–PDT RCTs adequately reported QoL results for both treatment groups. Pariser *et al.*<sup>49</sup> reported that investigator-assessed cosmetic outcome was ‘excellent’ or ‘good’ in 97% of patients, and that of 32 patients who had received previous types of other treatment (cryotherapy, 5-FU, operation) 73% preferred MAL–PDT.

Of the ALA–PDT trials, only Hauschild *et al.*<sup>60</sup> reported comparative QoL data, finding no significant differences in cosmetic assessment of cleared lesions.

#### Evidence summary

Results from four generally well-conducted RCTs indicate that MAL–PDT is significantly more effective than placebo PDT in achieving lesion CR. The evidence for ALA–PDT, although less robust, also indicates superiority over placebo PDT. However, there remains uncertainty around which are the optimal ALA incubation times, and QoL outcomes were inadequately assessed in most trials.

### PDT using different treatment parameters

Twelve RCTs evaluated the use of PDT using different treatment parameters. Five of these trials studied light sources<sup>50,53</sup> or light doses/durations,<sup>36,38,43</sup> and another five evaluated photosensitisers/photosensitiser doses<sup>37,40</sup> or incubation times (duration of photosensitiser),<sup>39,55</sup> including one which examined both doses and incubation times.<sup>54</sup> One compared the number of PDT sessions<sup>52</sup> and one studied incubation times and light doses.<sup>57</sup>

### Morbidity

Five trials evaluated the effects of varying PDT light parameters, three using MAL<sup>36,38,53</sup> and two using ALA<sup>43,50</sup> as a photosensitiser.

Two RCTs looked at differing light sources. One trial,<sup>50</sup> using ALA as a photosensitiser, reported cumulative clearance rates of 80% using a blue light illuminator compared with 50% using a laser. The trial using MAL as a photosensitiser<sup>53</sup> concluded that PDT with daylight (79% decrease in lesions) was as effective as PDT with red LED light (71% decrease).

Three RCTs looked at differing light doses/durations. Ericson *et al.*<sup>43</sup> reported a significant correlation ( $p < 0.02$ ) between fluence rate and

treatment response (the remaining actinic area) with 30 mW/cm<sup>2</sup> (with a narrow filter) showing the best results. Legat *et al.*<sup>36</sup> reported, in an abstract, that PDT with fractionated and unfractionated illumination were similarly effective in reducing AKs. Szeimies *et al.*<sup>38</sup> reported no significant differences in lesion scores between groups receiving LED light or variable pulsed light (VPL).

Five RCTs evaluated photosensitisers/photosensitiser doses and/or incubation times; two studied ALA,<sup>39,55</sup> two studied MAL<sup>40,54</sup> and one studied both photosensitisers.<sup>37</sup>

Of the two RCTs studying photosensitiser incubation times, Hauschild *et al.*<sup>55</sup> reported that receiving an ALA patch with a 4-hour incubation showed the best response compared with 0.5-, 1- or 2-hour incubations. Touma *et al.*<sup>39</sup> evaluated ALA incubation times of 1, 2 or 3 hours; although the abstract did not report results by treatment group, the authors did report that incubation time had no effect on outcomes.

The small study by Moloney and Collins<sup>37</sup> compared ALA–PDT with MAL–PDT and found no significant differences in efficacy (although ALA was applied for a longer incubation period). Similarly, Wiegell *et al.*<sup>40</sup> reported no differences in response rates when comparing 8% MAL with 16% MAL, with patients receiving daylight as the light source. Braathen *et al.*<sup>54</sup> compared MAL incubation times (1 or 3 hours) and doses (160 or 80 mg/g), in a study with some methodological problems (e.g. the trial protocol was often not followed), suggested that a 1-hour incubation with 160 mg/g may have potential for treating mild AK lesions.

Puizina-Ivic *et al.*<sup>57</sup> reported that a longer ALA incubation with fractionated illumination resulted in fewer patients with persistent lesions at 24 weeks than a shorter incubation with a single illumination (13% vs 75%). However, the extent of the relative contributions of the incubation time and fractionation was unclear.

Tarstedt *et al.*<sup>52</sup> concluded that a single MAL–PDT treatment was as effective as a two-treatment schedule (1 week apart) for thin AK lesions, and recommended repeat treatment for thicker or non-responding lesions.

### Quality of life

For the two light sources studies, Smith *et al.*<sup>50</sup> found that, for signs of photoageing, both light treatment groups showed improvement in global

response, but the signs completely resolved in two patients in the group receiving light from a blue light illuminator, compared with no patients in the laser (595 nm) group. Wiegell *et al.*,<sup>53</sup> in a within-participant comparison study, found that 62% of patients preferred treatment with daylight: 14% with LED light and 21% had no preference.

For the three light doses/durations studies, Szeimies *et al.*<sup>38</sup> found no significant differences in patient satisfaction between the LED light and variable pulsed-light treatments. However, none of the other studies reported QoL outcome.

Very few of the five trials looking at photosensitisers/photosensitiser doses and/or incubation times reported QoL outcomes, and none reported them by treatment group.

Tarstedt *et al.*<sup>52</sup> reported that cosmetic outcome was rated (by the investigator) as excellent in over 75% of lesions in both treatment groups, and that patients who had previously been treated with cryotherapy tended to prefer treatment with PDT.

#### Evidence summary

The 11 trials evaluating PDT parameters were varied in their objectives, and their results suggest further research is needed to ascertain the optimum parameters; particularly since several studies provided limited details on methods/results, and/or had small sample sizes.

However, two RCTs – including one good quality study – suggest that PDT using daylight (as a light source) appears to be a promising option.

## Results of safety

Of the 28 RCTs, 11 assessed AEs in trials of ALA-PDT, 15 in trials of MAL-PDT, one assessed AEs for both photosensitisers, and one did not assess AEs.<sup>57</sup> The extent of assessment varied greatly, and was not always presented by treatment group.

### MAL-PDT vs placebo

Overall, local AEs were reported by between 85% and 98% of patients receiving active PDT and in 45–60% of patients receiving placebo PDT.<sup>49,56,58</sup> Where an AE had been reported by patients receiving active treatment this was judged to be mild in 32–53% of cases, moderate in 42–49% and severe in 5–33%. Between 38% and 93% of patients receiving placebo reported mild AEs, 6–8% reported moderate AEs and 0–4% reported severe AEs. Dragieva *et al.*<sup>42</sup> reported that for placebo

areas discomfort was judged to be mild in all cases while for active PDT discomfort was largely mild or moderate.<sup>42</sup>

Severe local AEs (described as causing considerable interference with daily activities, may be incapacitating or life threatening) included skin-burning sensations, pain of the skin, erythema, skin exfoliation or blisters.<sup>49,56,58</sup> Common local AEs occurred as detailed in *Table 3*.<sup>49,56,58</sup>

Szeimies *et al.*<sup>58</sup> reported that most AEs started during illumination and in the case of skin pain or burning sensations these were transient, resolving within 1 day. Erythema tended to be more persistent (median 4 days' duration) and was also reported after treatment in around 40% of cases.

### ALA-PDT vs placebo

Fowler and Zax<sup>44</sup> found the proportion of patients reporting some or all lesions being oedematous (35% vs 0%) or erythematous shortly after treatment (99% vs 79%), to be higher in the ALA-PDT group compared with the placebo group. All AEs resolved or improved by 4 weeks. PostPDT itching was reported by more patients receiving ALA-PDT than patients receiving placebo (26% vs 7%, respectively). Seven patients had a serious AE (SAE), but none was deemed to be related to treatment.

Hauschild *et al.*,<sup>60</sup> in trial AK03, deemed that transient skin discoloration in one patient was related to ALA-PDT treatment. The same trial also found that patients treated with ALA-PDT had more overall local reactions compared with patients on placebo when treatment was applied (mostly itching, 42% vs 13%, although the 13% placebo figure appeared to be pooled from the two trials). In trial AK04 the authors reported AE rates related to study treatment as being 3% in the ALA group versus 2% in the placebo group.<sup>60</sup>

Jeffes *et al.*<sup>41</sup> reported no differences in hyperpigmentation between the treatment groups, but reported a figure only for the ALA-PDT group (11%).

### MAL-PDT using different treatment parameters

One RCT ( $n = 25$ ) compared LED versus VPL illumination and reported on pain scores assessed immediately after treatment using a visual



**TABLE 3** Common local AEs for MAL-PDT vs placebo

| Local AE                 | Percentage range reported (active) | Percentage range reported (placebo) |
|--------------------------|------------------------------------|-------------------------------------|
| Burning sensations       | 36–72                              | 11–12                               |
| Erythema                 | 52–77                              | 5–21                                |
| Crusting                 | 38                                 | 16                                  |
| Skin pain                | 24–60                              | 0–22                                |
| Blisters                 | 15–19                              | 0–5                                 |
| Skin oedema              | 14–28                              | 2–3                                 |
| Skin ulceration          | 12                                 | 0                                   |
| Scab                     | 26                                 | 0                                   |
| Pruritis                 | 23                                 | 11                                  |
| Skin exfoliation         | 11                                 | 4                                   |
| Stinging skin/discomfort | 14–23                              | 2–3                                 |

analogue scale (VAS) scale.<sup>38</sup> Patients receiving VPL reported significantly lower levels of pain (4.3) than with LED illumination (6.4) ( $p < 0.001$ ).

Legat *et al.*<sup>36</sup> ( $n = 22$ ) compared fractionated and un-fractionated illumination. Two patients terminated treatment due to extreme pain and six areas assigned to un-fractionated illumination had to be treated with an alternative fractionated protocol after the patients complained of intense pain. PDT-induced pain was significantly less in the fractionated area according to VAS score (6.0) than in the un-fractionated area (6.7) ( $p = 0.02$ ).

Braathen *et al.*<sup>54</sup> ( $n = 119$ ) compared different doses and incubation times of MAL-PDT across four groups. No SAEs related to the treatment were reported and most AEs were both mild and local in nature. Between 96% and 99% of patients in each group reported at least one treatment-related AE. Erythema was the most commonly reported AE by 32–50% across groups, with a median duration of 17 days. Skin pain lasted around 12 days and other AEs were transient ( $< 1$  day).

Tarstedt *et al.*<sup>52</sup> ( $n = 211$ ) compared single-session versus double-session MAL-PDT. Although more AEs were reported in the double-PDT group, there was no indication of cumulative local phototoxicity (76 events after first treatment, 46 after the second). Overall 40% of patients receiving single PDT and 50% receiving double PDT reported any AE. The majority of the AEs were mild to moderate intensity and lasted less than 1 day including pain. Median erythema duration was 5 days for single treatment and 2 days for double treatment.

One RCT comparing two doses of MAL cream with daylight as the illumination ( $n = 29$ ) reported that, generally, patients had mild to moderate pain (mean 3.7 on the VAS scale).<sup>40</sup> Erythema and crusting were reported in both 8% and 16% groups but no further details were available.

An RCT of 30 patients compared daylight versus red LED illumination for MAL-PDT and reported that pain was significantly less for the daylight exposed areas during treatment, mean pain score 2 versus 6.7 for LED ( $p < 0.001$ ).<sup>53</sup> These differences were no longer statistically significant 6 hours post treatment. In the LED group, 50% of patients required cold-water spray to control the pain and 25% needed mid-treatment breaks. Both treatment areas developed erythema and crusting.

### ALA-PDT using different treatment parameters

Touma *et al.*,<sup>39</sup> after studying different ALA incubation times, only stated (in an abstract) that phototoxic reactions were well tolerated. Ericson *et al.*<sup>43</sup> found no correlation between fluence rates and pain scores. Hauschild *et al.*<sup>55</sup> reported that five patients had AEs that were considered to be related to study medication (patch ALA), which were: headache, moderate epistaxis and a mild increase in alanine transaminase. The study also found that local reactions during illumination appeared to be dose dependent (26% in the 0.5-hour incubation group vs 66% in the 4-hour group), and that almost all patients had local reactions after treatment. Patients with clearance experienced local reactions to a greater extent than patients without clearance.

### MAL-PDT vs cryotherapy

No systemic AEs were reported by any trial. Overall levels of AE in the PDT groups ranged from 43% to 75%, and 26–72% for cryotherapy. The majority of all reported AEs were recorded as mild/moderate and were transient in nature. Only one trial<sup>46</sup> reported any SAEs – two cases of severe cold exposure injury in the cryotherapy arm.

One trial<sup>48</sup> reported skin discomfort after the first treatment session using a VAS scale and found no significant differences between PDT (5.2) and cryotherapy (4.9) ( $p = 0.24$ ). However, data from Wennberg *et al.*<sup>59</sup> showed that 6% of patients receiving PDT discontinued treatment due to pain despite fans and cold water sprays being used, and most reports of pain were of moderate intensity.

All trials reported that common AEs included skin pain/discomfort, erythema, blistering and crusting. Szeimies *et al.*<sup>51</sup> presented percentages of these AEs by treatment group as follows: burning sensation (PDT 32%, cryotherapy 9%), skin pain (PDT 10%, cryotherapy 13%) and crusting (PDT 5%, cryotherapy 6%).

### ALA-PDT vs cryotherapy

Hauschild *et al.*,<sup>60</sup> in trial AK04, reported AEs related to study treatment as being at 3% in both the ALA-PDT and cryotherapy groups.

### ALA-PDT vs chemotherapy creams (5-FU and imiquimod)

Gupta,<sup>35</sup> in an abstract, reported only that after 1 week patients receiving ALA-PDT showed few signs of irritation (e.g. erythema), but patients treated with 5-FU exhibited moderate to severe erythema. Kurwa *et al.*<sup>47</sup> found that in the first week after treatment the ALA-PDT sites were significantly more painful than the 5-FU sites, but the difference was absent in week 2, and was reversed in week 4; overall there was no significant difference between the groups. A very similar pattern of results was reported for level of erythema. One patient experienced contact sensitivity to 5-FU.

Smith *et al.*<sup>50</sup> found erythema to be the most pronounced AE, with patients receiving 5-FU having the largest average increase. Crusting was only seen in the 5-FU group.

In the imiquimod study reactions to both treatments were reported as being well-tolerated, with erythema being very common in both groups.

All patients experienced burning and pain after PDT, compared to 11% (burning) and 4% (pain) after treatment with imiquimod.<sup>61</sup>

### MAL-PDT vs ALA-PDT

Moloney and Collins,<sup>37</sup> in a split-scalp study of 16 patients, reported statistically significant greater pain at 3, 6, 12 and 16 minutes, and longer duration of discomfort post treatment, on the side treated with ALA-PDT (although ALA was applied for a longer incubation period).

#### Evidence summary

**MAL-PDT:** No systemic or SAEs were reported in any study. Based on 16 RCTs, local skin-related AEs appear to be fairly common in patients receiving MAL-PDT. These include skin pain or discomfort, erythema, crusting, blisters and oedema of the skin. While usually transient, erythema and skin pain, in particular, may have a longer duration, and it is worth noting that despite the use of cooling fans and water sprays a small proportion of patients are unable to tolerate the pain during illumination. There is limited evidence from single small RCTs that fractionated, daylight or VPL illuminations may be less painful than standard LED illumination.

**ALA-PDT:** AE reporting in the ALA-PDT trials was inconsistent, but both ALA-PDT and the alternative treatments generally appear to be well tolerated.

The one study that compared ALA-PDT with MAL-PDT concluded that ALA-PDT was the more painful treatment, but the small sample size, lack of methodological details and a difference in incubation times mean that the reliability of this conclusion is uncertain.

### Ongoing trials

There were eight ongoing or unpublished trials for which we could obtain no results details (*Table 4*).

### Discussion

The placebo-controlled trials were generally well conducted and clearly illustrate that PDT is an effective treatment for AK. But the MAL-PDT-versus-cryotherapy trials produced conflicting results, probably due to methodological weaknesses, suggesting that further high-quality RCTs are required. These trials would need clearly defined protocols for administering all study treatments, longer follow-up periods, and adequate blinding of outcome assessors. Only one RCT has been conducted that compared ALA-PDT with cryotherapy, so similar uncertainties of relative efficacy also exist.

**TABLE 4** Ongoing studies in AK

| Investigator  | Interventions  | Start date     | Status   |
|---------------|--|----------------|--|
| Witherspoon J | ALA-PDT with pulsed-light PDT vs no treatment                                  | August 2007    | Expected December 2008, but listed as recruiting in September 2008 |
| Hauschild A   | PDT + red light vs placebo   | March 2006     | December 2007 – listed as completed                                |
| Szeimies RM   | PDT (using PD P 506 A) vs placebo or cryotherapy                               | March 2006     | November 2007 – listed as completed                                |
| Oseroff A     | ALA-PDT – various exposure periods and laser doses                             | May 2005       | Listed as recruiting   |
| Wulf H        | MAL-PDT with daylight  | June 2008      | Expected January 2009  |
| Roberts F     | ALA-PDT – investigation for Bowen's disease and AK, dose fractionation for BCC | February 2002  | February 2004 – listed as completed                                |
| Wulf H        | MAL-PDT using sunlight   | May 2006       | February 2007 – listed as completed                                |
| Pariser D     | MAL-PDT vs placebo (using LED light source)                                    | September 2007 | Expected October 2007, listed as completed                         |

The two RCTs of PDT versus 5-FU had small sample sizes and were of uncertain quality, so further research is needed. There is also a noticeable dearth of RCTs comparing PDT with imiquimod, diclofenac and retinoids. The results of any future PDT versus cryotherapy trials should be viewed in the context of the results of trials comparing topical chemotherapy agents for AK (e.g. 5-FU vs imiquimod).

Factors such as patient preference, lesion thickness and number, availability of treatments and expertise, and whether a treatment can be given at home can all play a role in determining which therapy is used to treat AK. Having a range of options, including PDT, is therefore preferable.

The results of trials comparing different ways of delivering PDT indicate that optimum parameters have yet to be found. The suggestion that daylight could be an effective light source appears worthy of further investigation, especially as there may be additional benefits in terms of time and cost savings.

Providing enough patients can be recruited (i.e. there are enough independent comparisons), the use of within-patient comparison trials should be favoured whenever possible – ideally randomising treatment to opposite sides of the body – as this eliminates the possibility of baseline differences. Patients acting as their own controls

would also mean that fewer patients would need recruiting than in conventional controlled trial designs. However, investigators would also need to be confident there would be no systemic study treatment effects, for example the possibility that PDT treatment may enhance outcomes in areas treated with cryotherapy. Systemic effects are theoretically possible as it is known that PDT can affect the immune system, although it should be noted that few systemic AEs were reported in the RCTs in this review (and no trials reported systemic photosensitisation effects). The results of 10 AK RCTs were reported in 2008, suggesting that this is still an active area of research.

## BOWEN'S DISEASE

### Background

Bowen's disease is a pre-invasive form of squamous cell skin cancer, also called SCC in situ. Lesions can be located on several different parts of the body but are commonly found on the head, neck and lower limbs.<sup>64</sup> Bowen's disease is most often seen in people in their 60s and 70s, and is about three times more common in women than men.<sup>65</sup> Whilst Bowen's disease often occurs on chronically sun exposed sites, sun exposure does not seem to be the only explanation for its aetiology. The incidence of Bowen's disease is about 15 per 100,000 people.<sup>66</sup>

In Bowen's disease the carcinoma is present within the epidermis and has not breached the basement membrane. If left untreated, the disease can invade the dermis (invasive SCC) and there is then the potential to metastasise. Approximately 3% of cases will develop into invasive disease.<sup>67</sup>

The choice of therapy depends on patient suitability, and location and number of lesions. As lesions of Bowen's disease are often large and multiple and commonly found on the lower legs in frail, elderly patients, treatment by destructive therapies can be associated with significant morbidity. Treatment options include surgery, cryotherapy, curettage, radiotherapy and topical therapies using 5-FU or imiquimod. Watchful waiting may be used if a patient is frail, as in Bowen's disease only a small number of cases will become invasive.

In PDT for the treatment of Bowen's disease a photosensitising cream is applied to the affected area, usually a few hours before treatment with the light. As with the above treatment options, it has a curative intent and can be repeated if response is incomplete. It can be used as an alternative to the options described above. It is considered to be the treatment of choice on a lower leg site. It may also be used where lesions are large or multiple or where other treatments have failed or are inappropriate.<sup>64</sup>

## Study characteristics

Seven RCTs investigated PDT for Bowen's disease (Table 5). Six trials had a total number of 362 patients and one trial did not state participant numbers.<sup>68</sup> All trials were published as full papers and often as abstracts too; references in the table relate to only the full papers.

Different methods of delivering PDT were explored in four trials.<sup>57,68-70</sup> PDT was compared with cryotherapy in two trials<sup>71,73</sup> and with 5-FU in two trials,<sup>72,73</sup> while one trial also had a placebo PDT treatment.<sup>73</sup> ALA or MAL creams or intravenous verteporfin were used as photosensitisers. The drug to light interval varied from 1 to 16 hours across the studies.

## Study quality

Five out of seven trials were published within the last 6 years,<sup>57,68,69,72,73</sup> with two being considerably older.<sup>70,71</sup> All except one trial had fewer than

50 patients. The largest trial (229 patients) was conducted in 40 centres across 11 countries, raising the possibility of institutional differences and protocol deviations.<sup>73</sup> In the majority of trials, procedures for randomisation, allocation concealment and blinding of outcome assessors were unclear. It was not always clear if results presented were statistically significant. All except two trials reported AEs.<sup>57,68</sup> Generally reporting was limited, making the reliability of studies difficult to assess. A graph illustrating study quality is presented in Figure 8.

## Results of effectiveness

Results are presented in a narrative synthesis. Meta-analysis was not possible due to heterogeneity between the trials. Mortality was not assessed in this group of studies; however, this outcome is less relevant for a non-invasive cancer. QoL outcomes were sparsely reported and resource use was not evaluated in any of the trials.

### PDT vs cryotherapy

Two trials by Morton *et al.*<sup>71,73</sup> compared PDT with cryotherapy. One of the trials also compared PDT with placebo PDT and 5-FU and is further discussed below.<sup>73</sup> The larger trial used MAL-PDT,<sup>73</sup> whereas the smaller one used ALA as a photosensitiser.<sup>71</sup>

### Morbidity

The larger, more recent trial by Morton *et al.*<sup>73</sup> found better CR rates and lower recurrence rates with PDT than with cryotherapy. There was a statistically significant difference between the two treatments at 12 months favouring PDT (OR = 1.77; 95% CI 1.01 to 3.12). At 24 months, sustained CR rates were similar (PDT 68%, cryotherapy 60%). The smaller, older trial by Morton *et al.* also found better CR rates for PDT (100%) than cryotherapy (90%) and lower recurrence rates. In this trial, taking size of lesion into account, the probability that a lesion is completely cleared at first treatment was statistically significantly better with PDT ( $p < 0.01$ ).<sup>71</sup>

### Quality of life

The larger trial by Morton *et al.*<sup>73</sup> found higher rates of 'good or excellent cosmetic outcome' with PDT at 3 months, which was maintained at 12 and 24 months. The smaller trial reported that 12 months following clearance, four lesions had visible scarring after cryotherapy, whereas none did after PDT.<sup>71</sup>

**TABLE 5** Bowen's study characteristics

| Authors   | No. of participants     | Trial treatments   |
|---|-------------------------|--|
| de Haas <i>et al.</i> (2007) <sup>69</sup>      | 40 (50 lesions)         | ALA-PDT using a single illumination vs ALA-PDT with a twofold illumination   |
| Morton <i>et al.</i> (2000) <sup>70</sup>       | 19 (70 lesions)         | ALA-PDT with red light vs ALA-PDT with green light   |
| Morton <i>et al.</i> (1996) <sup>71</sup>       | 19 (40 lesions)         | ALA-PDT vs cryotherapy   |
| Puizina-Ivic <i>et al.</i> (2008) <sup>57</sup> | 15                      | ALA-PDT with 16-hour incubation and two light fractions vs ALA-PDT with 5-hour incubation and a single illumination    |
| Salim <i>et al.</i> (2003) <sup>72</sup>        | 40 (66 lesions)         | ALA-PDT vs 5-FU  |
| Lui <i>et al.</i> (2004) <sup>68</sup>          | Not stated (34 lesions) | PDT at 60J/cm <sup>2</sup> vs PDT at 120J/cm <sup>2</sup> vs PDT at 180J/cm <sup>2</sup> using intravenous verteporfin |
| Morton <i>et al.</i> (2006) <sup>73</sup>       | 229 (275 lesions)       | MAL-PDT vs placebo PDT vs cryotherapy vs 5-FU  |

**Evidence summary**

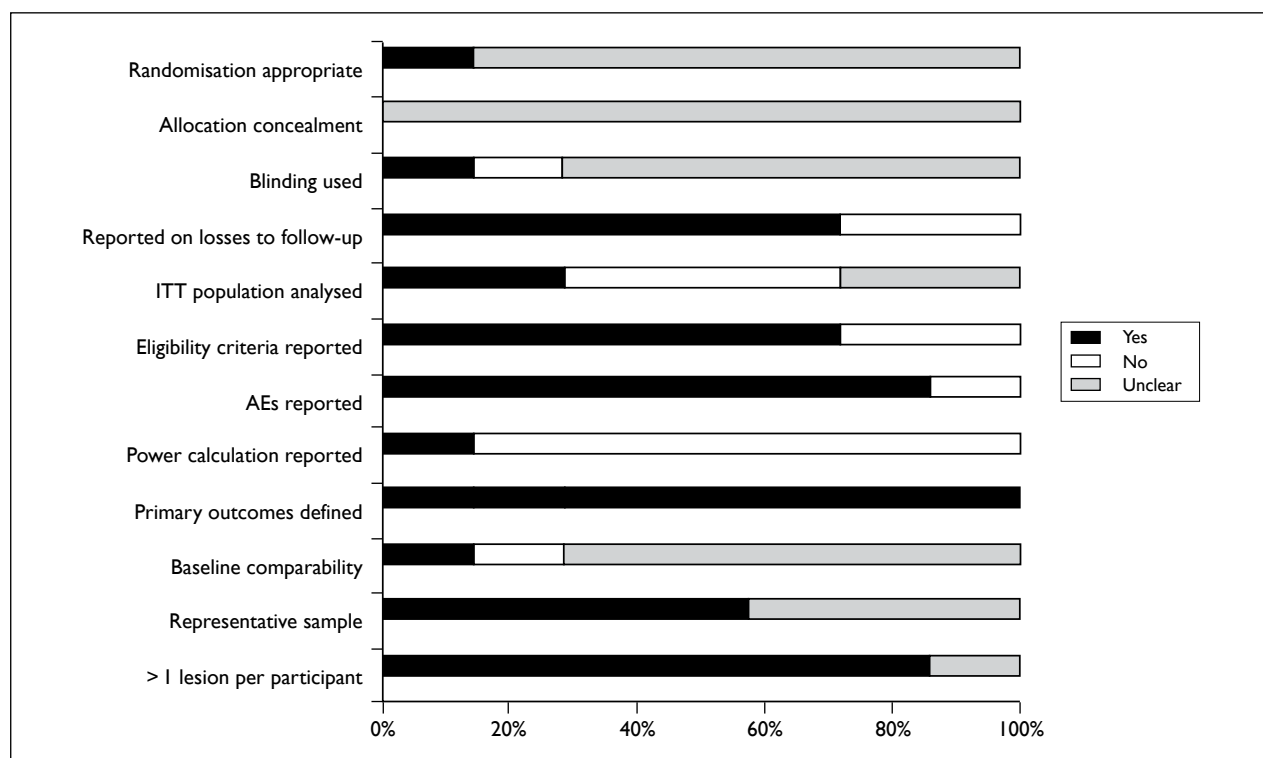
Based on two RCTs with some methodological limitations, PDT appears to result in better rates of CR and has a better cosmetic outcome with PDT than cryotherapy.

**PDT vs 5-FU**

Two trials compared PDT with 5-FU.<sup>72,73</sup> The larger trial by Morton *et al.*,<sup>73</sup> described above, used MAL-PDT, whereas the smaller one by Salim *et al.*<sup>72</sup> used ALA as a photosensitiser.

**Morbidity**

The larger, more recent trial by Morton *et al.*<sup>73</sup> found better CR rates and lower recurrence rates with PDT when compared with 5-FU. In the trial by Salim *et al.*,<sup>72</sup> after adjustment for lesion size on response, the difference in initial clearance rates was not significant. However, overall clearance at 12 months was statistically significant. The PDT group had clearance of 27 out of 33 lesions (82%), whereas the 5-FU group had clearance of 16 out of 33 lesions (48%) (OR = 4.78; 95% CI 1.56 to 14.62,  $p = 0.006$ ). At 24 months sustained CR rates were similar (PDT 68%, cryotherapy 59%).

**FIGURE 8** Bowen's study quality.

### Quality of life

The trial by Morton *et al.*<sup>73</sup> found higher rates of 'good or excellent cosmetic outcome' with PDT at 3 months, maintained at 12 months. The trial by Salim *et al.*<sup>72</sup> did not assess this outcome.

#### Evidence summary

Based on two RCTs with some methodological limitations, PDT appears to result in lower recurrence rates and hence better overall clearance than 5-FU. Cosmetic outcomes may be better but this is based on only one RCT.

### PDT with different treatment parameters

Different methods of delivering PDT were explored in four trials.<sup>57,68–70</sup> All four trials were small. One trial had a patient population of patients with various non-melanoma skin cancers in addition to a very small number with Bowen's disease. This trial did not present all results by diagnosis and is not discussed here.<sup>68</sup> One trial had a sample with either AK or Bowen's disease, again not presenting all results by diagnosis.<sup>57</sup> Three trials used ALA as a sensitiser but one evaluated red versus green light,<sup>70</sup> whereas the other two considered the relative benefits of single and twofold illumination.<sup>57,69</sup>

### Morbidity

In the trial by de Haas *et al.*,<sup>69</sup> CR rates at 12 months were not statistically significantly different between the single and twofold-illumination treatment groups. Equally, healing time was not statistically significantly different. However, the trial by Puizina-Ivic *et al.*<sup>57</sup> found fewer residual tumours at 24 months in the fractionated, longer incubation group than in the single-illumination group. In the trial by Morton *et al.* treatment with red light was superior to treatment with green light. Initial response rates were 94% with red light and 72% for green light ( $p = 0.002$ ). There were also statistically fewer recurrences with red light (OR = 0.13; 95% CI 0.04 to 0.48).

### Quality of life

Two trials did not discuss this outcome,<sup>57,69</sup> whereas the other reported that no clinically obvious scars were evident at 1 year in either red or green light conditions.<sup>70</sup>

#### Evidence summary

This small group of trials points to the need for ongoing research into the optimum parameters for the delivery of PDT to ensure the best patient outcomes.

## Results of safety

Five trials reported AEs relating to PDT and Bowen's disease.<sup>69–73</sup> Results for ALA,<sup>69–72</sup> and MAL<sup>73</sup> are presented separately; AEs were not reported for the only trial using verteporfin.<sup>68</sup>

### ALA-PDT

In one trial comparing single with twofold illumination, no SAEs were observed in either group.<sup>69</sup>

In the trial by Morton *et al.*<sup>71</sup> comparing PDT with cryotherapy, PDT resulted in statistically significantly less pain during treatment ( $p = 0.01$ ). Six patients in this trial who received both treatments reported PDT as less painful. The trial by Salim *et al.*<sup>72</sup> found that in a comparison of intensity and duration of pain, more pain was experienced in the 5-FU group than in the PDT group ( $p = 0.01$ ). However, comparison of total pain over time resulted in no statistically significant difference in the median pain scores between the two treatment groups. In the trial by de Haas *et al.*,<sup>69</sup> pain during treatment was experienced by five patients in the twofold-illumination group and by none of the patients in the single-illumination group. In the trial by Morton *et al.*<sup>70</sup> comparing red and green light, no significant difference in pain was observed between the treatment groups.

Morton *et al.*<sup>71</sup> found that there were no instances of blistering and infection in the PDT groups in a trial comparing PDT with cryotherapy. In the trial by Morton *et al.*<sup>70</sup> of red and green light, no ulceration or infection was reported in either of the red- or green-light treatment groups. In the trial by Salim *et al.*,<sup>72</sup> no patients in the PDT group experienced ulceration of the lesions and there was no clinically obvious scar formation at 12 months at any PDT treatment site.

No photosensitivity reactions were found in either group in the trial comparing red and green light,<sup>70</sup> and in the trial comparing PDT with cryotherapy.<sup>71</sup>

### MAL-PDT

In the trial by Morton *et al.*,<sup>73</sup> most treatment-related AEs were mild (60%) or moderate (34%). Severe AEs were noted in 6% of patients treated with PDT and 12% of patients undergoing cryotherapy. SAEs were reported in four PDT patients, two placebo patients and three cryotherapy patients, of which only one event in

the cryotherapy group, and none of the others, were considered to be treatment related. At 24 months, AEs were said to be of a shorter duration than with other treatments (no data provided).

#### Evidence summary

Serious treatment-related AEs have not been reported for PDT in the treatment of Bowen's disease. However, trials are generally small and rarer AEs might not, therefore, be observed. It is unclear whether PDT is more or less painful than other treatments and how altering PDT parameters might impact on pain. In the trials where this outcome was reported, photosensitivity did not emerge as a significant issue.

## Ongoing trials

We are aware of two potentially ongoing/unpublished trials of PDT for Bowen's disease but could not obtain any further information about them (Table 6).

## Discussion

The majority of the trials of PDT in Bowen's disease are small and have methodological limitations. Only three trials compared PDT to another treatment (cryotherapy and/or 5-FU). There was no investigation of imiquimod in relation to PDT. There are suggestions of better outcomes, especially of a cosmetic nature, with PDT but these would need confirmation in further, well-designed comparative trials. Such trials would also need to consider differences in AE profiles between treatments. More clarification of the optimal parameters for PDT is also needed in terms of effectiveness and safety.

## BASAL CELL CARCINOMA

### Background

Basal cell carcinoma is the most common form of skin cancer, and around 85% of lesions affect the

head and neck areas.<sup>74</sup> Generally slow growing and locally invasive, BCC may take a variety of clinical appearances such as nodular, cystic, superficial, morpoeic, ulcerated or pigmented. Risk factors for BCC include fair skin phototype, tendency to freckles, and excessive exposure to ultraviolet light, male gender and smoking. Nodular BCC is the most common type in the UK, while in other countries such as the USA and Australia superficial BCC is particularly common.<sup>75</sup>

Incidence rates for BCC vary widely across the literature, partly due to differences in latitude and sun exposure, and possibly due to incomplete registration of tumours (Table 7 provides examples).<sup>75,76</sup> If left untreated, BCCs can cause extensive tissue damage, particularly on the face. Superficial BCCs often occur in large multiple patches on the trunk and may not be amenable to surgery.

Treatment options for BCC include the following: surgical excision (with margins of normal tissue/excision under frozen section control/Mohs micrographic surgery in complex cases); curettage; cryosurgery; laser; radiotherapy; intralesional therapy; immunomodulation, where agents, such as imiquimod, are used to stimulate the immune system to eradicate the tumour; chemotherapy (topical 5-FU) and PDT.

Photodynamic therapy for the treatment of BCC is usually given to lesions prepared by preliminary surface curettage, although it may be given without preparation. A cream containing a photosensitising agent is applied to the area of the lesion and pre-defined margin, and a light-occlusive dressing is then applied for the incubation period. In some cases the photosensitiser may be given intravenously. Excess cream is removed and an appropriate wavelength of light used to activate the photosensitiser, resulting in tumour destruction.

The guidelines for topical PDT produced by the British Photodermatology Group emphasised that there are a number of possible light sources, and as yet disease-specific irradiance, wavelength and

TABLE 6 Ongoing Bowen's studies

| Investigator           | Interventions  | Start date    | Status                              |
|------------------------|--|---------------|-------------------------------------|
| Verzijl A or Krekels G | Excision vs PDT for Bowens   | May 2007      | Listed as recruiting                |
| Roberts F              | ALA-PDT – investigation for Bowen's and AK, dose fractionation for BCC | February 2002 | February 2004 – listed as completed |

**TABLE 7** Incidence rates for BCC

| Country        | BCC rate per 100,000 people |
|----------------|-----------------------------|
| Australia      | 788                         |
| USA            | 146                         |
| Western Europe | 200                         |
| UK             | 100                         |

dose characteristics have not been agreed upon.<sup>5</sup> Experts suggest that the pre-illumination interval is likely to be disease dependent. Light sources for cutaneous PDT include lasers, xenon arc/discharge lamps and incandescent filament lamps; however, solid-state LEDs are now the most commonly used. The sources are usually aimed at producing the 'red' spectrum, around 630 nm, to maximise tissue penetration.

Early studies have indicated that photosensitiser absorption may vary between types of skin cancer, suggesting that effectiveness in one type, for example nodular, may not be a transferable finding to superficial BCC; this review therefore deals with nodular and superficial separately.<sup>5</sup>

The key outcomes for PDT treating BCC are lesion clearance (partial or total), recurrence of lesions and cosmetic appearance. PDT may be considered where cosmetic outcomes are of a high priority and/or the lesion is too large for surgery.<sup>12</sup>

## Study characteristics

A total of 13 between-participant comparative RCTs were included, which reported on PDT for BCC (Table 8). All trials were curative in nature, and 11 were reported in full papers, the remaining two were available as single or multiple abstracts only.<sup>77,78</sup> Cosmetic outcomes were reported as investigator-assessed in most studies with patient-reported outcomes largely absent.

Five RCTs assessed PDT as a treatment for primary superficial BCC: one study compared different photosensitisers,<sup>81</sup> two trials looked at different light sources,<sup>83,89</sup> one study compared PDT with cryotherapy,<sup>79</sup> and the final study compared MAL-PDT with surgery.<sup>80</sup> The following topical photosensitisers were used in these studies: 160 mg/g of methyl aminolevulinic acid (MAL), 10% or 20% aminolevulinic acid (ALA) cream, 10% methyl-aminolevulinic acid (mALA) cream.

Photosensitising creams were applied for 3 hours prior to MAL-PDT and 3–6 hours for ALA-PDT; light dosage and sources varied.

Six RCTs reported on PDT for nodular BCC, four studies compared MAL-PDT with various other alternatives (placebo photosensitiser, ALA-PDT),<sup>77,78,84,90</sup> and the remaining trials compared ALA-PDT with excision surgery.<sup>87,91</sup> In all studies the lesions were prepared with superficial curettage or debridement before application of the topical photosensitiser: 20% ALA cream or 160 mg/g of MAL cream. In some studies PDT was routinely repeated after 7 days, and in all but one trial PDT was repeated after 3 months if there was evidence of residual lesions. The drug to light interval was between 3 and 6 hours. Light was delivered at between 570 and 730 nm across the studies, most trials reported using a total light dose of 75 J/cm<sup>2</sup>, although Berroeta *et al.*<sup>87</sup> used 125 J/cm<sup>2</sup>.<sup>87</sup>

Two further RCTs reported on mixed populations with nodular, superficial or non-specified BCCs.<sup>68,88</sup> One trial<sup>68</sup> compared three different wavelengths of PDT reporting results according to BCC type; however, this older study was the only one to use intravenous verteporfin and the results were not considered to add significantly to the evidence base. The second study<sup>88</sup> compared ALA-PDT with cryotherapy but did not report the results by BCC type, making it difficult to draw useful conclusions from the data. Full results for both studies are available in the relevant data extraction tables (Appendix 15).

## Study quality

The trials on primary superficial BCC were difficult to assess as most publications did not provide detailed information on aspects of methodology that are used to assess quality, for example methods of randomisation, blinding and dropouts. One study was well conducted but questions about the implementation of the PDT treatment suggested that the results may not be reliable.<sup>82</sup> The trials comparing MAL-PDT with cryotherapy<sup>79</sup> and surgery<sup>80</sup> did not report power calculations, meaning that it is unclear if the studies were underpowered to have detected differences between treatments.

Of the six trials on nodular BCC, two were relatively small but appeared to be robust,<sup>84,87</sup> two trials were reasonably sized, well reported and



TABLE 8 BCC study characteristics

| Authors  | No. of participants        | Trial treatments  |
|--|----------------------------|---|
| <b>Superficial</b>                               |                            |   |
| Bassett-Seguín (2008) <sup>79</sup>              | 118 patients (219 lesions) | MAL-PDT vs cryotherapy  |
| Szeimies (2008) <sup>80</sup>                    | 196 patients               | MAL-PDT vs excision surgery   |
| Schleier (2007) <sup>81</sup>                    | 24 patients (112 lesions)  | ALA-PDT vs mALA-PDT   |
| Soler (2000) <sup>82</sup>                       | 83 patients (245 lesions)  | Laser ALA-PDT vs broadband lamp ALA-PDT   |
| de Haas (2006) <sup>83</sup>                     | 154 patients (505 lesions) | Fractionated-illumination ALA-PDT vs single-illumination ALA-PDT                                  |
| <b>Nodular</b>                                   |                            |   |
| Foley (2003) <sup>77</sup> (abstract only)       | 66 patients                | MAL-PDT vs placebo cream PDT  |
| Tope (2004) <sup>78</sup> (abstract only)        | 65 patients (80 lesions)   | MAL-PDT vs placebo cream PDT  |
| Kuijpers (2006) <sup>84</sup>                    | 39 patients (43 lesions)   | ALA-PDT vs MAL-PDT  |
| Rhodes (2007) <sup>85</sup>                      | 103 patients (118 lesions) | MAL-PDT vs excision surgery   |
| Mosterd (2008) <sup>86</sup>                     | 149 patients (173 lesions) | Fractionated-illumination ALA-PDT vs excision surgery   |
| Berroeta (2007) <sup>87</sup>                    | 31 patients (40 lesions)   | ALA-PDT vs excision surgery   |
| <b>Superficial, nodular, BCC unspecified</b>     |                            |   |
| Lui (2004) <sup>68</sup>                         | (387 BCC lesions total)    | Systemic PDT at 60J/cm <sup>2</sup> vs PDT at 120J/cm <sup>2</sup> vs PDT at 180J/cm <sup>2</sup> |
| <b>Superficial and nodular reported together</b> |                            |   |
| Wang (2001) <sup>88</sup>                        | 88 patients                | ALA-PDT vs cryotherapy  |
| mALA, methyl-aminolevulinic acid.                |                            |   |

included longer-term follow-up,<sup>85,86</sup> while the final two studies were difficult to assess based on the limited information provided.<sup>77,78</sup>

The trial that compared different wavelengths in PDT on various types of BCC was poorly reported, little detail on the trial methods was given and the results appeared to be incomplete.<sup>68</sup> Wang *et al.*'s trial<sup>88</sup> was clearly reported and well conducted, suggesting that the results were likely to be reliable, although this was the only study that did not look at a particular subtype of BCC. A graph illustrating study quality is presented in *Figure 9*.

## Results of effectiveness for superficial basal cell carcinoma

Results are presented in a narrative synthesis. Meta-analysis was not possible due to heterogeneity between the trials. Five RCTs ( $n = 575$  patients,

> 1000 lesions) compared types of PDT, PDT with cryotherapy or with surgery. None of the trials reported mortality or resource use data.

### PDT vs cryotherapy

One RCT by Bassett-Seguín *et al.*<sup>79</sup> compared MAL-PDT with double-freeze thaw cryotherapy with long-term follow-up. Data were reported at 3 months ( $n = 115$  patients), 12 months (105 patients), 36 months ( $n = 107$  patients) and 5 years.

### Morbidity

There were no statistically significant differences in lesion recurrence or CR rates between the two treatments at any follow-up point.

### Quality of life

PDT resulted in statistically better cosmetic appearance when compared with cryotherapy at both 3-month and 5-year follow-up points. The investigators reported an 'excellent' outcome for

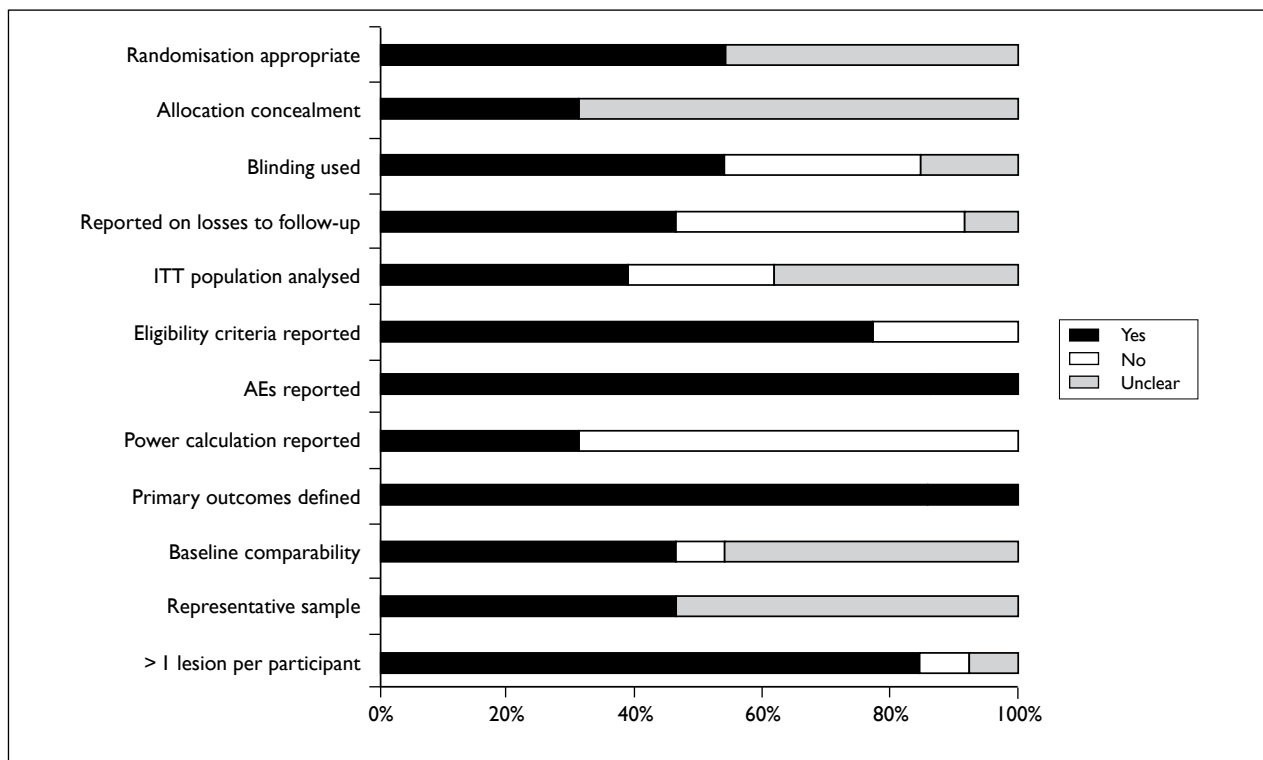


FIGURE 9 Basal cell carcinoma study quality.

30% of PDT patients at 3 months and 60% at 5 years, compared with 4% and 16% of cryotherapy patients, respectively (3-month  $p$ -value = 0.005, 5-year  $p$ -value = 0.00078).

### PDT vs surgery

One RCT by Szeimies *et al.*<sup>80</sup> compared MAL-PDT with surgical excision ( $n = 196$ ) and reported results from 12 months of follow-up.

#### Morbidity

Per-protocol analyses found similar lesion response rates for PDT and surgery, but recurrence in only the PDT arm (no statistical tests reported).

#### Quality of life

Cosmetic outcome was judged to be superior for patients receiving PDT by both patients and investigators, and this was reported as statistically significant ( $p$ -values not reported). Investigator assessments at 12 months were grouped such that a judgement of ‘success’ indicated cosmetic outcome across lesions was at least ‘good’. Overall, 92.8% of patients receiving PDT were considered a ‘success’ compared with 51.2% of surgery patients at 12 months ( $p < 0.001$ ).

### PDT with different treatment parameters

#### Morbidity

Schleier *et al.*<sup>81</sup> compared MAL-PDT versus ALA-PDT and recorded data for up to 6 months’ follow-up. No significant differences were found between groups for either partial success or CR in superficial BCC lesions.

De Haas *et al.*<sup>83</sup> compared fractionated ALA-PDT (laser, LED or broadband source) with single-illumination ALA-PDT. In the fractionated group, light was delivered on two occasions with 2 hours between treatments. CR rates of lesions were significantly higher in the fractionated group ( $p = 0.002$ ) at 1-year follow-up; however, there were no differences between light sources noted.

Soler *et al.*<sup>92</sup> compared laser versus broadband illumination for ALA-PDT. Follow-up lasted a minimum of 6 months but was continued for patients with a CR. No significant differences were found between groups for complete, partial or non-response rates.

#### Quality of life

One study comparing laser versus broadband illumination PDT found no differences between

the two groups;<sup>92</sup> the other trials did not report this outcome.

#### Evidence summary

These trials of PDT for superficial BCC appear to suggest that there may be few differences between light-delivery methods for ALA-PDT in terms of partial or complete lesion response rates. PDT may be no better or worse than cryotherapy or surgery at long- or short-term follow-up for lesion clearance rates; however, recurrence has not yet been fully explored. In terms of cosmesis, MAL and ALA-PDT may not differ in outcome. Cryotherapy and surgery may both result in poorer cosmetic outcomes when compared with PDT.

It is difficult to draw any definitive conclusions as the trials of cryotherapy and surgery versus PDT did not report power calculations, and it is unclear if they were suitably powered to show equivalence.

## Results of effectiveness for nodular basal cell carcinoma

Results are presented in a narrative synthesis. Meta-analysis was not possible due to heterogeneity between the trials. No trials reported mortality or resource use data.

### MAL-PDT vs placebo PDT

Two RCTs compared MAL-PDT versus placebo PDT ( $n = 131$  patients).<sup>77,78</sup> Both trials used surface debridement prior to application of MAL or placebo creams and treatment was repeated after 7 days in both studies. Insufficient details regarding the intervention parameters were reported to establish if the treatment was similar. Follow-up appeared to last around 6 months.

#### Morbidity

Tope *et al.*<sup>78</sup> reported significant differences in favour of active PDT for complete clinical and histological responses. Foley *et al.*<sup>77</sup> found a significant difference in histological evaluations at 6 months; patients who received active PDT were found to have significantly fewer signs of malignancy.

#### Quality of life

Cosmetic outcome for the active PDT patients was reported as 'excellent' or 'good' by investigators for between 93% and 95% of patients in both trials, with one study reported similar results (90%) for the placebo group.<sup>78</sup>

### PDT vs excision surgery

Three RCTs compared PDT with excision surgery; the first<sup>87</sup> looked at ALA-PDT versus surgery ( $n = 31$  patients, 40 lesions); the second<sup>86</sup> compared fractionated ALA-PDT with surgery ( $n = 149$  patients, 173 lesions) and the third<sup>85</sup> compared MAL-PDT versus surgery ( $n = 103$  patients, 118 lesions). In all trials the lesion was prepared using superficial curettage before application of the photosensitiser in the PDT groups. It was not clear if patients received either one or two cycles of PDT. Each trial used illumination appropriate to the photosensitiser.

#### Morbidity

All three trials initially reported no significant differences between PDT and surgery at 3-month follow-up. Five-year follow-up data on MAL-PDT from one RCT reported CR rates were significantly better in the surgery group (76% for PDT vs 96% for surgery), while recurrence was more frequent in the PDT arm (14%) compared with surgery (4%) but this difference was not statistically significant.<sup>85</sup> Interim results from Mosterd *et al.*<sup>86</sup> at a median of 28 months' follow-up reported significantly higher failure rates in the fractionated ALA-PDT arm (30.3%) than with surgery (2.3%) but final 5-year data are not yet available. Berroeta *et al.*<sup>87</sup> reported only 12-month follow-up data and found no significant difference in clearance rates between ALA-PDT and excision surgery in low-risk nodular BCC.

#### Quality of life

One trial<sup>85</sup> reported patient-rated cosmetic outcome and found similar results for both PDT and surgery at 3 months and significant better results for PDT at 12 and 24 months. Berroeta *et al.*<sup>87</sup> reported collecting blinded cosmetic outcome data but results were not reported in the publications.

### ALA-PDT vs MAL-PDT

One RCT<sup>84</sup> compared ALA versus MAL-PDT ( $n = 39$  patients, 43 lesions). This study used superficial curettage plus anaesthetic spray prior to application of the photosensitiser. The follow-up lasted 8 weeks.

#### Morbidity

Data were reported only for incomplete lesion clearance and rates did not significantly differ between treatment arms.

## Quality of life

No QoL data were reported in this trial.

### Evidence summary

These trials suggest that MAL-PDT is superior to placebo PDT, but that PDT is less effective than surgical excision in terms of lesion clearance, although it may have a better cosmetic outcome. MAL-PDT may not offer any advantages over ALA-PDT; however, the trials to date have been relatively small and poorly reported. Further research to establish equivalence of treatments would require large well-designed RCTs.

### Evidence summary

Overall, SAEs have not been reported and systemic photosensitisation is not a likely risk. The most commonly reported side effects were pain and discomfort during and shortly after light exposure. It was not clear in all studies if pain relieving medication was used, and in one trial the use of topical anaesthetic appeared to effectively reduce this pain.

## Results of safety

No SAEs were reported by any trials, and pain was the most commonly reported AE in trials of superficial BCC. When comparing single illumination versus fractionated illumination, 27% of patients in the fractionated group required pain relief as opposed to 5% in the single group.<sup>83</sup> Comparing MAL-PDT and ALA-PDT – 8/13 and 5/11 patients, respectively – reported moderately painful sensations during treatment and two MAL-PDT patients received local anaesthetic.<sup>81</sup> Laser versus broadband ALA-PDT: 68% of laser and 74% of broadband lamp patients reported some degree of discomfort but this was not significantly different between the groups.<sup>82</sup>

No serious or systemic AEs for PDT in nodular BCC were reported. The most common side effects were mild to moderate burning, stinging, erythema and pain. Where PDT was compared with a placebo, these effects occurred in both active and placebo groups.<sup>77,78</sup> Rhodes *et al.*<sup>85</sup> found that patients treated with PDT reported significantly more AEs than patients undergoing surgery, while Berroeta *et al.*<sup>87</sup> reported that patients treated with PDT experienced more pain than surgery patients (lidocaine was not used during treatment – confirmed by author). In one trial<sup>84</sup> in which topical anaesthetic was administered during curettage and available after PDT treatment, there were no differences in pain ratings between MAL-PDT and ALA-PDT.

Most photosensitisers were applied topically therefore there were no problems with systemic sensitisation in these trials; however, only one trial mentioned precautions being taken subsequent to treatment (area was covered with an occlusive dressing for 1 day). In the one study that used an intravenous photosensitiser, photosensitivity was not recorded as an AE.

## Ongoing trials

We are aware of the following potentially ongoing/unpublished trials of PDT for the treatment of BCC but could not obtain any further information about them (*Table 9*). In addition we are aware of the following paper, which is in press, but not yet published when the report was written: Foley P. PDT with methyl aminolevulinic acid for primary nodular BCC: results of two randomized studies (accepted for publication in the *International Journal of Dermatology*).

## Discussion

We identified 13 unique RCTs of PDT for nodular and/or superficial BCC, which varied in sample size and methodological quality. Although not always clearly reported, it appears that in at least 10 trials multiple lesions per patient were included and analysed. As in other cancerous and pre-cancerous skin conditions, counting multiple patient lesions independently may have implications for the overall results. We did not locate any trials of PDT for morpheic or pigmented BCC.

Of the five RCTs in superficial BCC, all used different treatment parameters and comparator arms. The limited evidence suggests that PDT may result in similar lesion response rates to surgery or cryotherapy with better cosmetic outcomes; however, these conclusions are tentative, as the trials do not appear to have been suitably powered to demonstrate equivalence. Further research is particularly needed to establish optimal treatment parameters for superficial BCC.

We identified three key RCTs comparing PDT for nodular BCC with surgery. Rhodes *et al.*<sup>85</sup> reported the longest follow-up data (5 years) for a sample of 103 patients, finding that surgery was superior to MAL-PDT for clearance rates but that PDT was significantly better for cosmetic outcomes. Interim results from a trial comparing fractionated ALA-PDT with surgery suggest that at 3 years'

**TABLE 9** Ongoing BCC trials

| Name               | Title  | Start date    | Completion date/status               |
|--------------------|--|---------------|--------------------------------------|
| Oseroff A          | 4- to 5-hour vs 18- to 24-hour ALA-PDT (BCC and AK)                            | February 1997 | Recruiting                           |
| Kurwa H            | PDT + Mohs microsurgery vs surgery alone                                       | February 2006 | October 2007 – listed as completed   |
| Foley P            | MAL-PDT vs placebo   | October 2000  | September 2002 – listed as completed |
| Neyndorff H        | Verteporfin PDT vs placebo for multiple BCC                                    |               | Terminated                           |
| Tope W             | MAL-PDT vs placebo   | December 2000 | April 2002 – listed as completed     |
| Roberts F          | ALA-PDT – investigation for Bowen's disease and AK, dose fractionation for BCC | February 2002 | February 2004 – listed as completed  |
| Kelleners-Smeets N | PDT vs imiquimod vs 5-FU   | March 2008    | March 2011                           |

treatment failure was more likely for patients receiving PDT, while a relatively small study of ALA-PDT found no difference between groups.<sup>86,87</sup> Overall, it appears that PDT may result in poorer long-term outcomes over 3–5 years, but cosmetic outcomes are significantly better. Therefore, there may still be scope to explore the optimal PDT regime and clarify which patients and/or lesion type will respond best, while balancing clearance or recurrence with cosmetic outcomes.

This is an active area of research, although it is interesting to note that of the ongoing or currently unpublished trials from which we were unable to obtain data, three are placebo-controlled studies, which seem less likely to add to the evidence base. The most important trials are likely to be those that compare PDT with a viable alternative such as imiquimod, 5-FU or surgery.



# Chapter 7

## Barrett's oesophagus

### Background

Barrett's oesophagus is caused by the backwash of stomach acid and bile into the oesophagus, known as gastrooesophageal reflux disease (GORD), which damages the normal lining. In about 10% of patients with GORD the injured lining of the oesophagus does not grow back but it is replaced by a new abnormal lining (specialised intestinal metaplasia). The Barrett's lining begins at the bottom of the oesophagus, where the oesophagus lines the stomach and extends upwards towards the mouth. Barrett's linings may be short (less than 3 cm) or long (3 cm or greater in length). Most people with Barrett's oesophagus also have a hiatal hernia. However, most people who have a hiatal hernia do not have Barrett's oesophagus. It is not known why only certain people go on to develop Barrett's oesophagus. However, it is known that men are more at risk than women, and older age, and possibly obesity, is a risk factor.<sup>93</sup>

Barrett's oesophagus is confirmed in a procedure known as upper gastrointestinal endoscopy complete with biopsy. If it is confirmed, a patient will need to undergo endoscopic biopsy surveillance to determine the grade of dysplasia (abnormal changes in cells or their growth patterns). Dysplasia is normally graded from negative, indefinite, low grade up to high grade. Those with high-grade dysplasia (HGD) are at the most increased risk of developing oesophageal adenocarcinoma. Although the majority of patients with Barrett's oesophagus do not develop cancer during long-term follow-up they are at increased risk when compared with the general population.<sup>93</sup>

Treatment for Barrett's oesophagus aims to control symptoms and repair oesophageal injury. Treatment with acid-suppressive treatment [e.g. proton pump inhibitors (PPIs)], antireflux surgery and lifestyle changes may be advised. Ongoing surveillance aims to detect progression to HGD and adenocarcinoma. Endoscopic therapies, such as endoscopic mucosal resection and PDT, may be offered to a patient with HGD but ongoing surveillance will still be used. Multipolar electrocoagulation (MPEC) may also be used. Radiofrequency ablation is offered in a few

specialist centres. Oesophagectomy (removal of the oesophagus) is normally performed only in patients with HGD; chemotherapy and radiotherapy may be used in conjunction with this surgical procedure.

Photodynamic therapy is used as a first-line treatment for patients with HGD in Barrett's oesophagus.<sup>94</sup> PDT can be used alone or in combination with a range of other therapies. The photosensitisers that have been used are Ps (Photofrin), meta-(tetrahydroxyphenyl) chlorine (mTHPC) [temoporfin (Foscan)] and 5-aminolevulinic acid (5-ALA); Photofrin and Foscan are given intravenously, and 5-ALA is given orally.

### Study characteristics

Eleven RCTs investigated PDT for Barrett's oesophagus with a total number of 594 patients (*Table 10*). Seven trials were published as full papers,<sup>95,97–100,102,105</sup> and four as abstracts only.<sup>96,101,103,104</sup> PDT was compared with different treatments in five trials (APC in four and omeprazole alone in one).<sup>97–101</sup> Different methods of delivering PDT were explored in six trials,<sup>96,97,102–105</sup> and PDT was compared with placebo in two trials.<sup>95,96</sup> (The numbers of trials do not add up to 11 due to some trials having three arms.) ALA was used as the photosensitiser in the majority of trials and was compared to Ps in one trial.<sup>104</sup>

Four trials specifically focused on patients with HGD,<sup>99,103–105</sup> one trial<sup>100</sup> included patients with LGD or HGD, one focused on LGD,<sup>95</sup> one on low-grade or without dysplasia,<sup>97</sup> two without dysplasia,<sup>98,102</sup> one was mixed,<sup>101</sup> and in one dysplasia was not specified.<sup>96</sup>

### Study quality

Eight out of the 11 RCTs were published within the last 5 years. However, the RCTs tended to be small, with the majority having fewer than 50 patients. These smaller trials are likely to have been underpowered to detect effects for

TABLE 10 Barrett's oesophagus study characteristics

| Authors   | No. of participants | Trial treatments   | Dysplasia                     |
|---|---------------------|--|-------------------------------|
| <b>PDT vs placebo PDT</b>                                     |                     |  |                               |
| Ackroyd <i>et al.</i> (2000) <sup>95</sup>                    | 36                  | ALA-PDT vs placebo PDT   | LGD                           |
| Ackroyd <i>et al.</i> (1996) <sup>96</sup> (abstract only)    | 28                  | ALA-PDT 30 mg/kg vs ALA-PDT 50 mg/kg vs placebo  | Dysplasia (not specified)     |
| <b>PDT vs other treatments</b>                                |                     |  |                               |
| Hage <i>et al.</i> (2004) <sup>97</sup>                       | 40                  | ALA-PDT with fractionated dose vs ALA-PDT single dose vs APC                                       | Without dysplasia or with LGD |
| Kelty <i>et al.</i> (2004) <sup>98</sup>                      | 72                  | ALA-PDT vs APC   | Without dysplasia             |
| Overholt <i>et al.</i> (2007) <sup>99</sup>                   | 208                 | PDT with Ps and omeprazole vs omeprazole alone   | HGD                           |
| Ragunath <i>et al.</i> (2005) <sup>100</sup>                  | 26                  | PDT with Ps vs APC   | LGD or HGD                    |
| Zoepf <i>et al.</i> (2003) <sup>101</sup> (abstract only)     | 20                  | ALA-PDT vs APC   | Mixed                         |
| <b>PDT delivery comparisons</b>                               |                     |  |                               |
| Kelty <i>et al.</i> (2004) <sup>102</sup>                     | 25                  | ALA-PDT at 30 mg/kg or 60 mg/kg at 4- or 6-hour incubation times or with fractionated illumination | Without dysplasia             |
| Mackenzie <i>et al.</i> (2007) <sup>103</sup> (abstract only) | 72                  | ALA-PDT with varying doses of light and comparing red or green light                               | HGD                           |
| Mackenzie <i>et al.</i> (2008) <sup>104</sup> (abstract only) | 40                  | ALA-PDT vs PDT with Ps   | HGD                           |
| Mackenzie <i>et al.</i> (2008) <sup>105</sup>                 | 27                  | ALA-PDT with red light vs ALA with green light at 30 or 60 mg/kg                                   | HGD                           |

APC, argon plasma coagulation; HGD, high-grade dysplasia; LGD, low-grade dysplasia.

all outcomes under investigation. The largest, well-conducted trial was conducted in 30 centres across four countries, raising the possibility of institutional differences and protocol deviations.<sup>99</sup> The majority of trials did not clearly report study methods. Procedures for randomisation, allocation concealment and blinding of outcome assessors were not always clear, making it difficult to assess the reliability of the results. The major reporting problem was that several trials were only available as abstracts, making an assessment of their quality and reliability challenging. A graph illustrating study quality is presented in *Figure 10*.

## Results of effectiveness

Results are presented in a narrative synthesis. Meta-analysis was not possible due to heterogeneity between the trials. None of the trials considered QoL outcomes. One trial investigated mortality,<sup>99</sup> and one considered resource use.<sup>100</sup> Outcomes are mainly related to morbidity and AEs.

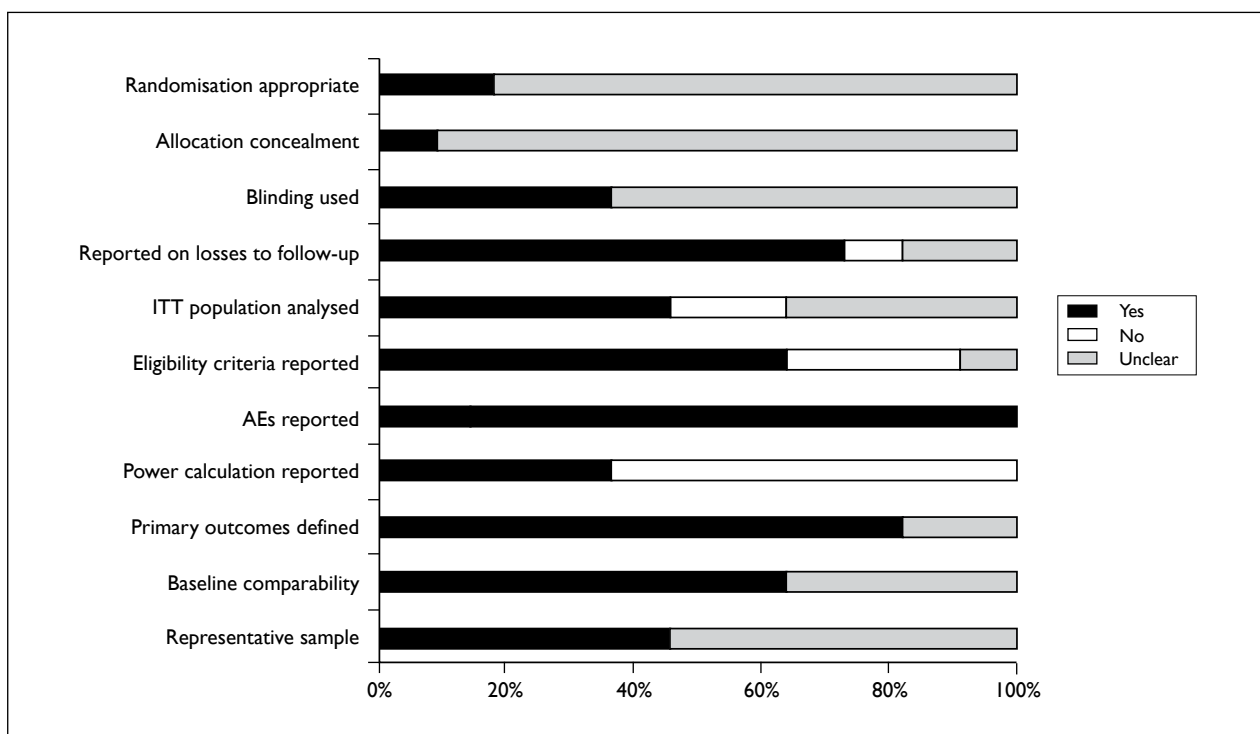
## PDT vs APC

Four trials compared PDT to APC.<sup>97,98,100,101</sup> Three trials used ALA as a photosensitiser and one used Ps.<sup>100</sup> One trial was of patients without dysplasia,<sup>98</sup> one without or with LGD,<sup>97</sup> one was LGD or HGD,<sup>100</sup> and one was not stated.<sup>101</sup>

## Morbidity

In a trial of patients without dysplasia or with LGD, both the group receiving fractionated-dose PDT with ALA and the group receiving APC had statistically significantly better results in terms of Barrett's oesophagus surface reduction than the group receiving single-dose PDT.<sup>97</sup> Differences between fractionated-dose PDT and APC were not significant. Rates of complete ablation were not significant between the groups. In a trial in patients without dysplasia, treatment led to complete reversal of the columnar segment to squamous epithelium in 50% of patients receiving ALA-PDT and 97% of patients receiving APC ( $p < 0.0001$ ).<sup>98</sup> In a trial with patients with mixed levels of dysplasia, reported in abstract only, reduction of





**FIGURE 10** Barrett's oesophagus study quality.

length was 90% for those undergoing ALA-PDT treatment and those receiving APC but fewer treatments were used for APC.<sup>101</sup>

The final trial compared Ps to APC in a group of 26 patients with LGD or HGD.<sup>100</sup> Dysplasia eradication was statistically significantly better at 4 months, but not at 12 months, with PDT. This was a small trial that may have been underpowered to detect treatment effects for all outcomes.

#### Resource use

The small UK trial described above was accompanied by a cost-effectiveness analysis.<sup>100</sup> The incremental cost-effectiveness ratios (ICERs) were calculated based on differences in effects and costs between PDT with Ps and APC for Barrett's oesophagus length eradication and dysplasia eradication. At 4 months, APC was less expensive and more effective. At 12 months, the ICER was £266; an additional £266 would be required for every percentage reduction in Barrett's oesophagus using PDT compared with APC.

#### Evidence summary

From this small body of evidence it is not possible to conclude whether PDT is superior to, equivalent to or inferior to APC. Nor is it possible to state with confidence which treatment (if any) would be most appropriate for the various levels of dysplasia.

### PDT plus omeprazole vs omeprazole alone

One trial compared PDT with Ps plus omeprazole (PHOPDT) versus omeprazole alone (OM).<sup>99</sup> This was the largest trial for Barrett's oesophagus (208 patients), although the 3- to 5-year follow-up phase of the trial had just 61 participants. All patients had HGD. The results of this multicentre trial were considered to be reliable but an unknown factor is the influence of any between-centre differences on the results found.

#### Mortality

Two patients in the PHOPDT and one in the OM group died within the first 2 years from events unrelated to Barrett's disease. There were no additional patients who died during the 3-year follow-up period.

#### Morbidity

The proportion of responders (complete ablation of HGD) was significantly higher in the PHOPDT group than with OM (77% vs 39%,  $p < 0.0001$ ). By the end of the 5-year follow-up period, the probability of maintaining complete ablation of HGD was 48% in PHOPDT compared with 4% in OM ( $p < 0.0001$ ). The median duration of the CR was 44.8 months in the PHOPDT group and 3.2 months in the OM group. Comparison between the two groups showed that patients in the PHOPDT

group had a significant delay in progression to cancer compared with patients in the OM group. After 5 years of follow-up, the rate of patients who progressed to cancer in PHOPDT was significantly lower than in OM ( $p = 0.027$ ).

#### **Evidence summary**

On the basis of one generally well-conducted trial, it appears that PDT with Ps in addition to omeprazole is more effective than omeprazole alone at producing long-term ablation of HGD and slowing/preventing progression to cancer.

### **PDT vs placebo**

Two trials compared PDT with placebo,<sup>95,96</sup> one of which was reported as abstract only and did not provide any effectiveness outcomes and is therefore not discussed here.<sup>96</sup>

#### **Morbidity**

In a trial in patients with LGD, a statistically significantly larger proportion of the ALA-PDT group showed evidence of regression (89% vs 11%) and reduction in Barrett's (30% vs 0%) than in the placebo group.<sup>95</sup> There was also a statistically significant reduction in prevalence of dysplasia in favour of the PDT group.

#### **Evidence summary**

On the basis of one small trial, ALA-PDT appears to be more effective than placebo in patients with low-grade dysplasia. However, it should be noted that all patients were taking omeprazole so the evidence could be interpreted as PDT being more effective than omeprazole alone, as stated above.

### **ALA-PDT vs PDT with Ps**

One trial compared ALA-PDT to Ps in patients with HGD but was reported in abstract only.<sup>104</sup> The trial reported preliminary data only, as recruitment is not yet complete.

#### **Morbidity**

Remission rates were statistically significantly superior in the ALA-PDT group than with the Ps group (100% vs 64%,  $p < 0.05$ ).

#### **Evidence summary**

The results of this ongoing trial suggest that ALA-PDT may be more effective than Ps, but conclusions cannot be drawn until all the planned patients have been treated and followed up for a longer period of time.

### **PDT with different treatment parameters**

Five trials compared PDT of varying parameters.<sup>96,97,102,103,105</sup> One trial, as previously mentioned in the placebo group, was reported as abstract only and did not have any effectiveness outcomes and so is not discussed here.<sup>96</sup> One trial has already been discussed in the PDT vs APC section but a reminder of the findings is provided here.<sup>97</sup>

Two of the three additional trials to be discussed in this section were reported as a full paper,<sup>102,105</sup> while the other was reported as an abstract only.<sup>103</sup> Patients had HGD in the trial published as an abstract<sup>103</sup> and in one of those reported as a full publication.<sup>105</sup> In the other full publication patients did not have dysplasia.<sup>102</sup> ALA was used as a photosensitiser in all three trials.

#### **Morbidity**

One trial found that in patients with no dysplasia the greatest reductions in Barrett's epithelium were seen in 30-mg/kg and fractionated groups but results were not statistically significant. However, each treatment group had just five patients so is unlikely to be able to detect all treatment differences where they exist.<sup>102</sup> In a trial of patients without dysplasia or with LGD previously discussed in the APC section, both the group receiving fractionated dose PDT with ALA and the group receiving APC had a statistically significantly better results in terms of Barrett's oesophagus surface reduction than the group receiving single-dose PDT.<sup>97</sup>

One trial found that patients with HGD receiving high-dose ALA-PDT (60 mg/kg) and high-dose red light (1000 J/cm) had a significant decrease in cancer risk compared with treatment groups with lower doses of photosensitiser and/or lower light doses at 36 months (3% risk vs 24% risk). Red light was associated with lower rates of adenocarcinoma than green light (8% vs 45%,  $p < 0.05$ ).<sup>103</sup> In the other trial, 60-mg ALA red light was more successful than 30-mg ALA red light ( $p = 0.03$ ) and than 30-mg ALA green light ( $p = 0.005$ ).<sup>105</sup>

#### **Evidence summary**

Based on the trials in this section, optimal parameters for PDT in patients without dysplasia are unknown. In HGD, according to two small trials, it appears that high-dose ALA-PDT may be more effective. Higher dose light may be more effective but this is based on one trial. The optimal parameters for PDT in HGD remain to be determined.

## Results of safety

All trials of PDT and Barrett's oesophagus reported AEs, albeit briefly. AEs are detailed separately for ALA and Ps and for the trial comparing the two.<sup>104</sup>

### ALA-PDT

Eight trials, comparing ALA with APC or placebo or ALA of various treatment parameters, provided information on AEs.<sup>95–98,101–103,105</sup>

Serious AEs have not been reported in this group of studies. Specifically, it was reported that no major side effects in terms of perforations or strictures occurred in two trials.<sup>98,102</sup> No patients developed strictures in one trial comparing various ALA regimens<sup>103</sup> and differences in stricture formation were not significant between PDT and APC groups in a further trial.<sup>97</sup> In a small trial comparing ALA with red or green light, there were no major complications.<sup>105</sup> Differences in fever and sudden death were not significant between PDT and APC groups in one trial.<sup>97</sup>

Adverse effects were mainly short term. In one trial all patients receiving PDT experienced chest pain during treatment, which persisted for 3–5 days and was aggravated by swallowing and coughing.<sup>95</sup> In a further trial 23 of 26 patients receiving PDT and 5 out of 14 patients receiving APC experienced pain during treatment ( $p < 0.01$ ).<sup>97</sup> Pain was not specifically mentioned in the other trials.

In two trials, PDT was found to result in more nausea and vomiting than APC. There were seven versus zero cases ( $p < 0.05$ ) in one trial.<sup>97</sup> All patients in the ALA arm of a trial comparing ALA at a dose of 60 mg/kg to APC developed nausea and vomiting over a period of 4 hours after treatment, whereas there were no cases of vomiting in the APC group.<sup>101</sup> In a further trial comparing different modes of ALA, significant nausea and vomiting occurred in 32% of patients receiving ALA, and was more common in patients who received the higher dose of ALA.<sup>102</sup>

Photosensitivity did not appear to be a significant problem in the trials in which this was reported. In two trials, one comparing PDT with APC and one testing various ALA treatment parameters, no patients suffered photosensitivity reactions.<sup>101,103</sup> In other trials small numbers experienced photosensitivity, which, where stated, tended to be mild and resolve fairly quickly.<sup>95,96</sup> Numbers were

slightly higher in two further trials; 5 out of 25 patients in one trial<sup>102</sup> and 5 out of 35 in another.<sup>98</sup>

Dysphagia was not found to be a problem with PDT in the trials that specifically mentioned this.<sup>95</sup> In two trials, instances of dysphagia were not significantly different between the PDT and APC groups.<sup>97,101</sup> In one trial that specifically mentioned this, instances of odynophagia were not significantly different between PDT and APC groups.<sup>101</sup>

Three trials suggested some disturbance in liver function tests.<sup>96,97,105</sup>

### Porfimer sodium

Two trials, one comparing Ps with APC and the other comparing PDT with Ps and omeprazole (PHOPDT) to omeprazole alone (OM) provided information on AEs.<sup>99,100</sup>

In the omeprazole trial, events of severe intensity were similar for PHOPDT (16%) and OM (15%), with 65% of the PHOPDT group being related to the treatment compared with 2% in the OM group.<sup>99</sup> From years 2 to 5 in the trial there were no SAEs and, of those AEs reported, none was attributed to the treatments. The trial found that 36% of PDT patients developed oesophageal strictures, but that 94% of those with strictures were stricture free in the initial phase of the trial.<sup>99</sup> In the trial comparing PDT with APC, two of 13 patients in both groups developed oesophageal strictures.<sup>100</sup>

In one trial, photosensitivity occurred in 69% of patients receiving PDT.<sup>99</sup> All photosensitivity events were resolved. In another trial 31% experienced photosensitivity.<sup>100</sup>

### ALA vs Ps

One trial of ALA versus Ps provided a direct comparison of the AEs of the two photosensitisers.<sup>104</sup> There was also a statistically significant difference in the development of strictures (6 out of 16 patients treated with Ps and 1 out of 16 treated with ALA).<sup>104</sup>

There was a statistically significant difference in photosensitivity [7 out of 16 patients treated with Ps (one of who had to be admitted to hospital) vs no cases with ALA]. There were no other significant differences between groups regarding side effects.

**Evidence summary**

In general, SAEs have not been reported for PDT in the treatment of Barrett's oesophagus. However, trials are mainly small and rarer AEs might not, therefore, be observed. There may be differences in the rates of stricture between PDT and other treatments such as APC. However, the evidence suggests, but does not confirm, that this is more of a problem when using Ps. Pain particularly during treatment was not always reported so it is unclear if there are differences in pain between PDT and other treatments, and how this might differ when PDT is delivered using different parameters. Nausea and vomiting appeared to be problematic with ALA but may relate to dose of ALA delivered. This outcome was not evaluated for Ps. Any effects on liver function merit further investigation. Dysphagia did not appear to be more problematic for PDT than APC in the ALA trials that investigated this. Photosensitivity either did not occur or was relatively mild in the ALA trials. The two Ps trials reported higher levels of photosensitivity than the ALA trials and this finding was supported by the trial comparing the two treatments.

**Discussion**

We concentrated on RCTs for the treatment of Barrett's oesophagus, as a large number appeared to be available. On closer inspection, we found that many publications related to the same trials. The 11 RCTs were published in 24 publications. Additionally, the evidence presented is diverse, with variation in PDT parameters including photosensitisers, comparators and patient level of dysplasia. A further barrier to drawing firm conclusions is that the majority of the trials are small, with methodological limitations.

Nevertheless, it appears from the evidence provided that PDT might be beneficial above and beyond PPIs alone. However, its relative effectiveness is unclear compared with APC and other treatment options as yet not evaluated in trials. The relative benefits and AEs of Ps versus ALA also need further research and there is an ongoing trial in this area.

A number of trials were conducted in patient groups with no or with LGD. However, these patients are unlikely to be treated in routine practice. The priority for Barrett's oesophagus would seem to be to determine more clearly the role of PDT and its optimal delivery to patients with HGD.

**Ongoing trials**

The following trial is ongoing and at the time of writing of this report had no detailed results to report (*Table 11*).

We are aware of the following potentially ongoing/unpublished trials of PDT for Barrett's disease but could not obtain any further information about them (*Table 12*).

**TABLE 11** Ongoing Barrett's oesophagus studies

| Investigator | Interventions  | Start date    | Status   |
|--------------|--|---------------|--|
| Lovat L      | ALA-PDT vs Ps PDT to study the side effect profile and to establish measures of efficacy in the eradication of dysplasia in Barrett's oesophagus | February 2006 | Expected end February 2009 – but authors stated that the trial was ongoing; 55 out of 66 patients were recruited by January 2009 |

**TABLE 12** Ongoing or unpublished Barrett's oesophagus studies

| Investigator | Interventions  | Start date     | Status                                  |
|--------------|--|----------------|---|
| Nava H       | PDT in two light regimes for HGD and early cancer                  | February 2004  | Suspended, no reply to e-mail           |
| Reed M       | ALA-PDT (green light) vs placebo (all patients to take omeprazole) | April 1995     | Finished March 1996, no reply to e-mail |
| Wang K       | Mucosal resection vs resection + PDT                               | September 2005 | Recruiting, no reply to e-mail          |

# Chapter 8

## Oesophageal cancer

### Background

A recent review highlighted the increasing incidence of oesophageal cancer over the last 30 years in the UK.<sup>94</sup> It now affects around 7800 people each year in the UK. The disease is more common in men than women, and most cases are in people aged 50 years and over.<sup>106</sup> Depth of penetration of the tumour determines tumour stage. Tumours that are superficial or have penetrated only the submucosa are defined as early-stage cancer. The two most common types of oesophageal cancer are SCCs and adenocarcinoma, described as being strongly associated with Barrett's oesophagus.

The prognosis for oesophageal cancer is not encouraging. Five-year survival rates for all patients diagnosed with oesophageal cancer in 2000–1 in England and Wales were 8% for both men and women.<sup>106</sup> Endoscopic therapies such as endoscopic mucosal resection and PDT may be offered to a patient with early cancer but ongoing surveillance will still be used. MPEC may also be used. Oesophagectomy (removal of the oesophagus) may be performed, and chemotherapy and radiotherapy may be used.

If cancer has spread or the cancer is otherwise unsuitable for surgery, palliative therapy may be offered. Options include stents to stretch the oesophagus narrowed by the tumour, ablative therapy, or possibly radiation and chemotherapy to shrink the tumour and improve symptoms, such as dysphagia, and hence maintain QoL.

Photodynamic therapy was first introduced as a palliative treatment for oesophageal cancer but it is now also used as a first-line treatment for patients with early oesophageal cancer.<sup>94</sup> The treatment objective in early-stage oesophageal cancer is cure, whereas in advanced cancer it continues to be a palliative option. PDT can be used alone or in combination with a range of other therapies for curative and palliative purposes.

### Study characteristics

A total of thirteen studies were included, which reported on PDT in the treatment of oesophageal cancer (*Table 13*).<sup>107–119</sup> Three studies were available only as abstracts,<sup>107,110,111</sup> the rest were published as full papers. In a small number of trials, the presented data did not appear to entirely support the authors' conclusions; this has been indicated in the data extraction tables.<sup>110,111,113</sup>

Five non-randomised trials focused on curative PDT for early or superficial oesophageal cancers.<sup>107–111</sup> In some studies the patients had received prior therapies, such as radiotherapy or surgery, and the cancer types varied (adenocarcinoma, squamous, oesophagogastric). A range of photosensitisers were used across the studies: Ps, HpD, mTHPC, although one did not report this detail. Three studies compared variants of PDT,<sup>107–109</sup> one compared primary and secondary PDT following chemoradiotherapy,<sup>111</sup> and the final study compared PDT with two different surgical procedures.<sup>110</sup>

Eight studies reported on palliative PDT treatments for oesophageal cancer, four RCTs<sup>112–114,119</sup> and four non-randomised comparative trials.<sup>115–118</sup> Participants in six studies were diagnosed with advanced oesophageal cancer, and overall most trials included only patients who were not eligible for resection due to anatomical restrictions, poor health or refusal. Comparators in these trials included chemotherapy, radiotherapy, neodymium-doped yttrium aluminium garnet (Nd:YAG) laser or PDT. Photosensitisers used were Ps, HpD, PsD-007 and ALA.

### Study quality

The non-randomised curative studies were generally poorly reported. Of the five trials only three were available as full published papers, making it difficult to assess quality based solely

TABLE 13 Oesophageal study characteristics

| Authors   | Study design | No. of participants | Trial treatments                             |
|---|--------------|---------------------|--|
| <b>Curative</b>   |              |                     |  |
| Canto <i>et al.</i> (2005) <sup>107</sup> (abstract only)       | Non-RCT      | 80                  | Ps-PDT vs Ps-PDT + EMR                       |
| Lecleire <i>et al.</i> (2008) <sup>111</sup> (abstract only)    | Non-RCT      | 35<br>(37 tumours)  | Primary Ps-PDT vs Ps-PDT following CRT       |
| Grosjean <i>et al.</i> (1997) <sup>108</sup>                    | Non-RCT      | 15<br>(22 tumours)  | Ps-PDT (630 nm vs 514 nm)                    |
| Scotiniotis <i>et al.</i> (2000) <sup>110</sup> (abstract only) | Non-RCT      | 37                  | PDT vs EMR vs oesophagectomy                 |
| Savary <i>et al.</i> (1998) <sup>109</sup>                      | Non-RCT      | 24<br>(31 tumours)  | HpD-PDT vs Ps-PDT vs mTHPC (various doses)   |
| <b>Palliative</b>   |              |                     |  |
| Lightdale <i>et al.</i> (1995) <sup>112</sup>                   | RCT          | 236                 | Ps-PDT vs Nd:YAG laser                       |
| Heier <i>et al.</i> (1995) <sup>114</sup>                       | RCT          | 42                  | HpD-PDT vs Nd:YAG laser                      |
| Zhang <i>et al.</i> (2003) <sup>119</sup>                       | RCT          | 60                  | HpD-PDT + radiotherapy vs radiotherapy alone |
| Maier <i>et al.</i> (2000) <sup>117</sup>                       | Non-RCT      | 119                 | HpD-PDT + brachytherapy vs brachytherapy     |
| Zhang <i>et al.</i> (2007) <sup>113</sup>                       | RCT          | 140                 | PsD-007 PDT vs PsD-007 + PDT + 5-FU          |
| Maier <i>et al.</i> (2000) <sup>115</sup>                       | Non-RCT      | 52                  | HpD-PDT vs HpD-PDT + HBO                     |
| Maier <i>et al.</i> (2000) <sup>116</sup>                       | Non-RCT      | 75                  | HpD-PDT vs HpD-PDT + HBO                     |
| Maier <i>et al.</i> (2001) <sup>118</sup>                       | Non-RCT      | 49                  | ALA-PDT (+HBO) vs HpD-PDT (+HBO)             |

HBO, hyperbaric oxygen; Nd:YAG, neodymium-doped yttrium aluminium garnet (laser).

on a brief abstract. As is common with non-randomised studies, most of these appeared to display important baseline differences between comparison groups, making it difficult to ascribe any differences in outcome to the intervention. Sample sizes were small overall, ranging from 15 to 80, although in some patients more than one tumour was treated and counted. Most trials did not report if they were single or multicentre. All studies reported on lesion clearance rates and AEs although assessors were often not reported as blinded, and in some reports no statistical tests appeared to have been carried out.

All eight palliative trials were available as full published papers; however, the standard of reporting was variable. The four RCTs were generally better reported, though few studies used blinded outcome assessors or ITT analyses. Samples sizes ranged from 49 to 119 in the non-randomised trials and from 42 to 236 in the RCTs. At least two studies used more than one recruiting centre but this aspect was poorly reported. All

trials reported on AEs, all but one trial reported mean survival time, and morbidity outcomes included stenosis length, dysphagia score and tumour length. Some trials also reported Karnofsky performance status. A graph illustrating study quality is presented in *Figure 11*.

## Results of effectiveness (curative intent)

Results are presented in a narrative synthesis. Meta-analysis was not possible due to heterogeneity between the trials. Outcomes reported mainly related to morbidity and AEs. Only one trial reported mortality<sup>107</sup> and no trials reported on QoL or resource use outcomes.

### PDT vs PDT (curative intent)

Two non-randomised trials have compared different kinds of PDT for early or superficial oesophageal cancer. Grosjean *et al.*<sup>108</sup> used Ps as

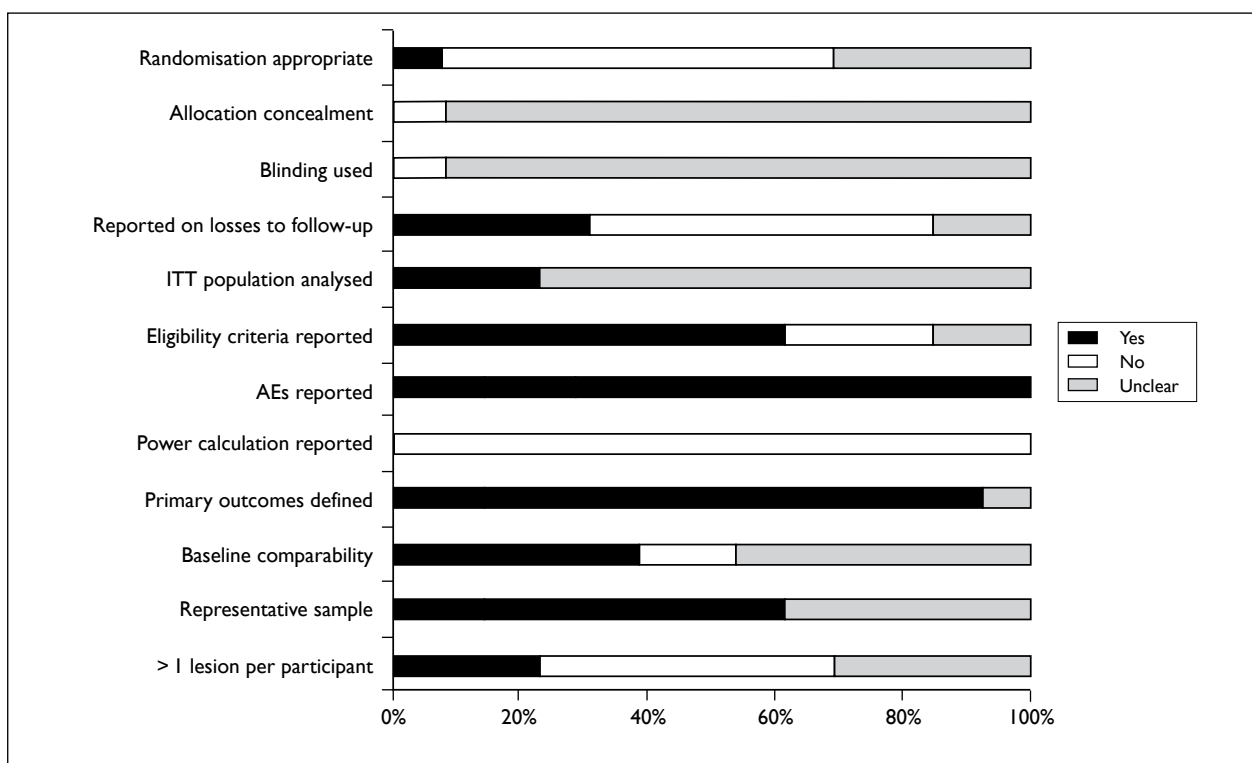


FIGURE 11 Oesophageal study quality.

the photosensitiser and compared two wavelengths ( $n = 15$  patients, 22 tumours) of light. In this study, patients with both oesophageal and bronchial tumours were included; however, the majority (14/22) were oesophageal. Savary *et al.*<sup>109</sup> compared Ps, HpD and three different dosages of mTHPC using varying light doses ( $n = 24$  patients, 31 tumours).

### Morbidity

Grosjean *et al.*<sup>108</sup> reported that both 630nm (69% CR) and 514nm (67% CR) were suitable wavelengths to cure superficial oesophageal cancer. Savary *et al.*<sup>109</sup> reported overall response and failure rates according to photosensitiser: HpD CR = 89%, mTHPC CR = 86%, Ps CR = 75%.

Using 514-nm green-light illumination reduced deep tissue damage in both trials.<sup>108,109</sup>

#### Evidence summary

Two small non-randomised trials suggest that 514 nm may be the preferred wavelength for treating early or superficial oesophageal cancer when using either Ps or mTHPC. These findings are drawn from poorly reported studies, which are likely to be underpowered, and so the results should not be considered conclusive.

### PDT vs CRT or EMR followed by PDT (curative intent)

Two non-randomised trials have examined primary PDT versus secondary PDT where another treatment is given initially. One trial looked at Ps-PDT versus endoscopic mucosal resection (EMR) followed by Ps-PDT ( $n = 80$  patients),<sup>107</sup> the second used PDT versus PDT following unsuccessful chemoradiotherapy (CRT) ( $n = 35$  patients, 37 tumours).<sup>111</sup> Both of these trials were available only as abstracts and further treatment details were not reported.

### Mortality

Canto *et al.*<sup>107</sup> reported that disease-specific 5-year survival was 100%.

### Morbidity

No significant differences were reported between CR rates for PDT (89.7%) and EMR + PDT (91.2%) ( $p = 0.67$ ).<sup>107</sup> There were also no significant differences in number of lesions treated successfully when PDT (73%) was compared with PDT following unsuccessful CRT (53%) ( $p = 0.3$ ).<sup>111</sup>

#### Evidence summary

Two small non-randomised trials found no differences between primary PDT treatment and PDT following either EMR or unsuccessful CRT. These results are based on small samples of unclear methodological quality.

## PDT vs EMR vs oesophagectomy (curative intent)

One non-randomised trial ( $n = 37$  patients) compared PDT or EMR in poor surgical candidates with oesophagectomy in good surgical candidates in a three-armed design.<sup>110</sup> Only a short abstract was available and no details were reported for any of the interventions.

### Morbidity

Eradication of lesions was reported for each study arm: 75% for PDT, 83% for EMR and 95% for oesophagectomy. No statistical tests were reported.

#### Evidence summary

It is not possible to draw any conclusions about the relative effects of PDT, EMR or oesophagectomy from this single trial.

## Results of effectiveness (palliative intent)

Results are presented in a narrative synthesis. Meta-analysis was not possible due to heterogeneity between the trials. All trials reported morbidity results, seven reported on mortality<sup>113–119</sup> and four reported on QoL outcomes.<sup>115–118</sup> Only two of the studies reported resource use, both in terms of days of hospitalisation.<sup>116,118</sup>

### PDT vs Nd:YAG laser

Two relatively old RCTs compared PDT with Nd:YAG laser for oesophageal carcinoma in patients who had refused, failed or were not suitable for surgery, and who had a Karnofsky performance status of  $> 30\%$ . One trial used Ps as the photosensitiser ( $n = 236$ )<sup>112</sup> and the second used HpD ( $n = 42$ ).<sup>114</sup> Both trials were reported as full papers, and were generally well conducted and reported.

### Mortality

This outcome was only assessed by Heier *et al.*,<sup>114</sup> who reported no significant difference in mean survival between HpD-PDT (145 days) and Nd:YAG (128 days) laser treatments ( $p = 0.419$ ).

### Morbidity

Heier *et al.*<sup>114</sup> reported significant increases in oesophageal grade for the PDT group, while Lightdale *et al.*<sup>112</sup> found no significant differences in dysphagia grade or response rates at 1 week but

did report a significant benefit in favour of PDT at 1 month.

### Quality of life

Heier *et al.*<sup>114</sup> found that patients receiving PDT were judged to have significantly greater improvements in dietary performance and Karnofsky performance status. Lightdale *et al.*<sup>112</sup> did not report on this outcome.

#### Evidence summary

One well-conducted, but small, RCT suggests that PDT with HpD may not be different from Nd:YAG laser in terms of mortality. PDT may also be equivalent to or better than Nd:YAG laser in terms of morbidity and QoL. One study was small and neither study reported a power calculation thus we cannot rule out the possibility that relevant differences were not detected.

## PDT vs radiotherapy

One RCT and one non-randomised trial have compared HpD-PDT plus radiotherapy versus radiotherapy alone. The RCT used standard radiotherapy of 40 grays (Gy) for 4 weeks,<sup>119</sup> while the non-randomised trial used brachytherapy and 5 Gy per session for one to four sessions.<sup>117</sup> In this second study, patients who were judged to be in 'fair condition' completed their radiotherapy via external-beam irradiation (57% of the combination group and 23% of the brachytherapy-alone group).

### Mortality

The RCT by Zhang *et al.*<sup>119</sup> showed longer survival rates at 5 years for PDT plus radiotherapy over radiotherapy alone (29.9% vs 16.7%,  $p = 0.05$ ), and again significantly longer for 10-year survival rates (16.7% vs 10.0%,  $p < 0.05$ ).

Maier *et al.*<sup>117</sup> reported mean survival for brachytherapy as 5.6 months, for brachytherapy and external beam irradiation as 7.7 months, for PDT plus brachytherapy as 6.3 months and for PDT plus brachytherapy plus external-beam irradiation as 13.0 months.

### Morbidity

Maier *et al.*<sup>117</sup> found significantly greater improvements for the PDT plus brachytherapy group versus brachytherapy alone for both dysphagia scores ( $p = 0.003$ ) and mean stenosis size ( $p = 0.001$ ).

### Quality of life

Only Maier *et al.*<sup>117</sup> reported this outcome and found no difference in 3-month Karnofsky scores.



**Evidence summary**

Two studies suggest that adding PDT to radiotherapy may be beneficial; however, the RCT was poorly reported and difficult to assess for quality, while the non-randomised study used two different forms of radiotherapy and pre-treated some patients with Nd:YAG laser. Firm conclusions cannot be drawn from these results.

**PDT vs PDT plus 5-FU**

One RCT compared PDT alone with PDT following 5-FU ( $n = 140$ ).<sup>113</sup> This study was poorly reported overall, but the paper reports that after treating over 40 patients and reviewing the clinical data the randomisation was abandoned and all further patients were treated with the combination of PDT and 5-FU (no further details reported).

**Mortality**

Combined treatment resulted in significantly longer mean survival times for the PDT plus 5-FU group (15.1 months) than with PDT alone (8.9 months) ( $p < 0.01$ ).

**Morbidity**

Combined treatment produced significantly greater rates of dysphagia remission (99%) than with PDT alone (87%) ( $p < 0.05$ ); however, there were no significant differences in pharyngeal pain or weight loss between groups.

**Evidence summary**

The evidence from this single study is difficult to assess, and so no firm conclusions can be drawn.

**PDT and HBO**

Two non-randomised trials have compared PDT alone versus PDT plus hyperbaric oxygen (HBO) (total  $n = 107$ )<sup>115,116</sup> and a third non-randomised trial has compared two types of photosensitiser (HpD vs ALA), where both were given under HBO.<sup>118</sup> All three studies were carried out with patients who had advanced oesophageal carcinoma. The PDT versus PDT-plus-HBO studies both used HpD at 2 mg/kg and 630-nm illumination, and in both some patients received Nd:YAG and dilatation prior to PDT.

**Mortality**

Patients receiving PDT plus HBO were reported to have significantly longer median survival times (13.8 months and 12 months) than patients receiving PDT without HBO (8.7 months and 7 months).<sup>115,116</sup>

Where ALA was compared with HpD, there was no significant difference in median survival (8 months vs 9 months).<sup>118</sup>

**Morbidity**

Both trials evaluating the impact of HBO in addition to PDT reported significantly greater decreases in tumour length in the HBO groups (2.8 cm and 3 cm) than in the PDT without HBO group (2 cm and 2 cm).<sup>115,116</sup> Dysphagia scores were significantly reduced in the PDT-plus-HBO group in only one trial.<sup>116</sup> Stenosis length decreased overall, between 5 and 6 mm, but these changes were not significantly different between groups.

At 1-month follow-up significantly greater improvements for dysphagia, tumour stenosis and tumour length were seen in the patients receiving ALA than in the patients receiving HpD.<sup>118</sup>

**Quality of life**

A semi-solid diet was possible in all groups following treatment for the two trials comparing the addition of HBO to PDT alone.<sup>115,116</sup> The comparison of HpD and ALA found no significant differences in Karnofsky status scores (44% vs 23%,  $p = 0.12$ ).<sup>120</sup>

**Resource use**

One trial evaluating the addition of HBO reported on duration of hospital stay, there was no difference between groups with an overall median of 4.9 days (range 3–9 days).<sup>116</sup> The duration of hospital stay in the comparison of HpD and ALA (both with HBO) ranged from 4 to 6 days in both groups.<sup>118</sup>

**Evidence summary**

Two non-randomised studies without blinded outcome assessors provide limited evidence that adding HBO to HpD-PDT can enhance the efficacy of this treatment. One small non-randomised study suggests that ALA may be more effective than HpD when used with HBO.

**Results of safety**

All trials of PDT and oesophageal cancer reported AEs, albeit briefly. AEs are detailed separately by treatment intention.

The AE most commonly reported in patients receiving curative PDT appears to be stricture formation. Those studies reporting this AE gave figures ranging from 10% to 50% of patients developing stricture.<sup>107,110,111</sup> Chest pains, fever and transient dysphagia were also reported.<sup>108</sup>

All patients who received mTHPC<sup>109</sup> reported a burning sensation at the injection site, and two patients who did not follow the recommended precautions developed second-degree sunburn on the face and hands.

Regarding those trials that were palliative in intention: a small RCT ( $n = 42$ )<sup>114</sup> found very few AEs for either PDT or Nd:YAG treatments, whereas a larger RCT ( $n = 236$ ) reported that patients undergoing PDT were more likely to suffer from pain, nausea and pleural effusion.<sup>112</sup> Patients receiving Nd:YAG, however, were significantly more likely to suffer from oesophageal perforations.

The RCT comparing PDT alone versus PDT plus 5-FU ( $n = 140$ ) reported no oesophageal stenosis or perforation in either group.<sup>113</sup> Small numbers of patients in both groups (PDT = 7, combination = 8) reported subternal pain due to oesophageal mucosa injury and gastroesophageal reflux 1–2 days after treatment. In total, eight patients accidentally exposed themselves to sunlight and developed discoloration of the skin.

One non-randomised study of 119 patients comparing HpD-PDT with brachytherapy reported 9% of all patients experienced major complications including oesophageal perforation and severe haemorrhaging, the authors suggest that care should be taken when selecting patients for treatment to prevent serious complications.<sup>117</sup>

The PDT plus radiotherapy RCT ( $n = 60$ ) stated that all patients receiving PDT reported swelling, itchiness, pigmentation and pain on swallowing. This last AE lasted for 3–5 days in most cases, but for some patients the duration was more than 10 days and sufficient for them to discontinue treatment.<sup>119</sup> Deaths by group were reported but not clearly attributed to the intervention or other extraneous factors.

In the three studies using HBO, no barotrauma to the ear was reported and no major complications were recorded.<sup>115,116,118</sup> Common minor complications includedodynophagia, fever and chest pain for up to 2 days. All patients receiving ALA reported nausea immediately after administration.

#### Evidence summary

*Curative:* Serious AEs have not been reported in the trials to date; however, trials are mainly small and rarer AEs might not, therefore, have been observed. The most common AE when curative PDT is given appears to be stricture formation. Both curative and palliative PDT may result in chest pain and fever although these are transient.

*Palliative:* Pain on swallowing or pain in the oesophageal area following PDT treatment was reported variably in the included studies and appears to be a common AE although the severity is unknown.

In both curative and palliative treatment, where patients did not follow the recommended precautions in terms of light exposure, photosensitivity reactions occurred.

Serious complications were reported by one non-randomised study however some of these may be attributable to the concomitant brachytherapy treatment. From the one trial where ALA was used, all patients receiving this photosensitiser reported nausea.

## Ongoing trials

We are not aware of any potentially ongoing/unpublished trials of PDT for oesophageal cancer.

## Discussion

To date PDT as a curative intervention for oesophageal cancer has only been studied in non-randomised trials. The patients receiving non-surgical interventions such as PDT or CRT appear to be markedly different from those receiving surgery, and this, combined with small sample sizes and lack of randomisation, makes it difficult to draw any firm conclusions.

Randomised controlled trials have been successfully carried out for palliative PDT, and there is evidence from one older study that Nd:YAG and PDT may not differ in terms of mortality. SAEs were only reported in one trial using Nd:YAG; however, these appear to be related to the comparator rather than the PDT treatment. Stricture formation is a concern in this area; however, the two more recent trials give substantially lower rates of stricture formation and this may reduce further as research refines the appropriate dose of photosensitiser and wavelength of light required.

There is some evidence from non-randomised studies that using HBO may enhance the effectiveness of PDT, but good-quality RCTs are required to clarify the degree to which the effectiveness can be increased. In all palliative studies, there was a lack of comparability between treatment arms and a lack of detail reported on the procedures given, making it difficult to draw conclusions.

Across both curative and palliative PDT treatments, there appears to be little consensus as to the optimal regime in terms of photosensitiser, light or duration of exposure; however, where patients fail to follow the recommendations in terms of light exposure then photosensitisation may be a concern. Further research is required to clarify these parameters.



# Chapter 9

## Lung cancer

### Background

More than 38,000 people are diagnosed with lung cancer in the UK each year. Although some people who have never smoked get lung cancer, smoking causes 90% of cases.<sup>106</sup> However, over 80% of patients present late with the disease, and only 15–20% are suitable for surgical resection.<sup>106</sup> These figures help to explain why the 5-year survival of patients with lung cancer is poor; only about 7% of patients will live for at least 5 years.<sup>106</sup>

Surgery (removal of part, or all, of the lung), chemotherapy, radiotherapy, or a combination of these treatments, can be used, depending on the stage when the cancer is diagnosed. If the cancer is at an advanced stage, a range of options are available to help alleviate symptoms. These include brachytherapy, electrocautery, laser therapy, PDT or cryotherapy.

Photodynamic therapy for lung cancer can be delivered under general or local anaesthetic. Removal of necrotic tumour is required usually 48 hours after each treatment. It can be repeated if necessary, and can be used alongside other lung cancer treatments. PDT can be given to patients with early-stage cancer who are surgically inoperable and can have a curative intent.

When lung cancer is advanced, PDT is used palliatively, aiming to reduce symptoms, such as shortness of breath by reducing tumour bulk. A previous systematic review has concluded that 'the palliative effect of PDT in late stage lung cancer is promising, although its effectiveness in comparison to traditional therapies requires further study'.<sup>16</sup>

### Study characteristics

Seven trials investigated PDT for lung cancer with a total number of 329 patients (*Table 14*).<sup>121–127</sup> Five trials were reported in full papers<sup>122–124,126,127</sup> and two as abstracts only.<sup>121,125</sup> All trials had a palliative intent in relation to non-small cell lung cancer.

Photodynamic radiotherapy was compared to radiotherapy [including external radiation therapy (ERT) and HDR + ERT]<sup>121,123,124</sup> and Nd:YAG laser

resection.<sup>122,125,126</sup> Photofrin and Photofrin II were used as photosensitisers in the six trials comparing PDT to other treatments.<sup>121–126</sup> Where stated, trials used a protocol of 2 mg/kg, together with light at 630 nm. The drug–light interval varied from 24 to 54 hours across the studies. However, not all intervention parameters were reported in full. ALA–PDT was compared with Photosan in one trial that also used PDT in conjunction with HBO.<sup>127</sup>

### Study quality

The most recent trial<sup>127</sup> was published in 2002, raising issues of relevance to current practice. All trials were relatively small (the largest had 141 patients) suggesting that they may have lacked power to detect significant effects. Procedures for randomisation, allocation concealment and blinding of outcome assessors were generally unclear. All trials reported AEs (albeit briefly). However, generally reporting was poor, making the reliability of a study difficult to assess. Two trials had clear baseline differences that could have impacted on results,<sup>122,124</sup> and only two clearly had no differences at baseline.<sup>123,126</sup> The trial comparing different types of PDT was not randomised and was therefore open to selection bias.<sup>127</sup> A graph summarising study quality is presented in *Figure 12*.

### Results of effectiveness

Results are presented in a narrative synthesis. Meta-analysis was not possible due to heterogeneity between the trials. Resource use data were not presented in any of the trials of PDT and lung cancer.

### PDT plus radiotherapy

Two trials ( $n = 52$ ) compared PDT plus radiotherapy with radiotherapy alone,<sup>123,124</sup> neither providing adequate methodology details, and one trial recruited only 11 participants.<sup>124</sup> One trial was of the effects of ERT alone versus PDT preceding ERT versus high-dose irradiation preceding ERT, but results were not presented by treatment group.<sup>121</sup>

TABLE 14 Lung study characteristics

| Authors   | Study design | No. of participants | Trial treatments   |
|---|--------------|---------------------|--|
| Baas <i>et al.</i> (1994) <sup>121</sup> (abstract only)  | RCT          | 39                  | ERT alone vs PDT with Photofrin preceding ERT vs endobronchial HDR preceding ERT |
| Diaz-Jimenez <i>et al.</i> (1999) <sup>122</sup>          | RCT          | 31                  | PDT with Photofrin vs Nd:YAG laser resection                                     |
| Lam <i>et al.</i> (1991) <sup>123</sup>                   | RCT          | 41                  | PDT with Photofrin + external radiotherapy vs external radiotherapy alone        |
| Lam <i>et al.</i> (1987) <sup>124</sup>                   | RCT          | 11                  | PDT with Photofrin + external radiotherapy vs radiotherapy alone                 |
| Leroy <i>et al.</i> (1998) <sup>125</sup> (abstract only) | RCT          | 141                 | PDT with Photofrin vs Nd:YAG laser resection                                     |
| Maier <i>et al.</i> (2002) <sup>127</sup>                 | Non-RCT      | 40                  | ALA-PDT with HBO vs PDT with Photosan with HBO                                   |
| Moghissi <i>et al.</i> (1993) <sup>126</sup>              | RCT          | 26                  | PDT with Photofrin or Photofrin II vs Nd:YAG laser resection                     |

ERT, external radiotherapy; HDR, high dose radiation.

### Mortality

Lam *et al.*<sup>123</sup> reported no differences in mortality rates or survival times (444 days PDT plus radiotherapy vs 445 days radiotherapy alone).

### Morbidity

Lam *et al.*<sup>123</sup> found a greater reduction of haemoptysis (coughing up blood) and shortness of

breath and cough at 1 and 3 months in the PDT-plus-radiotherapy group ( $p < 0.05$ ).<sup>123</sup> There was also a substantial difference in both the success rate of bronchial lumen re-opening (14/20 PDT plus radiotherapy vs 2/21 radiotherapy alone) and the median interval between treatment and local recurrence (233 days' PDT plus radiotherapy vs 107 days radiotherapy alone,  $p = 0.005$ ).

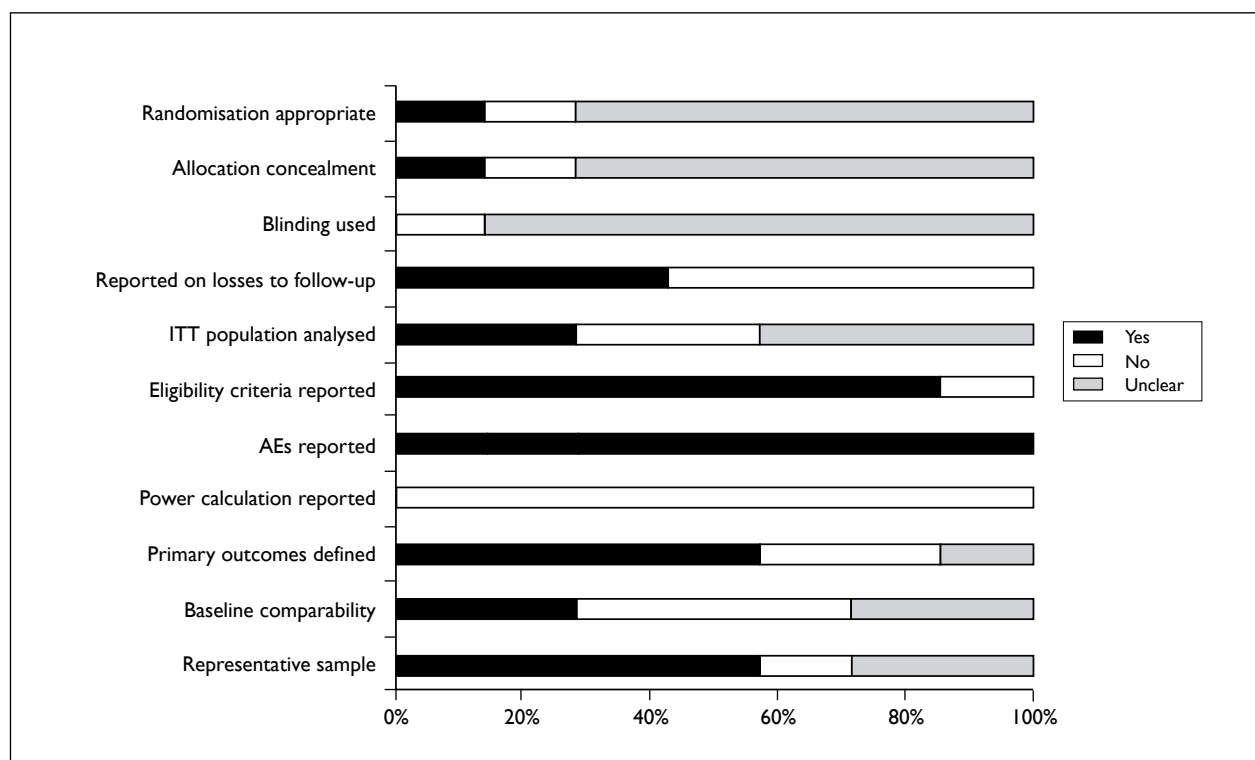


FIGURE 12 Lung study quality.

### Quality of life

Both trials assessed this outcome, but only the very small trial reported results, which suggested improvements from baseline in QoL and Karnofsky rating for the PDT-plus-radiotherapy group.<sup>124</sup>

#### Evidence summary

Two trials suggest that PDT plus radiotherapy may be more effective than radiotherapy alone in the palliative treatment of non-small cell lung cancer. However the small numbers involved, coupled with a lack of reporting of study methods and some outcomes, mean firmer conclusions cannot be drawn.

### PDT vs Nd:YAG laser resection

Three trials ( $n = 198$ ) compared PDT with Nd:YAG.<sup>122,125,126</sup> All had methodological limitations and did not report methods in full.

#### Mortality

In one trial, survival was significantly longer in the PDT group (265 days vs 95 days,  $p = 0.007$ ), but the groups had important baseline differences.<sup>122</sup> The other two trials did not assess this outcome.

#### Morbidity

Similar response rates between treatment groups were found by Diaz-Jimenez *et al.*<sup>122</sup> At 1 month (but not at 1 week), Leroy *et al.*<sup>125</sup> found significant differences with a response rate of 61% for PDT versus 35% for Nd:YAG ( $p < 0.05$ ). Diaz-Jimenez *et al.* found time elapsed to failure to be 50 days in the PDT group and 38 days in the Nd:YAG group ( $p = 0.03$ ).

Leroy *et al.*<sup>125</sup> found symptomatic control to be better with PDT, although it was unclear if this result was statistically significant. Moghissi *et al.*<sup>126</sup> found that forced vital capacity (FVC) and forced expiratory volume in one second ( $FEV_1$ ) improved significantly more with PDT than with Nd:YAG at 1 month after treatment. Mean difference between baseline and 1 month in FVC was 0.47 for PDT versus  $-0.06$  for Nd:YAG ( $p < 0.05$ ). The corresponding data for  $FEV_1$  was 0.35 for PDT versus 0.01 Nd:YAG ( $p < 0.05$ ).

#### Quality of life

One trial assessed this outcome but did not report results,<sup>122</sup> and the other two did not assess this outcome.<sup>125,126</sup>

#### Evidence summary

On the basis of three trials with methodological limitations and small numbers, it is not possible to conclude whether PDT is superior, equivalent or inferior to Nd:YAG. It is equally not possible to conclude which treatment, if any, might be most appropriate for which patients. There are suggestions of better symptomatic control with PDT but these would require further investigation. Any effects on survival would also need further investigation alongside any QoL issues that have so far not been assessed.

### ALA-PDT plus HBO vs PDT plus Photosan plus HBO

One non-randomised trial, conducted as a pilot study ( $n = 40$ ), compared ALA-PDT with HBO versus PDT plus Photosan plus HBO.<sup>127</sup>

#### Mortality

The mean survival for the ALA groups was 9 months and the Photosan group 14 months ( $p = 0.020$ ).

#### Morbidity

Difference in change in stenosis diameter post treatment favoured Photosan, but there was no statistically significant difference between groups on pulmonary function parameters.

#### Quality of life

A statistically significant difference in change in Karnofsky score was observed in favour of the Photosan group. None of the patients in the Photosan group reported a decrease in QoL due to long-lasting need for skin protection.

#### Evidence summary

Although one trial suggested that Photosan was more effective than ALA, it was small and non-randomised. In addition, treatment groups had differences at baseline, and these may have impacted on results. The survival data do not solely reflect PDT treatment, as, 4 weeks after PDT, patients were allowed to receive a variety of other treatments.

### Results of safety

Moghissi *et al.*<sup>126</sup> reported that there was no treatment-related mortality, but Diaz-Jimenez *et al.*<sup>122</sup> stated that one death was probably related to PDT. Lam *et al.*<sup>123</sup> noted mild skin photosensitivity in 20% of patients receiving PDT

plus radiotherapy. Diaz-Jimenez *et al.*<sup>122</sup> reported photosensitisation in four of 14 PDT patients, while Leroy *et al.*<sup>125</sup> reported skin photosensitivity in 21% of the PDT patients, and Moghissi *et al.*<sup>126</sup> stated that there were no cases of photosensitivity. In the trial comparing ALA-PDT with Photosan, no major complications relating to photosensitisation were observed.<sup>127</sup> This same trial found only minor complications (fever and mild chest pain) in both groups, none of which required specific treatment. Diaz-Jimenez *et al.*<sup>122</sup> found bronchitis to be the most common AE (4/14 in the PDT group compared to one in the Nd:Yag group). This trial also reported that all five patients who experienced no AEs were in the Nd:YAG comparator group. Baas *et al.*<sup>121</sup> reported minor haemoptysis in 2 out of 15 combined PDT-ERT patients. Moghissi *et al.*<sup>126</sup> stated that there were no serious post-treatment complications.

#### Evidence summary

Serious AEs do not appear to be common but the impact of photosensitisation is unclear. Not all trials reported the duration and seriousness of this AE, and the influence of advice and counselling is unclear. The one trial that reported such advice noted no instances of photosensitisation.

## Ongoing trials

We are not aware of any potentially ongoing/unpublished trials of PDT for lung cancer.

## Discussion

No trials were located in relation to early lung cancer using PDT with a curative intent. All of the trials we located related to PDT in a palliative setting where there is some uncertainty about

effectiveness in relation to other treatments. However, it should be borne in mind that palliative radiotherapy, a common alternative to PDT, has significant variation in the way it is delivered across the medical community.<sup>128</sup> Additionally, it is not usually delivered in isolation and other agents may be used to improve symptoms. Treatment effects are measured by a variety of techniques and any improvement in symptom severity is subjective for both patient and clinician.<sup>128</sup> All of these present challenges in any comparison with PDT.

In any examination of the relative effectiveness of one or more treatments, it is important to identify whether there are subgroups of patients who might benefit particularly from one of the treatments. The trials identified do not enable us to identify the type of patient who might benefit from PDT. We have been advised that the small group of patients with large-airway (trachea or major bronchi) clinically invasive and inoperable tumours, which do not tend to metastasise and cause airway obstruction, might benefit most from PDT. Maintaining a patent airway in these patients is most beneficial in terms of symptoms and life expectancy (Dr JH Winter, Clinical Group Director/Respiratory Consultant, Medicine & Cardiovascular Clinical Group, Ninewells Hospital, Dundee, 24 July 2009, personal communication).

Apart from one trial that compared different photosensitisers, all of the evidence dates from the 1990s or 1980s, which may not reflect current practice. Further research is needed to determine the role of PDT in lung cancer. The scoping review identified 177 publications that did not meet the study design criteria for the review reporting on PDT in the treatment of lung cancer (see Appendix 9). Examination of these publications, including an assessment of quality, could inform the design of further trials.



# Chapter 10

## Biliary tract cancer

### Background

Biliary tract cancer involves cancerous growths in the gall bladder and/or the bile duct. The uncontrolled epithelial cell growth occurs in the inner lining of the gall bladder and bile duct. These cancerous tumours block the flow of bile as they grow. Bile duct cancer, or cholangiocarcinoma, can occur intrahepatically or extrahepatically. Although there are some known risk factors, the majority of patients do not present with these.<sup>129</sup>

Primary cholangiocarcinoma is relatively rare with an incidence of up to 3 per 100,000 per year,<sup>130</sup> accounting for approximately 3% of all gastrointestinal malignancies.<sup>33</sup> However, incidence rates have been increasing, particularly with respect to intrahepatic cholangiocarcinoma. The 5-year relative survival rate for people diagnosed with early-stage cholangiocarcinoma is about 30%; however, only 20% of patients are diagnosed at the early stages.<sup>131</sup> Early cholangiocarcinoma is often asymptomatic, but as the cancer progresses and prevents bile flowing to the small intestine symptoms such as jaundice, itchy skin, abdominal discomfort, loss of appetite or weight, and fever may occur. The key efficacy outcomes for biliary tract cancers are survival, disease progression, recurrence of jaundice/stent failure and QoL.

This cancer may be treated with potentially curative surgery if detected in the early stages before vascular invasion or metastasis formation has occurred, or with a variety of palliative interventions. The survival rate at 5-years after curative resection is only 30–40%,<sup>130</sup> and for the majority of cases surgery is not possible due to the position and extension of the tumour. Common palliative strategies include surgical bypass of the bile duct, percutaneous or endoscopic stenting and, more recently, chemotherapy, while more experimental options such as PDT, radiotherapy or brachytherapy are under investigation.

Cholangiocarcinomas have been classified in various ways according to location, extent and severity of the tumour. In general cholangiocarcinoma may be staged using the TNM

system as for other cancers (see Appendix 3). The Bismuth–Corlette classification system is used for perihilar cholangiocarcinoma and is useful when decisions are being made about the possibility of successful resection:

- tumours below the confluence of the left and right hepatic ducts (type I)
- tumours reaching the confluence (type II)
- tumours occluding the common hepatic duct and either the right or left hepatic duct (types IIIa and IIIb, respectively)
- tumours that are multicentric, or that involve the confluence and both the right or left hepatic duct (type IV).

Photodynamic therapy is usually given alongside biliary stenting following endoscopic retrograde cholangiopancreatography (ERCP) rather than as a stand-alone treatment, and is a palliative option. The protocol for treatment is as follows: the photosensitising agent is injected intravenously and exposure to the light takes place around 48 hours later. The light is delivered to the target area via translucent endoscopic catheter or the light source is placed across the stricture caused by the tumour. Radiological control is used to determine correct positioning of the laser fibre. Patients are required to remain in subdued light for up to 3 days following the injection of the photosensitiser before being gradually re-adapted to bright indoor light. The treatment is repeatable. One or more percutaneous or endoscopic stents are placed to relieve biliary obstruction by facilitating drainage, reducing pruritis and therefore improving QoL. Stents may be either plastic or metal; metal mesh stents remain patent (open and unobstructed) for longer and need replacing less often but can also result in occlusion.

### Study characteristics

Five controlled trials, of which two were RCTs, evaluated PDT for cholangiocarcinoma with a total number of 332 patients (*Table 15*).<sup>132–136</sup> All were available as full published papers, except one trial which was published only as an abstract.<sup>132</sup>

TABLE 15 Biliary tract study characteristics

| Authors   | Study design | No. of patients    | Trial treatments  | Type of cholangiocarcinoma                        | Treatment intention          |
|---|--------------|--------------------|---|---|------------------------------|
| Dechene <i>et al.</i> (2007) <sup>132</sup> (abstract only) | Non-RCT      | 29                 | PDT with Photosan-3 vs PDT with Photofrin II (all + plastic stents) | Not reported                                      | Palliative                   |
| Kahaleh <i>et al.</i> (2008) <sup>133</sup>                 | Non-RCT      | 48                 | PDT + ERCP + stenting vs ERCP + stenting alone                      | Perihilar – mostly Bismuth types III and IV       | Palliative                   |
| Ortner <i>et al.</i> (2003) <sup>134</sup>                  | RCT          | 39                 | Stent + PDT + ERCP + stent vs ERCP + stenting (all double stenting) | Perihilar – mostly Bismuth type IV                | Palliative                   |
| Witzigmann <i>et al.</i> (2006) <sup>135</sup>              | Non-RCT      | 191 (184 analysed) | PDT + double stenting vs double stenting alone vs resection         | Perihilar – stenting arms mostly Bismuth stage IV | Curative and palliative arms |
| Zoepf <i>et al.</i> (2005) <sup>136</sup>                   | RCT          | 32                 | PDT + stenting vs stenting alone                                    | Perihilar, Bismuth stage IV                       | Palliative                   |

Two RCTs compared PDT plus stenting with stenting alone ( $n = 71$ );<sup>134,136</sup> however, in Ortner *et al.*<sup>134</sup> stenting was given both before and after PDT. One non-randomised study also compared stenting and PDT plus stenting.<sup>133</sup> One non-randomised study compared two types of photosensitiser for palliation,<sup>132</sup> and the final non-randomised prospective study explored curative and palliative treatments (PDT, stenting and resection).<sup>135</sup>

All studies, apart from Witzigmann *et al.*,<sup>135</sup> included only patients with non-resectable cholangiocarcinoma. Ortner *et al.*'s RCT<sup>134</sup> was unusual in obtaining 100% histological confirmation of cholangiocarcinoma. In both trials and clinical practice, the diagnosis of cholangiocarcinoma is often not established in all patients.<sup>137</sup> Where other trials reported this information, histopathological confirmation was established for between 60% and 70% of all cases. In the study by Ortner *et al.*<sup>134</sup> patients were randomised only following technically successful stent placement, while in all other studies the patient group may have included those who did not achieve technically successful stenting.

These studies used a variety of photosensitisers, including Photosan-3, Photofrin II and Photofrin. The dosage of all photosensitisers was set at 2 mg/kg and light was delivered at between 630 and 635 nm across the studies where reported. The drug to light interval was 48 hours in all studies where this parameter was reported.

One trial was halted part of the way through recruitment based on established trial monitoring and stoppage rules.<sup>134</sup>

## Study quality

Although RCTs in this area were published in 2003 and 2005,<sup>134,136</sup> more recent publications have tended to be non-randomised.<sup>132,133,135</sup> It is more difficult to draw firm conclusions from this kind of evidence. Overall, the two RCTs were of relatively good quality and reported their methods clearly; however, neither used large sample sizes. The non-randomised studies were generally less well reported, and only one study used groups that were comparable at baseline. All of the non-RCT studies reported on AEs, but none used power calculations or reported using ITT analysis. A graph illustrating study quality is presented in *Figure 13*.

## Results of effectiveness

Results are presented in a narrative synthesis. Meta-analysis was not possible due to heterogeneity between the trials.

### PDT plus stenting vs stenting alone

Two RCTs ( $n = 71$ ) compared PDT plus stenting with stenting alone.<sup>134,136</sup> Both were reported in full papers and seemed to be well conducted. One non-RCT also compared PDT plus stenting

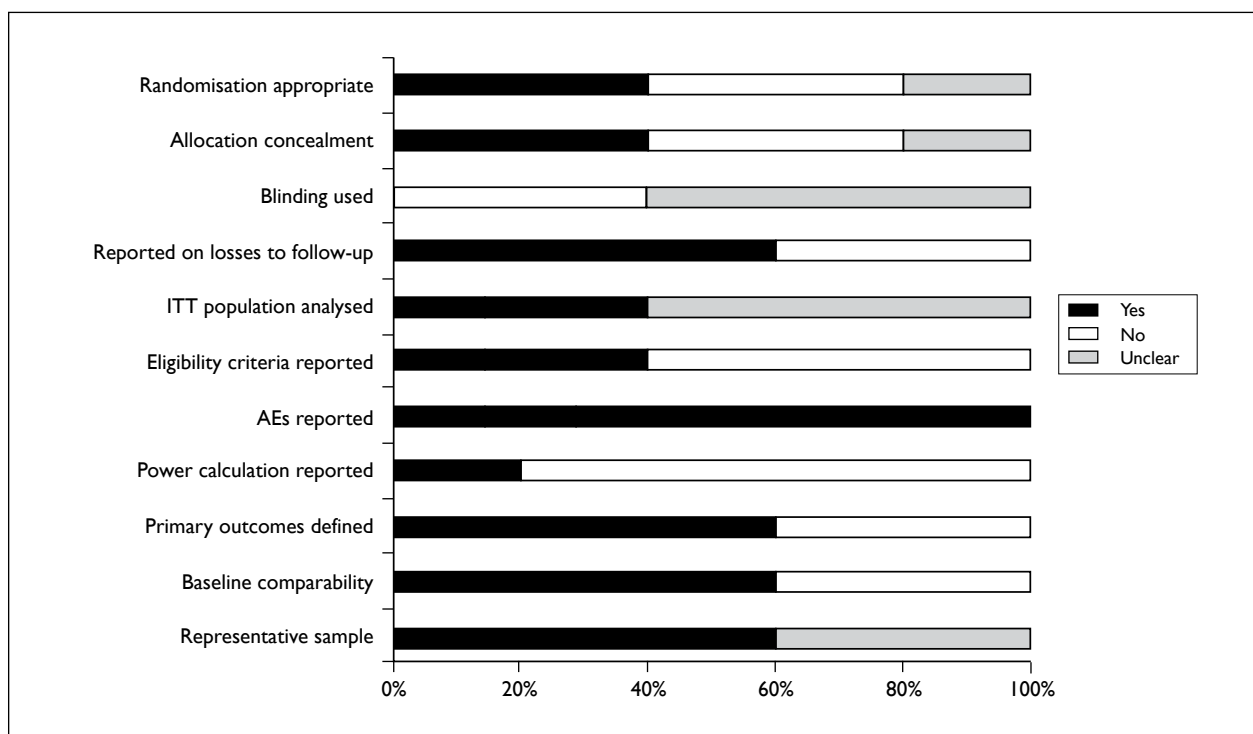


FIGURE 13 Biliary tract study quality.

with stenting alone ( $n = 48$ ), although there were important differences in baseline characteristics between the groups and definitive conclusions were difficult to draw.<sup>133</sup>

One non-RCT ( $n = 191$ , 184 analysed) compared stenting alone with PDT plus stenting and resection for hilar cholangiocarcinoma in a prospective study over 10 years in one centre.<sup>135</sup> This was an unusual study, which appeared to include patients of varying cancer stages, and some patients in the resection group also received adjuvant PDT or stenting where required. Therefore, only the results of the PDT plus stenting versus stenting alone have been described here as these patients appear to be broadly comparable.

### Mortality

Both RCTs found statistically significant increases in survival time in the PDT-plus-stenting groups compared with stenting alone. In the study by Ortner *et al.*<sup>134</sup> median survival in the PDT group was 493 days, and 98 days in the stenting-only group ( $p < 0.0001$ ), whereas in the Zoepf *et al.* trial<sup>136</sup> the PDT group had a survival time of around 21 months compared with 7 months in the stenting group ( $p = 0.01$ ).

Both non-RCTs also reported statistically significant prolonged survival rates in the PDT groups.<sup>133,135</sup> Mortality rates were initially lower in the PDT groups but not statistically significantly different by the end of each study when the majority of patients had died (usually a result of tumour progression and complications of chronic cholangitis).

### Morbidity

In the two RCTs, successful drainage and relief of bile duct stenosis was generally achieved. Zoepf *et al.*<sup>136</sup> reported the median bilirubin level after first intervention was not significantly different between the groups, while Ortner *et al.*<sup>134</sup> found that after PDT serum bilirubin reached lower levels relative to baseline and stenting alone ( $p < 0.01$ ).

Kahaleh *et al.*<sup>133</sup> reported both groups having significantly decreased levels of serum bilirubin at 3 months when compared with baseline levels ( $p = 0.008$  for PDT and  $p = 0.0001$  for stent only), but no significant differences between the two groups in the degree of decrease ( $p = 0.78$ ). In contrast, Witzigmann *et al.*<sup>135</sup> found significant reductions from baseline and significant differences in favour of the PDT treatment group ( $p < 0.05$ ); successful drainage was achieved in 75% of PDT-plus-stent patients versus 39% receiving stents alone.

### Quality of life

Zoepf *et al.*<sup>136</sup> found that QoL as assessed by the Karnofsky scale did not significantly change after treatment for either group, while Ortner *et al.*<sup>134</sup> reported that Karnofsky index improved after PDT, with a median 80% score, but did not improve in the stenting-only group. Ortner *et al.*<sup>134</sup> also reported that after PDT physical functioning ( $p < 0.01$ ) and global QoL ( $p < 0.001$ ) improved in the PDT group but not in the stenting-alone group.

Quality of life was assessed by one non-RCT study, which reported that QoL decreased in the stenting-alone patients but increased significantly in the PDT-plus-stenting group ( $p < 0.01$ ).<sup>135</sup>

### Resource use

This outcome was reported for one non-RCT study.<sup>135</sup> Median hospital stay duration was reported as 65 days for PDT plus stenting versus 44 days for stenting alone.

#### Evidence summary

Based on two relatively small RCTs and two non-randomised studies, the evidence suggests that survival is increased when PDT is given alongside stenting but it is not yet possible to draw firm conclusions regarding morbidity. The QoL results differ between trials; there is no evidence that patients' QoL significantly declines following treatment, but there was no consistent increase across studies. This evidence base includes studies that have used different treatment protocols for stenting and those that have chosen different photosensitisers and recruited patient groups which differed in baseline health status.

These studies appear to have included perihilar cholangiocarcinoma patients only, therefore caution is advised in extending these results to other cholangiocarcinomas or to biliary obstruction due to gall bladder cancer.

### Photosan-3 vs Photofrin II

One non-RCT ( $n=29$ ) compared two different photosensitisers for the treatment of non-resectable cholangiocarcinoma (further details not reported).<sup>132</sup> This study was available only as an abstract, therefore it was difficult to quality assess. It was a small trial and may have been underpowered to detect any possible differences between photosensitisers.

### Mortality

Mortality did not differ significantly between the two groups: median survival for the Photosan-3 arm was 690 days, and 494 days for the Photofrin II arm ( $p = 0.87$ ).<sup>132</sup>

Morbidity, QoL and resource use were not reported in this study.

#### Evidence summary

It is not possible to draw firm conclusions on the comparative efficacy of photosensitisers based on one small study reported only in abstract form.

### Results of safety

Photosensitivity is the most common AE associated with PDT treatment, these studies reported only mild reactions occurring in between 0% and 10% of patients.<sup>132-136</sup> Cholangitis was reported in both the PDT-plus-stent and the stenting-alone groups, although where these rates were compared there were no significant differences. Cholangitis was usually managed with antibiotics. Other AEs included cholecystitis and stenosis (although not usually related to the intervention).

#### Evidence summary

Serious AEs do not appear to be common and photosensitisation was not reported as a frequent AE. Only one study reported patients being required to remain in a darkened room following photosensitiser injection; it is unclear if this is common practice, as most trials did not report these details. Not all trials reported the duration and seriousness of this AE, and the influence of advice and counselling is unclear.

### Ongoing trials

We are aware of the following trials and S Pereira has confirmed that their trial is still recruiting with no results currently available (*Table 16*). Efforts to contact the other trialists and obtain results have been unsuccessful.

### Discussion

Overall, the evidence base for PDT in biliary tract cancers is relatively small; however, further well-designed RCTs are under way and should provide more definitive answers. The scoping review only identified 30 publications of potential relevance in this area (see Appendix 10). The majority of these have been published in the last 10 years and, compared to other sites, appear to include a larger proportion of experimental uncontrolled trials (Phase I and II and pilot studies).

It appears that PDT plus stenting may improve survival rates compared with stenting alone and

**TABLE 16** Ongoing biliary tract studies

| Name         | Title   | Start date    | Completion date/status             |
|--------------|---|---------------|------------------------------------|
| Farrell J    | Stent vs stent + PDT for inoperable stage III or IV cancer                  | Unknown       | Withdrawn                          |
| Pereira S    | PDT + stenting vs stent alone for advanced inoperable biliary tract tumours | July 2007     | July 2009 – ongoing                |
| Trichereau N | Photofrin PDT vs unknown  | November 2007 | November 2008 – not yet recruiting |
| Rauws E      | PDT + endoscopic treatment vs endoscopic treatment alone                    | January 2005  | January 2008 – listed as completed |

SAEs are rare overall. The strongest evidence comes from an RCT by Ortner *et al.*<sup>134</sup> but it is worth noting that this was a highly selected non-resectable population; only patients who had not previously been technically successfully stented, and therefore presumably had persistent jaundice, were eligible; additionally, only those patients

who were then technically successfully stented were randomised into the trial. It could be argued therefore that the results of this trial may not be generalisable to the broader population of patients. Further trials may be useful to further refine the PDT treatment procedure and identify the most suitable photosensitisers for cancers in this area.



# Chapter 11

## Brain cancer

### Background

In the UK, there are nearly 2500 new cases of brain cancer in men, 1700 in women and 300 in children each year.<sup>106</sup> The growth of brain tumours causes pressure and damage to healthy brain tissue. They are categorised according to growth rate: 'low grade' (grades I and II) are generally regarded as being benign, and 'high grade' (grades III and IV) as being malignant. There are numerous different types of brain tumour, with around one-half being gliomas (of which there are three main types: astrocytoma, ependymoma and oligodendroglioma). The cause of brain tumours remains unknown. Malignant gliomas have a poor prognosis; patients who receive treatment will typically survive for only around 1 year.

Resection surgery, followed by radiotherapy and/or chemotherapy, is the treatment most commonly used for malignant brain tumours, and can be used with curative or palliative intent. Surgery rarely results in the removal of all tumour cells, hence the need for adjuvant treatment. Ultrasonic aspiration (where ultrasonic waves fragment the tumour, with fragments being removed by suction) may sometimes be an alternative to standard surgery (with a scalpel). Stereotactic radiosurgery (using highly focused X-rays) is a non-invasive procedure that can be used when invasive surgery is not appropriate, although generally it is an option only for tumours of less than 4 cm in size. Radiosurgery may also be used after conventional surgery, and is often used in combination with conventional radiotherapy.

Photodynamic therapy has been used little in the treatment of malignant brain tumours. When PDT is used it is done so by administration of photosensitiser (currently usually ALA, Photofrin or Foscan), followed up to many hours later (ranging from 3 to over 100 hours) by tumour resection, and subsequent light delivery via a special illuminating device. PDT has been used in addition to radiotherapy and/or chemotherapy, and is normally preceded by photodynamic diagnosis (PDD) to identify tumour tissue. The scope of this review does not cover studies of PDD without the use of PDT as a treatment.

### Study characteristics and quality

Two trials evaluated the use of PDT for brain cancer.<sup>138,139</sup> Both trials recruited fewer than 30 patients, and both were reported as full papers. The treatments for the trial by Krishnamurthy *et al.*<sup>138</sup> were Ps-PDT (at 630 nm) with three different light dose ranges, in patients with recurrent or residual tumours  $\leq 5$  cm in diameter. This trial was non-randomised, and it was unclear whether it recruited comparable groups or used blinding. The very small sample size suggests that the study lacked power to detect significant effects.

The other trial was an RCT by Eljamel *et al.*<sup>139</sup> – for patients with glioblastoma multiforme – comparing fluorescence-guided resection followed by repetitive ALA-PDT, with standard resection (both groups also received radiotherapy). It was unclear both how many participants were randomised into the study, and what kind of randomisation and allocation processes were used, although outcome assessors were blinded to treatment allocation.

### Results of effectiveness and safety

In the Ps trial, the group receiving the medium light dose (3700–4400 J), survived longer than the group receiving the highest dose (4400–5900 J) – 314 days versus 238 days. Results were not reported for the low-dose group. Five patients had postoperative permanent neurological defects (two in the medium-dose group and three in the high-dose group).<sup>138</sup>

In the repetitive ALA-PDT trial, the PDT group survived significantly longer than the surgery group (52.8 weeks vs 24.2 weeks), and had a significantly longer time to tumour recurrence (8.6 months vs 4.8 months). Three patients had deep vein thrombosis, two of which were in the PDT group.<sup>139</sup>

#### Evidence summary

Of the two trials of PDT in brain cancer, one was of too poor quality to yield any useful evidence. The other showed interesting results for the effectiveness of fluorescence-guided resection with repetitive ALA-PDT,

which need further investigation in larger trials that include safety assessment, as the incomplete and inconsistent reporting, coupled with the small sample size, limit the reliability of the authors' conclusions.

## Ongoing trials

Results from a North American RCT looking at PDT (with Ps IV) using high-light dose versus low-light dose for patients with recurrent malignant astrocytoma are due to be published in 2010. The study aimed to recruit around 120 participants. Results of a non-RCT (including around 60 participants) conducted in Belarus, of high-grade gliomas treated with surgery and Photolon (also known as Fotolon) PDT versus surgery and chemotherapy (temozolamide), were to be presented at the 2009 World Congress of the International Photodynamic Association, Seattle.

## Stopped trials

Two randomised trials of Photofrin-PDT for gliomas – both by the same investigators – were not completed.<sup>140</sup> No peer-reviewed publication of results is available. One trial aimed to determine the effectiveness of PDT as an addition to standard therapy (surgery, radiotherapy and/or chemotherapy) in newly diagnosed patients, and the other to see whether surgery and PDT with high-light dose was superior to surgery and PDT with low-light dose, in patients with recurrent

tumours. The trials were stopped prematurely after the second predetermined interim analysis showed that the statistical power would not be sufficient to show a survival advantage for PDT treatment. Differences in site recruitment and treatment techniques were also a factor (L Lilge, Associate Professor, University of Toronto, 23 July 2009, personal communication).

## Discussion

The evidence-base for PDT in brain cancer is very limited, but PDD, followed by PDT, may be the way forward, as identification of the entire tumour is first needed for a curative outcome to be possible. However, although in most cancer sites the stem cells are found within the clinical target volume, and so are subject to therapy, the brain is differently organised, with the normal stem cells found only in four locations (e.g. subventricular space). This means that stem cells may be outside the clinical target volume, so *any* focal treatment is bound to fail if these zones are not included in the therapy (L Lilge, Associate Professor, University of Toronto, 23 July 2009, personal communication). It is therefore questionable whether PDT using current technology is a suitable treatment worthy of further study. Furthermore, the results of the scoping review (see Appendix 11) reveal there to be generally few studies of PDT in brain cancer. Of these, only two studies had comparator groups, and there have been only 10 studies published since 2004.



# Chapter 12

## Head and neck cancer

### Background

The term 'head and neck cancer' encompasses, among others, cancers of the mouth, tongue, lip (oral cancers), pharynx, larynx, sinuses, salivary gland and middle ear. Head and neck cancers account for more than 5% of cancers in Western countries. Tumours commonly arise in mucosal linings and may spread locally, but most do not metastasise. The tumours may affect a patient's ability to breathe, drink and eat. The 5-year survival rates are around 50%, but vary by type and stage. Although the cause of head and neck cancer is unknown for many patients, cancers of the mouth, larynx and pharynx are far more common in people who smoke and drink a lot of alcohol (especially spirits).

Most head and neck cancer treatment involves surgery and/or radiotherapy. Chemotherapy is sometimes used to treat certain cancers (e.g. nasopharynx). Treatment can be given with curative or palliative intent. Even for small tumours, surgery and radiotherapy can both often result in significant morbidity, disabling AEs and loss of function (swallowing, taste, speech). For advanced tumours, resection is often followed by reconstruction surgery involving free flap grafts from other parts of the body (e.g. arm, leg or hip).

Photodynamic therapy in the treatment of head and neck cancer – which is used with either curative or palliative intent – is normally a stand-alone treatment, but can be used in combination with other treatments. Laser light is normally used, with delivery via fiberoptic cables. A possible advantage of using PDT as an alternative is the prospect of preserving function with minimal toxicity, resulting in repeat treatment being an option when necessary.

### Study characteristics

Four trials investigated PDT in the treatment of cancer of the head and neck with a total number of 276 participants (*Table 17*).<sup>141-144</sup> Only one trial was reported in a full paper,<sup>141</sup> with the other three being reported as abstracts.<sup>142-144</sup>

The trials studied different cancer sites, different PDT treatments (apart from two that used methylene blue as photosensitiser<sup>142,143</sup>), and different comparator treatments. Not all treatment parameters were reported in full. Two trials were of curative intent<sup>142,143</sup> and in two the intent was not stated.<sup>141,144</sup>

### Study quality

Trial sample sizes ranged from 30 to 145, with three trials having fewer than 60 participants. This raises questions about whether trials were sufficiently powered to detect significant effects. Use of procedures for blinding of outcome assessors (and randomisation, and allocation concealment procedures, for the one RCT) was unclear in all studies. All trials did, however, report AEs (with varying amounts of detail). Only one trial reported on whether there were losses to follow-up.<sup>141</sup> A graph summarising study quality is presented in *Figure 14*.

### Results of effectiveness and safety

#### PDT vs chemotherapy

One RCT ( $n = 30$ ), which compared Photofrin-PDT with chemotherapy (cisplatin and 5-FU) in patients with nasopharyngeal carcinoma, was only a small pilot study, which provided no details on randomisation procedures or use of blinding.<sup>141</sup> Overall, clinical response was better with PDT ( $p = 0.001$ ), and there was a greater improvement in Karnofsky score (from 45 to 70 vs 40 to 50,  $p = 0.02$ ). In those patients with nasal obstruction PDT was more effective at debulking of tumours (7/8 improved vs 2/8,  $p = 0.04$ ).

The authors reported that the PDT related adverse reactions and side effects were generally tolerable. See Appendix 21 for fuller details.

#### PDT vs other treatments

The two non-RCTs studying PDT and/or surgery compared with other PDT treatments (including PDT with laser only, or photosensitiser only)

**TABLE 17** Head and neck study characteristics

| Authors  | Study design | No. of participants | Cancer site               | Trial treatments  |
|--|--------------|---------------------|---------------------------|---|
| Li <i>et al.</i> (2006) <sup>141</sup>                       | RCT          | 30                  | Nasopharynx               | PDT-Photofrin vs chemotherapy (cisplatin and 5-FU)            |
| Loukatch <i>et al.</i> (1995) <sup>142</sup> (abstract only) | Non-RCT      | 145                 | Larynx                    | Surgery + PDT vs Surgery + PDT without laser vs surgery alone |
| Loukatch <i>et al.</i> (1996) <sup>143</sup> (abstract only) | Non-RCT      | 49                  | Laryngeal part of pharynx | PDT vs PDT-laser only vs PDT-photosensitiser only             |
| Vakulovskaya (2007) <sup>144</sup> (abstract only)           | Non-RCT      | 52                  | Mouth                     | PDT-Photosense vs PDT-Radachlorin                             |

had limited relevance to clinical practice.<sup>142,143</sup> One non-RCT compared PDT using different photosensitisers (Photosense and Radachlorin).<sup>144</sup> All three studies were on different cancer sites. All were also reported as abstracts, and had minimal reporting of methods and results. Results are therefore not discussed in detail here but are available in Appendix 21.

**Evidence summary**

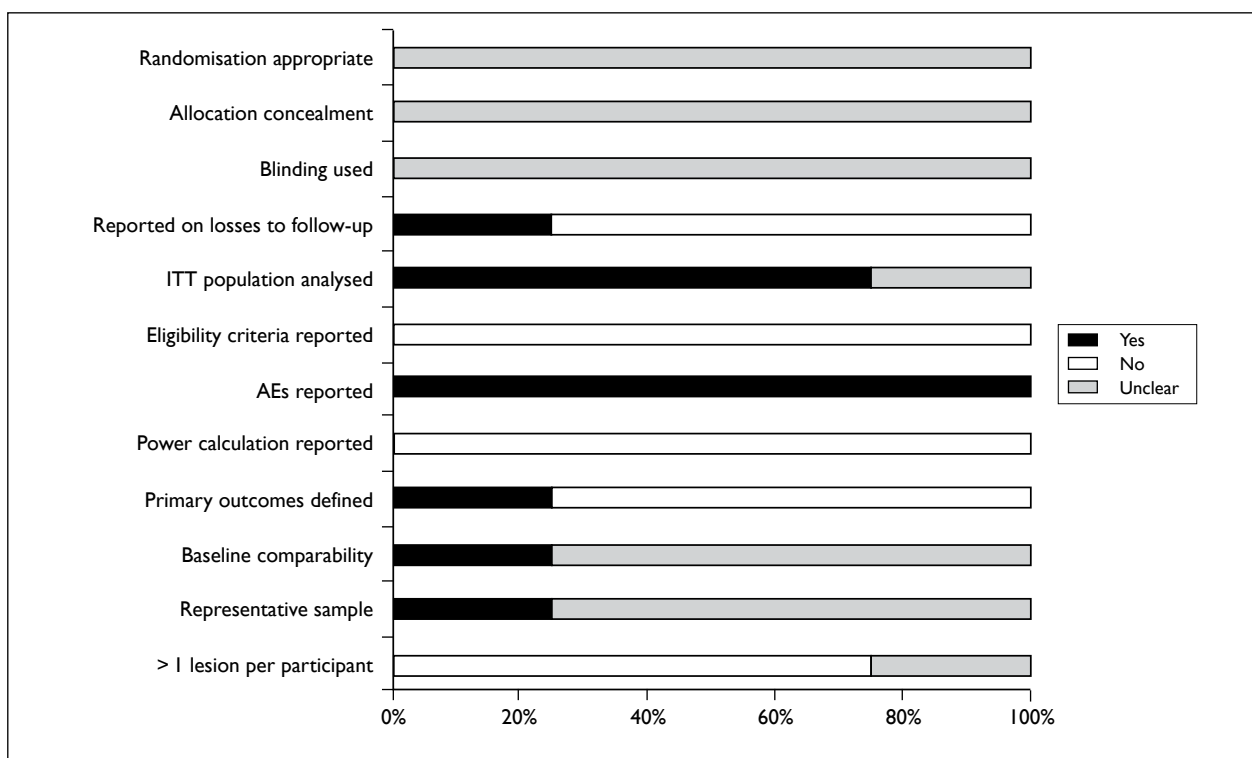
The only RCT on PDT in head and neck cancer suggested that the use of PDT to treat patients with nasopharyngeal cancer is worthy of further investigation, both with regard to effectiveness and adverse effects. Little useful evidence could be gleaned from the three non-RCTs.

**Ongoing trials**

We are not aware of any ongoing/unpublished comparative trials of PDT for head and neck cancer.

**Discussion**

Only one small RCT and three non-RCTs (all three reported only as abstracts) of PDT in head and neck cancer were identified, yielding little useful effectiveness and safety data. The true value of PDT, in relation to other treatment options, has



**FIGURE 14** Head and neck study quality.

therefore yet to be established. In light of its ability to preserve connective tissue, PDT has potential to be of great value, especially as there are few barriers to multiple re-treatments with PDT. Re-treatment by conventional means is very difficult, as there is a limit to the amount of tissue that can be surgically excised.

However, a recent editorial in a PDT journal questioned why so few people with head and neck tumours are treated with PDT, concluding it was due to a dearth of prospective clinical trials, exacerbated by a lack of advancement (in clinical PDT) in terms of photosensitisers and light sources.<sup>145</sup> It is also generally acknowledged that PDT cannot successfully control multiple lymphatic metastases, whereas both surgery and radiotherapy easily can, meaning that PDT is unlikely to be a primary treatment modality in the vast majority of patients with head and neck cancer.

Nevertheless, PDT may still have a key role to play, particularly in primary palliative treatment, and in the treatment of early cancers. It is, perhaps, patients with early head and neck cancer who could theoretically gain the most from PDT, as these patients are at low risk for nodal metastases. Randomised trials of PDT in patients with early-stage head and neck cancer, versus usual treatment (surgery/radiotherapy), and of palliative PDT versus re-irradiation (with or without chemotherapy) are therefore warranted. The population(s) and PDT parameters most suitable for investigation (e.g. which photosensitiser,

method of light delivery, etc.) could be informed by an examination of the studies listed in the scoping section of this report (see Appendix 12). This should include an assessment of study quality.

An example of the slowed progress in PDT research is the development of the photosensitiser Foscan. It was finally licensed in the EU in 2001 but is indicated for only the palliative treatment of patients with advanced head and neck SCC who are failing prior therapies, and is unsuitable for radiotherapy, surgery or systemic chemotherapy. Foscan being licensed for use in such a minority of patients may be a reflection of its chequered history of development, rather than its true efficacy.

In 2000, the US Food and Drug Administration (FDA), shortly followed by the European Agency for the Evaluation of Medicinal Products (EMA), rejected a licence application for Foscan as a palliative treatment for late-stage head and neck cancer. This failure to obtain licences has been attributed to a change of leadership, in 1998, in the company producing Foscan, which led to the termination of ongoing early-stage cancer research projects, and to the changing of Foscan's modality from a treatment for early-stage cancer, to a palliative treatment for late-stage cancer, where it may not have a major advantage over other treatment modalities.<sup>146</sup> The licence rejections ultimately resulted in reduced investment, which consequently delayed the further development of Foscan.



# Chapter 13

## Discussion

### Review methodology

We have conducted a rigorous systematic review of the effectiveness and safety of PDT across a range of clinical conditions. To do this, we pre-specified in a protocol inclusion and exclusion criteria for populations, intervention, comparators and outcomes. We did not place restrictions on the population, intervention or comparator. PDT, in all its variations, was eligible, as were trials that compared different PDT parameters. This comprehensive and rigorous approach also extended to the search strategy. In addition to a thorough search of a range of electronic references, we also contacted experts in the field including trialists, manufacturers and other researchers. All included trials and existing reviews were checked for eligible studies and the review was kept up to date by a further search conducted towards the end of the project. The lack of language restriction and efforts to translate foreign language studies ensured that the international literature was fully explored. Assessment of study quality is paramount in systematic reviews, to understand the weight that can be given to the evidence found.<sup>22</sup> In our assessment of quality we were particularly mindful of how deficiencies in study design might impact on results. The use of evidence summaries in the results narrative provides an interpretation of the findings in the context of quality. We were cautious in our approach to synthesising the data, giving careful consideration to clinical heterogeneity before deciding to pool certain study results. We were only able to conduct meta-analysis in the area of AK, and only for two comparisons. We also assessed the reliability of the pooled results of the meta-analyses conducted. In summary, we believe that the systematic review can be considered relevant, reliable and thorough.

We aimed to base the systematic review on the best evidence for each clinical area. Hence we restricted study design to RCTs where many had been conducted and to non-RCTs where not. At the same time, we were aware that in some areas PDT is an emerging field of research where few comparative trials have been conducted. Therefore, we also conducted a scoping review of the remaining, mainly observational, studies to produce a map

of the complete literature. Within the time and resources available for this review, we have not been able to assess the scoping literature in any detail. However, we have categorised publications by broad study design in those areas where controlled trial evidence is lacking. Further assessment and analysis of this data may provide useful insights into informing future research.

Every systematic review has its limitations. There is the issue of unpublished studies (the file drawer problem).<sup>147</sup> Despite our best efforts, we did not receive replies from most trialists contacted for ongoing and unpublished studies. We do not believe that this would have altered our overall conclusions, but valuable information could have been added to the evidence base. A further problem was poor indexing on some of the electronic databases we searched. Studies may have been missed despite our rigorous search strategy. Finally, our review was limited by the quality of the underlying primary evidence.

### Appraisal of the evidence base

An assessment of the quality of the primary studies allowed us to identify several shortcomings across the PDT literature. There was generally a paucity of well-conducted, adequately powered RCTs which are recognised as the gold standard of health-care research and the least prone to bias.<sup>22</sup> While it is acknowledged that there can be many barriers to conducting high-quality RCTs in cancer,<sup>148</sup> there is also a need to base decisions on the best evidence available. AK had the greatest number of RCTs (28), while brain cancer had just one; the remaining sites had varying numbers and clearly RCTs present challenges in many areas. However, we identified at least one RCT in each clinical condition, suggesting that ethical and funding considerations can be overcome. We recommend that future research, where ethically possible, and where true clinical equipoise exists, should be in the form of well-designed and rigorously conducted RCTs.

Trials of adequate size to detect effects can be challenging to conduct, particularly in rarer

cancers. However, we found that even in more common pre-cancerous conditions such as AK, a lack of study power appeared to be evident in several trials. A complicating factor in skin conditions was that often lesions randomised rather than patients. It was not always clear whether the analyses had taken into account the likely correlation between lesion responses within patients. Multicentre, international trials exist across the PDT literature. Potentially, they can enable larger numbers of patients to be recruited, and possibly enhance generalisability; however, statistical analyses should take centre effects in account.<sup>149</sup> It was not always clear from publications whether institutional differences and protocol deviations had been addressed when analysing data and interpreting results of multicentre trials.

Poor reporting of methodology is a common problem across the clinical trial literature.<sup>150,151</sup> The PDT literature was no exception. Randomisation and allocation concealment procedures in RCTs were generally not well reported. This means that the presence of selection bias cannot be discounted. Although blinding of patients and physicians is sometimes challenging in PDT and its comparators, even attempts to blind outcome assessors were not always reported. This is especially important where outcomes are subjective, such as cosmetic appearance. Therefore, the presence of outcome bias cannot be discounted in the majority of the clinical areas of this review. Across the review AEs were documented in the trial reports. However, improvements could be made in reporting the detail of AEs, such as duration of symptoms and need for auxiliary treatment. It should also be acknowledged that rarer AEs are unlikely to emerge in small-scale trials.

A key issue in any comparative trial is that the outcomes of effectiveness and safety relate only to the treatments being studied. Across the review, we identified trials that had clear baseline differences between groups, making it difficult to relate outcomes solely to interventions.

To provide a robust assessment of effect, trials should ideally detail any dropouts and withdrawals, and conduct an ITT analysis (where results are analysed according to allocation whether the designated treatment was received or not, or only partially completed). Such an analysis was often not conducted (or it was unclear), raising issues of attrition bias through selective dropout. Furthermore, certain trials did not always perform

a test of statistical significance but merely reported differences in treatment groups in terms of raw numbers or percentages. Conclusions on improvements in outcome may not be reliable in these circumstances.

Reported outcomes mainly related to morbidity (response rates, recurrence rates and relief of symptoms), AEs and mortality where relevant to the condition. While these are obviously essential outcomes to assess, outcomes relating to QoL are also important to consider but these were reported more sparsely. Where reported, they tended to be related to cosmetic appearance, with ratings not always provided by blinded outcome assessors. Some trialists made use of the Karnofsky scale to assess QoL (see Appendix 3). Patient-reported outcomes appear to be underutilised across the PDT literature. Resource use was even more rarely assessed, and, in fact, was investigated only in the oesophageal trials and one biliary tract trial.

Often it was not possible to know whether there were problems with the design, conduct or analysis of a trial or whether there was simply poor reporting. This is a common problem in the medical literature.<sup>152</sup> This problem was exacerbated by the fact that several trials were reported as abstracts only. There are advantages and disadvantages in including abstracts in a systematic review. Inclusion ensures that all evidence has been found and documented. A disadvantage is that the abstract rarely presents sufficient detail for reliable critical appraisal. A further issue relating to reporting is the unclear overlap between publications. Unique studies were difficult to identify, as previous publications were not always referenced. Often an assessment of author names and participant numbers and characteristics was the only way to determine whether a publication represented a follow-up to an existing trial or even a publication reporting the same results from the same patients. Ideally, follow-up and associated publications should be clearly linked and referenced, and duplicate publication avoided in order to ensure no double counting of participants in systematic reviews and other technology assessments.

The above limitations were taken into account when assessing the weight that could be attributed to results. They are detailed here as recommendations for improvement in the conduct and reporting of research in this area.

Not all of the research located in this review was subject to the limitations detailed so far. Where trials were more robust we have been able to draw firmer conclusions. PDT is an active area of ongoing, dynamic research. Over one-half of the included trials in this review were conducted in the last 5 years. As an example, 11 RCTs of PDT for AK were reported in 2008 (out of a total of 28, altogether, in this area). The exception to this is lung cancer, for which the most recent trial was published in 2003, with all others conducted in the 1980s or 1990s.

## Statement of principal findings and uncertainties

The appraisal of the evidence above helps to explain why we are unable to draw many definitive conclusions across the cancer sites and conditions investigated. What we are able to conclude, however, is that, overall, PDT appears to be a promising treatment in the majority of conditions we have reviewed. The potential place of PDT amongst the range of other treatments available for each condition is not yet clearly defined.

### Skin conditions

Although 28 RCTs have been conducted on PDT for AK, the only clear evidence of effectiveness found was that both MAL-PDT and ALA-PDT appear to be superior to placebo PDT. Uncertainties still exist regarding PDT's effectiveness relative to cryotherapy, 5-FU and other topical treatments. While optimum parameters for PDT in treating AK remain to be determined, PDT using daylight as a light source may warrant further investigation. The treatment variation found in the cryotherapy studies indicates that the optimal freezing regimens for cryotherapy also appear yet to be determined. SAEs do not appear to be common with PDT, but local skin-related AEs are fairly common. It was unclear – due to inconsistent reporting – whether ALA-PDT and MAL-PDT have different AE profiles.

A small number of trials compared PDT with either cryotherapy or 5-FU for the treatment of Bowen's disease. There are suggestions of better outcomes with PDT, but these would need further confirmation from larger, well-designed trials. All relevant comparators should be investigated. Further research is also needed to

clarify the optimal parameters for PDT in terms of effectiveness and safety.

For superficial BCC, PDT may result in similar lesion response rates to surgery or cryotherapy with better cosmetic outcomes; however, these conclusions are tentative.

The use of MAL-PDT appears superior to placebo for CR in nodular lesions. PDT has been found to be less effective than surgery for nodular BCC in terms of lesion response, but may have better cosmetic outcome. SAEs have not been reported but level of pain needs further investigation in both superficial and nodular BCC. All relevant comparators should be investigated. Further research is also needed to clarify the optimal parameters for PDT in terms of effectiveness and safety.

### Barrett's oesophagus

The 11 RCTs relating to PDT and Barrett's oesophagus are mainly small, and there is variation between trials in levels of dysplasia, comparators and parameters of PDT, making general statements more challenging. PDT with Ps in addition to omeprazole appears to be more effective than omeprazole alone at long-term ablation of HGD and slowing/preventing progression to cancer in Barrett's oesophagus. However, PDT's relative effectiveness compared with other relevant treatment options is unclear. SAEs have not been reported for PDT in Barrett's oesophagus but AE profiles need to be more clearly established. The priority for PDT research in the area of Barrett's oesophagus is to determine more clearly the role of PDT and its optimal delivery to patients with HGD.

### Oesophageal cancer

Trials have been conducted with curative and palliative intent in oesophageal cancer, but the evidence is not yet sufficiently robust to draw firm conclusions of effectiveness when compared with other treatments such as surgery, radiotherapy or 5-FU. HBO appears to enhance the efficacy of PDT in oesophageal cancer but has not yet been tested in an RCT. It is not yet clear what are the optimal parameters or preferred photosensitisers for PDT in oesophageal cancer, and this is an area of ongoing research. Questions remain around the place of PDT; for example, should PDT be offered as a primary treatment for early-stage oesophageal

cancer or following endoscopic mucosal resection or unsuccessful chemoradiotherapy in a palliative setting?

The most likely AEs from the PDT treatments were stricture formation and dysphagia, which may occur in either curative or palliative treatments. Patients who did not follow recommended precautions to prevent over exposure to light were vulnerable to photosensitivity.

## Lung cancer

No trials were located for early-stage lung cancer. All included trials related to PDT used with palliative intent. Additionally, with the exception of one trial, the literature dates from the 1980s and 1990s. Further research is needed to determine the role of PDT in lung cancer in relation to current comparators and to identify particular subgroups who might benefit from PDT.

## Cancers of the biliary tract

Photodynamic therapy may improve survival when compared with stenting alone, and an ongoing trial should provide more definitive evidence in a more generalisable patient population. SAEs do not appear to be common. Equally, photosensitisation has not been reported as a major issue. It is unclear if there are variations in effectiveness between photosensitisers in the treatment of cholangiocarcinoma, and there do not appear to have been any controlled trials carried out in other biliary tract cancer sites.

## Brain cancer

There is very limited evidence available on PDT for brain cancer and no definitive statements can currently be made. Fluorescence-guided resection with repeated ALA-PDT may possibly have some effectiveness, but whether PDT has any role in treating brain cancer, using current technologies, is a subject needing further debate.

## Head and neck cancer

There is a lack of good trial evidence for head and neck cancer. The true value of PDT, in relation to other treatment options, has therefore yet to be established, as have the optimum PDT parameters. PDT's ability to preserve connective tissue and therefore allow re-treatment makes it worthy of investigation in RCTs for both early head and neck cancers, and palliative treatment.

## General uncertainties

The following uncertainties arise due to the evolving nature of PDT research and to existing gaps in the research literature.

- As more knowledge is gained on the optimal parameters for PDT in each clinical area how will this affect the comparisons between PDT and other treatments? What effect will new developments in PDT have on effectiveness and treatment tolerability? For example, research is ongoing to investigate attaching photosensitisers to antibodies to obtain better tumour selectivity.<sup>153</sup> Another potential development is that of generating light chemically, so that it is not necessary to know the location of every area of cancer in order to deliver light effectively.<sup>154</sup>
- Patient-reported outcomes are not commonly sought across the PDT literature. We do not have patient preference data in the included trials. However, we have some anecdotal evidence of selected patient preferences for PDT (D Longman, KILLING Cancer charity, 2009, personal communication]. We also located a small number of qualitative and survey studies that aimed to assess patients' experience of PDT<sup>155,156</sup> but there is more work to be done in this area. In addition, it would be beneficial to examine the barriers to conducting RCTs in PDT from the perspective of the patient and the clinician.



# Chapter 14

## Conclusions

### Implications for health care

Photodynamic therapy is currently most accepted in the treatment of malignant and pre-malignant non-melanoma skin lesions. In this review we found evidence of effectiveness for the treatment of AK and nodular BCC in relation to placebo. However, we do not yet fully know the effectiveness of PDT in relation to other treatments and optimal parameters for PDT do not appear to be firmly established. The evidence suggests that PDT might be a useful option in Barrett's oesophagus but its effectiveness in relation to other treatments is not yet apparent.

The ideal model of delivery for the above conditions is not clear. The review did not examine cost-effectiveness and we located very little evidence on resource use. Further work would need to be done on implications for infrastructure, resourcing and development of staff to provide access to PDT in a fair and equitable way.

We did not find any clear evidence implying that PDT should definitely not be used for certain clinical conditions. Rather, there are a number of uncertainties outlined in the previous chapter that require further investigation.

### Suggested research priorities

Further research is needed to clarify the uncertainties identified in this report and to continue to develop the field of PDT for cancer. Future studies should bear in mind the quality issues highlighted in the appraisal of the current evidence. The need for further research in each of the clinical areas in this review is detailed in the previous chapter; the priorities listed here apply to all the clinical areas and identify the methodologies that will allow the field of PDT to develop more robust evidence.

- The optimal parameters of PDT need to be identified across the conditions studied.
- Future trials need to compare PDT against all relevant comparators to establish its place in the treatment of a given condition and to identify whether subgroups of patients might respond better to PDT.
- Future trials should study all relevant outcomes, including QoL. They need to balance an assessment of the effectiveness of PDT against the assessment of AEs, and should include a detailed assessment of any such events. Cosmetic ratings should be conducted by patients and blinded outcome assessors.
- Research is needed on the patient experience of PDT. While QoL and cosmetic outcome data have been gathered to some extent, a deep insight into the acceptability of the treatment should be beneficial. There is no reason why this research should not be embedded in a trial. An example from the field of prostate cancer demonstrates the validity of this approach.<sup>157</sup>
- While the difficulties of conducting high-quality trials in rarer cancers, such as those of the brain and head and neck, are recognised, there is a need to establish where barriers are insurmountable. If RCTs cannot be conducted, other types of evidence could be considered. In some of the rarer sites further evaluation of the observational literature may be informative.

PDT is an active field of research and, as the results of ongoing trials become available, there will be a need to update this review. Research evidence exists in a number of other sites,<sup>17</sup> and so far these have not been subject to a thorough, systematic review. Further work should focus on the cost-effectiveness of PDT in those areas where effectiveness and safety have been established.





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|                          |  |
|--------------------------|--|
| Mr Roger Ackroyd         | Consultant Upper Gastrointestinal Surgeon, Sheffield Teaching Hospitals NHS Trust  |
| Professor Steve Bown     | Professor of Laser Medicine and Surgery, Director, National Medical Laser Centre   |
| Dr David DeBerker        | Consultant Dermatologist, University Hospitals Bristol NHS Foundation Trust  |
| Mr Sam Eljamel           | Consultant Neurological Surgeon, Ninewells Hospital and Medical School, University of Dundee   |
| Mr Colin Hopper          | Head of the Unit of Oral and Maxillofacial Surgery, Eastman Dental Institute and Hospital; Senior Research Fellow, National Medical Laser Centre, London |
| Dr Sally Ibbotson        | Clinical Senior Lecturer in Photobiology, Ninewells Hospital and Medical School, University of Dundee  |
| Professor Andrew H Kaye  | James Stewart Professor of Surgery, Head of Department of Surgery, The University of Melbourne   |
| Professor Herwig Kostron | Department of Neurosurgery, Medical University Innsbruck   |
| Dr Robert Milroy         | Consultant in Respiratory Medicine, Stobhill Hospital, Glasgow   |
| Dr Steve Pereira         | Senior Lecturer in Hepatology & Gastroenterology, Royal Free and University College London Medical School  |

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Dr John Winter      Consultant Respiratory Physician, King's Cross Hospital, Dundee

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### Contribution of authors

Debra Fayter contributed to all stages of the systematic review from the development of the

protocol to the production of the final report, she also took day-to-day responsibility for the project. Mark Corbett contributed to all stages of the systematic review from the development of the protocol to the production of the final report. He managed the project software and devised the meta-analyses. Morag Heirs contributed to all stages of the systematic review from the development of the protocol to the production of

the final report. She also took responsibility for managing the papers and the project software, and for contacting researchers and study authors. David Fox devised the search strategy, carried out the literature searches and wrote the search methodology sections of the report. Alison Eastwood contributed to all stages of the review, commented on drafts of the report and took overall responsibility for the project.



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# Appendix I

## Search strategy

The core search strategy used for this review was as follows:

1. photochemotherapy/
2. photosensitizing agents/
3. ((photodynamic or (photo adj dynamic)) adj2 therap\$.tw.
4. PDT.tw.
5. (photosensitise\$or photosensitize\$or photosensiti?ing or photochemotherapy or (photo adj chemotherapy)).tw.
6. ((photoradiation or (photo adj radiation)) adj2 therap\$.tw.
7. PRT.tw.
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. exp neoplasms/
10. (cancer\$or neoplas\$or oncolog\$or tumour\$or tumor\$or lump or lumps).tw.
11. (sarcoma\$or malignan\$or carcinoma\$or growth\$or mass or masses or lesion\$or glioma\$.tw.
12. (premalig\$or pre-malig\$or pre malig\$or cyst or cysts).tw.
13. (metastatic or metastases or metastasis or squamous cell\$.tw.
14. "Barrett Esophagus"/
15. (barret\$adj (oesophagus or esophagus)).tw.
16. 9 or 10 or 11 or 12 or 13 or 14 or 15
17. 8 and 16
18. exp Animals/not humans/
19. 17 not 18

This strategy was designed for searching MEDLINE through the Ovid interface and was adapted as appropriate for all other databases searched, taking into account differences in indexing terms and search syntax for each database.

Full details of all databases searched and search strategies are provided below.

### MEDLINE and MEDLINE In-Process: Ovid

<http://gateway.ovid.com/athens>

The MEDLINE search covered the date range 1950 to present. The search was carried out on 14 August 2008 and identified 7178 records.

1. photochemotherapy/(8857)
2. photosensitizing agents/(5949)
3. ((photodynamic or (photo adj dynamic)) adj2 therap\$.tw. (7397)
4. PDT.tw. (4852)
5. (photosensitise\$or photosensitize\$or photosensiti?ing or photochemotherapy or (photo adj chemotherapy)).tw. (8234)
6. ((photoradiation or (photo adj radiation)) adj2 therap\$.tw. (174)
7. PRT.tw. (651)
8. 1 or 2 or 3 or 4 or 5 or 6 or 7 (17787)
9. exp neoplasms/(2011836)
10. (cancer\$or neoplas\$or oncolog\$or tumour\$or tumor\$or lump or lumps).tw. (1412061)
11. (sarcoma\$or malignan\$or carcinoma\$or growth\$or mass or masses or lesion\$or glioma\$.tw. (2012713)
12. (premalig\$or pre-malig\$or pre malig\$or cyst or cysts).tw. (78803)
13. (metastatic or metastases or metastasis or squamous cell\$.tw. (250958)
14. "Barrett Esophagus"/(4295)
15. (barret\$adj (oesophagus or esophagus)).tw. (4411)
16. 9 or 10 or 11 or 12 or 13 or 14 or 15 (3478621)
17. 8 and 16 (9326)
18. exp Animals/not humans/(3344509)
19. 17 not 18 (7178)

The search was re-run on 28 May 2009, using the same strategy to capture recent studies, and identified 460 additional records.

### EMBASE: Ovid

<http://gateway.ovid.com/athens>

The EMBASE search covered the date range 1980–2008 (week 32). The search was carried out on 14 August 2008 and identified 5690 records.

1. photochemotherapy/(1635)
2. photosensitizing agent/(3791)

3. ((photodynamic or (photo adj dynamic)) adj2 therap\$).tw. (6228)
4. PDT.tw. (3983)
5. (photosensitise\$or photosensitize\$or photosensiti?ing or photochemotherapy or (photo adj chemotherapy)).tw. (6580)
6. ((photoradiation or (photo adj radiation)) adj2 therap\$).tw. (130)
7. PRT.tw. (487)
8. 1 or 2 or 3 or 4 or 5 or 6 or 7 (13196)
9. exp neoplasm/(1439539)
10. (cancer\$or neoplas\$or oncolog\$or tumour\$or tumor\$or lump or lumps).tw. (1054121)
11. (sarcoma\$or malignan\$or carcinoma\$or growth\$or mass or masses or lesion\$or glioma\$).tw. (1531626)
12. (premalig\$or pre-malig\$or pre malig\$or cyst or cysts).tw. (51404)
13. (metastatic or metastases or metastasis or squamous cell\$).tw. (198043)
14. "Barrett Esophagus"/(5465)
15. (barret\$adj (oesophagus or esophagus)).tw. (3915)
16. 9 or 10 or 11 or 12 or 13 or 14 or 15 (2518901)
17. 8 and 16 (7538)
18. exp animal/(18250)
19. exp animal-experiment/(1251475)
20. nonhuman/(3097648)
21. (rat or rats or mouse or mice or hamster or hamsters or animal or animals or dog or dogs or cat or cats or bovine or sheep).ti,ab,sh. (2000565)
22. 18 or 19 or 20 or 21 (3512709)
23. exp human/(6267311)
24. exp human-experiment/(249466)
25. 23 or 24 (6268176)
26. 22 and 25 (620556)
27. 22 not 26 (2892153)
28. 17 not 27 (5690)

The search was re-run using the same strategy on 21 May 2009 (2009, week 20) to capture recent studies and identified 357 additional records.

### CINAHL: Ovid

<http://gateway.ovid.com/athens>

The CINAHL search covered the date range 1982–2008 (August, week 2). The search was carried out on 14 August 2008 and identified 229 records.

1. photochemotherapy/(124)
2. photosensitizing agents/(112)
3. ((photodynamic or (photo adj dynamic)) adj2 therap\$).tw. (213)

4. PDT.tw. (119)
5. (photosensitise\$or photosensitize\$or photosensiti?ing or photochemotherapy or (photo adj chemotherapy)).tw. (55)
6. ((photoradiation or (photo adj radiation)) adj2 therap\$).tw. (2)
7. PRT.tw. (50)
8. 1 or 2 or 3 or 4 or 5 or 6 or 7 (453)
9. exp neoplasm/(88899)
10. (cancer\$or neoplas\$or oncolog\$or tumour\$or tumor\$or lump or lumps).tw. (72661)
11. (sarcoma\$or malignan\$or carcinoma\$or growth\$or mass or masses or lesion\$or glioma\$).tw. (54848)
12. (premalig\$or pre-malig\$or pre malig\$or cyst or cysts).tw. (1672)
13. (metastatic or metastases or metastasis or squamous cell\$).tw. (6333)
14. "Barrett Esophagus"/(249)
15. (barret\$adj (oesophagus or esophagus)).tw. (214)
16. 9 or 10 or 11 or 12 or 13 or 14 or 15 (146875)
17. 8 and 16 (235)
18. "animal studies"/(7317)
19. 17 not 18 (229)

The search was re-run on 26 May 2009 (1982 to 15 May 2009) to capture recent studies, and identified 47 additional records. An amended strategy was used to search via EBSCO interface (<http://web.ebscohost.com>) as CINAHL was no longer available via the Ovid interface.

S20 S10 AND S19

S19 S11 or S12 or S13 or S14 or S15 or S16 or S17 or S18

S18 TX barret\* N1 esophagus

S17 TX barret\* N1 oesophagus

S16 MH Barrett Esophagus

S15 TX metastatic or metastases or metastasis or squamous cell\*

S14 TX premalig\* or pre-malig\* or pre malig\* or cyst or cysts

S13 TX sarcoma\* or malignan\* or carcinoma\* or growth\* or mass or masses or lesion\* or glioma\*

S12 TX cancer\* or neoplas\* or oncolog\* or tumour\* or tumor\* or lump or

lumps

S11 MH neoplasms

S10 S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9

S9 TX PRT

S8 TX photo radiation N2 therap\*

S7 TX photoradiation N2 therap\*

S6 TX photosensitise\* or photosensitize\* or photosensiti?ing or photochemotherapy or photo  
 S5 TX PDT  
 S4 TX photo dynamic N2 therap\*  
 S3 TX photodynamic N2 therap\*  
 S2 MH photosensitizing agents  
 S1 MH photochemotherapy

## Cochrane Library

www3.interscience.wiley.com

Including:

- Cochrane Database of Systematic Reviews (CDSR)
- Health Technology Assessment Database (HTA)
- Cochrane Central Register of Controlled Trials (CENTRAL)
- NHS Economic Evaluation Database (NHS EED)

The search was carried out on 1 September 2008 and identified 334 records. No date limits applied.

- #1 MeSH descriptor Photochemotherapy, this term only  
 #2 MeSH descriptor Photosensitizing Agents, this term only  
 #3 (photodynamic near/2 therap\*):ti,ab  
 #4 PDT:ti,ab  
 #5 (photosensitise\* or photosensitize\* or photochemotherapy or photo chemotherapy or photo-chemotherapy):ti,ab  
 #6 (photoradiation near/2 therap\*):ti,ab  
 #7 PRT:ti,ab  
 #8 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7)  
 #9 MeSH descriptor Neoplasms explode all trees  
 #10 (cancer\* or neoplas\* or oncolog\* or tumour\* or tumor\* or lump or lumps):ti,ab  
 #11 (sarcoma\* or malignan\* or carcinoma\* or growth\* or mass or masses or lesion\* or glioma\*):ti,ab  
 #12 (premalig\* or pre-malig\* or pre malig\* or cyst or cysts):ti,ab  
 #13 (metastatic or metastases or metastasis or squamous cell\*):ti,ab  
 #14 MeSH descriptor Barrett Esophagus, this term only  
 #15 (barret\* near/1 (oesophagus or esophagus)):ti,ab

#16 (#9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15)  
 #17 (#8 AND #16)

The search was re-run using the same strategy on 26 May 2009 to capture recent studies, and identified 5 additional records.

## Database of Abstracts of Reviews of Effects (DARE)

The search was carried out on 7 September 2008, using the internal CRD administration system, and identified 122 records. No date limits applied.

RESTRICT MH Photochemotherapy  
 photochemotherapy:OK  
 photochemotherapy:CK  
 RESTRICT MH Photosensitizing Agents  
 Photosensitizing Agents:OK  
 Photosensitizing Agents:CK  
 photodynamic\*  
 photo dynamic  
 PDT  
 photosensiti\*  
 photochemotherapy  
 photoradiation  
 PRT  
 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13  
 RESTRICT MH Neoplasms  
 Neoplasms:OK  
 Neoplasms:CK  
 cancer\$or neoplas\$or oncolog\$or tumour\$or tumor\$or lump or lumps  
 sarcoma\* or malignan\* or carcinoma\* or growth\* or mass or masses or lesion\* or glioma\*  
 premalig\* or pre-malig\* or pre malig\* or cyst or cysts  
 metastatic or metastases or metastasis or squamous cell\*  
 RESTRICT MH Barrett Esophagus  
 Barrett Esophagus:OK  
 Barrett Esophagus:CK  
 barret\* esophagus  
 barret\* oesophagus  
 #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26  
 #14 and #27

The search was re-run using the same strategy on 20 May 2009 to capture recent studies, and identified 19 additional records.

## LILACS (Latin American and Caribbean Health Sciences Literature)

<http://bases.bireme.br/cgi-bin/wxislind.exe/iah/online/?IsisScript=iah/iah.xis&base=LILACS&lang=i>

The search was carried out on 1 September 2008 and identified 80 records. No date limits applied.

- photochemotherapy or photosensiti\$or photodynamic therap\$or PDT or photoradiation therap\$(in WORDS)

AND

cancer\$or neoplas\$or oncolog\$or tumour\$or tumor\$or lump or lumps or sarcoma\$or malignan\$or carcinoma\$or mass or masses or lesion\$or glioma\$or premalig\$or pre-malig\$or pre malig\$or cyst or cysts or metastatic or metastases or metastasis or squamous cell\$or barret\$oesophagus or barret\$esophagus (in WORDS)

## PASCAL [database of INIST (Institut de l'Information Scientifique et Technique)]

[www.dialogclassic.com/](http://www.dialogclassic.com/)

The search was carried out on 12 September 2008 and identified 2278 records. No date limits applied.

b 144

s (photodynamic or photo(w)dynamic)(2n)(therapy or therapies)

s (photoradiation or photo(w)radiation)(2n)(therapy or therapies)

s PDT or PRT

s photosensitiz? or photosensitiz? or

photochemotherapy or photo(w)chemotherapy

s s1:s4

s cancer? or neoplas? or oncolog? or tumour?

or tumor? or lump or lumps or sarcoma? or

malignan? or carcinoma? or growth? or mass or

masses or lesion? or glioma? or premalig? or pre(w)

malig? or cyst or cysts or metastatic or metastases

or metastasis or squamous(w)cell?

s barret?(w)(oesophagus or esophagus)

s s6:s7

s s5 and s8

## Current Controlled Trials

<http://controlled-trials.com/>

The search was carried out on 12 September 2008 and identified 204 records. No date limits applied.

photochemotherapy OR photosensitiser OR photosensitizer OR "photodynamic therapy" or "photodynamic therapies" or PDT or "photoradiation therapy" or PRT

## ISI Conference Proceedings Citation Index- Science (CPCI-S)

<http://apps.isiknowledge.com>

The search was carried out on 20 October 2008 and identified 958 records. No date limits applied.

Basic search (restricted to CPCI-S);  
photochemotherapy OR photosensiti\*  
OR photodynamic therap\* OR PDT OR  
photoradiation therap\* OR PRT

AND

cancer\* OR neoplas\* OR oncolog\* OR tumour\*  
OR tumor\* OR lump OR lumps OR sarcoma\*  
OR malignan\* OR carcinoma\* OR mass OR  
masses OR lesion\* OR glioma\* OR premalig\*  
OR pre-malig\* OR pre malig\* OR cyst OR cysts  
OR metastatic OR metastases OR metastasis OR  
squamous cell\* OR barret\* oesophagus OR barret\*  
esophagus OR Bowen\* OR keratos\*

## Zetoc (British Library's Electronic Table of Contents)

<http://zetoc.mimas.ac.uk>

The search was carried out on 22 October 2008 and identified 754 records. No date limits applied. Searches were run separately, and results combined and de-duplicated.

conference: photodynamic neoplas\* (22)  
conference: photochemotherapy neoplas\* (16)  
conference: PDT neoplas\* (3)  
conference: photosensiti\* neoplas\* (2)  
conference: photoradiation neoplas\* (nil)  
conference: PRT neoplas\* (nil)  
conference: photodynamic cancer\* (426)  
conference: photochemotherapy cancer\* (52)  
conference: PDT cancer\* (86)  
conference: photosensiti\* cancer\* (98)  
conference: photoradiation cancer\* (1)  
conference: PRT cancer\* (nil)  
conference: photodynamic barret\* (26)  
conference: photochemotherapy barret\* (2)

conference: PDT barret\* (4)  
conference: photosensiti\* barret\* (1)  
conference: photoradiation barret\* (nil)  
conference: PRT barret\* (nil)  
conference: photodynamic bowen\* (14)

conference: photochemotherapy bowen\* (1)  
conference: PDT bowen\* (nil)  
conference: photosensiti\* bowen\* (nil)  
conference: photoradiation bowen\* (nil)  
conference: PRT bowen\* (nil)



## Appendix 2

### Data extraction and quality assessment

#### Guidelines for data extraction

##### Population details

##### Type of cancer and histology

Tick box for type then provide numbers on histology in text box.

##### Patient characteristics

Use 'overall population' figures where available, or where they can be calculated (e.g. 56% male, even though results were given by treatment group), and only break down figures by treatment group when the overall figure cannot be calculated.

##### Characteristics to look out for, and extract

- Percentage male: (just state number, no % after).
- Age range.
- Mean age.
- Cancer stage: state numbers if provided, stage II, 2; stage III, 4; stage IV: 7.
- Number with recurrent tumour.

*If this section is lengthy say that 'Further patient characteristics were reported'.*

##### Eligibility criteria: check for

Age, Karnofsky status, time since last chemotherapy/radiotherapy, inoperability, previous treatment allowed? Other details such as 'non-pregnant women' may be extracted.

*If this section is lengthy say that 'Further eligibility criteria were reported'.*

##### Treatment details

##### Describing PDT (use 'Not stated' when necessary)

Check for the following:

- photosensitiser used (including mode of application)
- dose of photosensitiser
- duration of photosensitiser (drug to light interval)
- light source and duration
- wavelength of light source
- power density (mW/cm)
- total light dose (J/cm)

- maximum number of sessions/doses allowed
- postoperative care/advice
- baseline bronchoscopy (only state if this is absent, using the Study appraisal field)
- postoperative care/advice.

*Rather than stating 'Dose, duration, etc., were not reported' state 'Further PDT parameters were not reported'.*

##### Describing comparators

- Type and mode of delivery.
- Dose and duration.
- Maximum number of sessions/doses allowed.
- Postoperative care/advice.

##### Results

Note: Only extract outcome data that are broken down by treatment group.

##### Morbidity

- Recurrence and tumour response measures.
- Symptom burden.
- Symptom improvement.
- Time to healing.

##### Quality of life

- Quality of life scores.
- Depression scores.
- Cosmetic appearance.

##### Resource use

- Length of hospital stay.

##### Adverse events

List all, especially detailing photosensitisation (mention if this is not reported). Treatment-related mortality is detailed here, not in 'mortality', which focuses on survival.

##### Interpretation

##### Brief study appraisal

In addition to study quality, highlight issues such as 'were all the assessed outcomes reported?'.

##### Quality assessment – additional notes

##### Distinction between 'no' and 'unclear'

Only enter 'no' if the paper is explicit.

**Losses to follow-up reported?**

That is, did the authors explicitly report on whether or not there were any losses to follow-up,

or did they say nothing on this issue? If the authors said that there were no losses to follow-up, then answer 'yes'.

**Section A: Study details**

|   |                            |
|---|----------------------------|
| A.1 Authors, year and master endnote number | A.1.1 Specify              |
| A.2 Linked endnote numbers                  | A.2.1 Specify              |
| A.3 Data source                             | A.3.1 Full published paper |
|   | A.3.2 Abstract             |
|   | A.3.3 Other (specify)      |
| A.4 Country                                 |                            |
| A.5 Language                                |                            |
| A.6 Study design                            | A.6.1 RCT                  |
|   | A.6.2 Non-RCT              |
| A.7 No. of participants                     | A.7.1 Total                |
|   | A.7.2 Intervention         |
|   | A.7.3 Comparator           |
|   | A.7.4 2nd comparator       |
|   | A.7.5 3rd comparator       |
|   | A.7.6 4th comparator       |
| A.8 No. of recruiting centres               | A.8.1 Specify              |
|   | A.8.2 Not stated           |
| A.9 Follow-up period and frequency          | A.9.1 Specify              |

**Section B: Population details**

|                                     |                  |
|-------------------------------------|------------------|
| B.1 Treatment intention             | B.1.1 Curative   |
|                                     | B.1.2 Palliative |
|                                     | B.1.3 Not stated |
| B.2 Type(s) of cancer and histology | B.2.1 Specify    |
|                                     | B.2.2 Not stated |
| B.3 Main eligibility criteria       | B.3.1 Specify    |
|                                     | B.3.2 Not stated |
| B.4 Patient characteristics         | B.4.1 Specify    |
|                                     | B.4.2 Not stated |
| B.5 Concomitant treatment           | B.5.1 Specify    |
|                                     | B.5.2 Not stated |
|                                     | B.5.3 None       |

**Section C: Treatment details**

|                      |               |
|----------------------|---------------|
| C.1 Trial treatments | C.1.1 Specify |
| C.2 Intervention     | C.2.1 Specify |
| C.3 Comparator       | C.3.1 Specify |
| C.4 2nd comparator   | C.4.1 Specify |
| C.5 3rd comparator   | C.5.1 Specify |
| C.6 4th comparator   | C.6.1 Specify |



**Section D: Results**

|                                       |                                 |
|---------------------------------------|---------------------------------|
| D.1 Mortality                         | D.1.1 Specify                   |
|                                       | D.1.2 Not assessed              |
|                                       | D.1.3 Assessed but not reported |
| D.2 Morbidity                         | D.2.1 Specify                   |
|                                       | D.2.2 Not assessed              |
|                                       | D.2.3 Assessed but not reported |
| D.3 QoL and return to normal activity | D.3.1 Specify                   |
|                                       | D.3.2 Not assessed              |
|                                       | D.3.3 Assessed but not reported |
| D.4 Adverse events                    | D.4.1 Specify                   |
|                                       | D.4.2 Not assessed              |
|                                       | D.4.3 Assessed but not reported |
| D.5 Resource use                      | D.5.1 Specify                   |
|                                       | D.5.2 Not assessed              |
|                                       | D.5.3 Assessed but not reported |

**Section E: Interpretation**

|                           |               |
|---------------------------|---------------|
| E.1 Authors' conclusions  | E.1.1 Specify |
| E.2 Brief study appraisal | E.2.1 Specify |

**Quality assessment tool**

|   |                |
|---|----------------|
| Was randomisation used appropriately?                       | Yes/no/unclear |
| Was allocation concealment used appropriately?              | Yes/no/unclear |
| Was blinding used appropriately?                            | Yes/no/unclear |
| Were any losses to FU reported?                             | Yes/no/unclear |
| Was an ITT analysis conducted?                              | Yes/no/unclear |
| Were trial eligibility criteria reported?                   | Yes/no/unclear |
| Were AEs reported?  | Yes/no         |
| Was a power calculation reported?                           | Yes/no         |
| Were primary outcomes defined?                              | Yes/no/unclear |
| Were groups comparable at baseline?                         | Yes/no/unclear |
| Did the trial have a representative sample of patients?     | Yes/no/unclear |
| Was there more than 1 lesion per patient (skin sites only)? | Yes/no/unclear |



## Appendix 3

### Karnofsky performance status

Quality of life may be proxied by performance status scores such as the Karnofsky Performance status.<sup>158</sup> The Karnofsky score runs from 100 to 0, where 100 is 'perfect' health and 0 is death. Although the score has been described with

intervals of 10, a practitioner may choose decimals if he or she feels that a patient's situation holds somewhere between two marks. It is named after Dr David A Karnofsky, who described the scale with Dr Joseph H Burchenal in 1949.

- 100% – normal, no complaints, no signs of disease
- 90% – capable of normal activity, few symptoms or signs of disease
- 80% – normal activity with some difficulty, some symptoms or signs
- 70% – caring for self, not capable of normal activity or work
- 60% – requiring some help, can take care of most personal requirements
- 50% – requires help often, requires frequent medical care
- 40% – disabled, requires special care and help
- 30% – severely disabled, hospital admission indicated but no risk of death
- 20% – very ill, urgently requiring admission, requires supportive measures or treatment
- 10% – moribund, rapidly progressive fatal disease processes
- 0% – death



## Appendix 4

### Classification systems

There are a number of different staging systems to classify cancer; one of the most common is the TNM classification but numerical systems are also used.

#### TNM stages

The TNM system<sup>159</sup> provides a framework for classifying solid tumours according to the site of the primary tumour, the histological type and degree to which the cancer has spread.

- 'T' refers to the primary tumour:
  - T0 – no evidence of primary tumour
  - Tis – carcinoma in situ
  - T1, T2, T3, T4 – size/extent of the primary tumour
  - TX – primary tumour cannot be evaluated.
- 'N' refers to regional lymph node involvement:
  - N0 – no regional lymph node involvement
  - N1, N2, N3 – involvement of regional lymph nodes (number/extent of spread)
  - NX – regional lymph nodes cannot be evaluated.
- 'M' refers to metastasis:
  - M0 – no metastasis (cancer has not spread to other parts of the body)
  - M1 – metastasis (cancer has spread to other parts of the body)
  - MX – metastasis cannot be evaluated.

#### Number staging systems

The number system<sup>159</sup> uses numerical values (often written using Roman numerals) to distinguish stages:

- **Stage 0** = carcinoma in situ.
- **Stage I** cancers are localized to one part of the body.
- **Stage II** cancers are locally advanced.

- **Stage III** cancers are also locally advanced. Whether a cancer is designated as Stage II or Stage III can depend on the specific type of cancer. The specific criteria for Stages II and III therefore differ according to diagnosis.
- **Stage IV** cancers have often metastasised (spread to other organs or throughout the body).

The stages can be further subdivided using the letters a, b, c, etc. (e.g. Stage IIIb).

The TNM combinations often correspond to one of these numbered stages, although the criteria for this differ for different types of cancer.

#### Fitzpatrick skin type

Within dermatology, generally, patient skin type may be described in terms of Fitzpatrick score.<sup>160</sup> This is a numerical schema that classifies skin according to how it reacts to UV light. The overall score includes genetic disposition, reaction to sun exposure and tanning habits.

- *Type I* (scores 0–7) White; very fair; red or blond hair; blue eyes; freckles. Always burns, never tans.
- *Type II* (scores 8–16) White; fair; red or blond hair; blue, hazel or green eyes. Usually burns, tans with difficulty.
- *Type III* (scores 17–25) Cream white; fair with any eye or hair color; very common. Sometimes mild burn, gradually tans.
- *Type IV* (scores 25–30) Dark brown; typical Mediterranean Caucasian skin. Rarely burns, tans with ease.
- *Type V* (scores over 30) Dark brown; Middle Eastern skin types. Very rarely burns, tans very easily.
- *Type VI* Black; never burns, tans very easily.



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Geriatric rehabilitation following fractures in older people: a systematic review.

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Unit, University of Sheffield

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Consultant Adviser, NETSCC,  
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Medicine, University of Oxford

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**Dr David Elliman,**  
Consultant Paediatrician and  
Honorary Senior Lecturer,  
Great Ormond Street Hospital,  
London

Professor Judith E Adams,  
Consultant Radiologist,  
Manchester Royal Infirmary,  
Central Manchester &  
Manchester Children's  
University Hospitals NHS  
Trust, and Professor of  
Diagnostic Radiology, Imaging  
Science and Biomedical  
Engineering, Cancer &  
Imaging Sciences, University of  
Manchester

Mr A S Arunkalaivanan,  
Honorary Senior Lecturer,  
University of Birmingham and  
Consultant Urogynaecologist  
and Obstetrician, City Hospital

Dr Dianne Baralle,  
Consultant & Senior Lecturer  
in Clinical Genetics, Human  
Genetics Division & Wessex  
Clinical Genetics Service,  
Southampton, University of  
Southampton

Dr Stephanie Dancer,  
Consultant Microbiologist,  
Hairmyres Hospital, East  
Kilbride

Dr Ron Gray,  
Consultant, National Perinatal  
Epidemiology Unit, Institute of  
Health Sciences, University of  
Oxford

Professor Paul D Griffiths,  
Professor of Radiology,  
Academic Unit of Radiology,  
University of Sheffield

Mr Martin Hooper,  
Service User Representative

Professor Anthony Robert  
Kendrick,  
Professor of Primary  
Medical Care, University of  
Southampton

Dr Susanne M Ludgate,  
Director, Medical Devices  
Agency, London

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Director of Programmes, UK  
National Screening Committee

Dr David Mathew  
Service User Representative

Dr Michael Millar, Lead  
Consultant in Microbiology,  
Department of Pathology &  
Microbiology, Barts and The  
London NHS Trust, Royal  
London Hospital

Mr Stephen Pilling,  
Director, Centre for Outcomes,  
Research & Effectiveness,  
University College London

Mrs Una Rennard,  
Service User Representative

Ms Jane Smith,  
Consultant Ultrasound  
Practitioner, Ultrasound  
Department, Leeds Teaching  
Hospital NHS Trust, Leeds

Dr W Stuart A Smellie,  
Consultant, Bishop Auckland  
General Hospital

Professor Lindsay Wilson  
Turnbull,  
Scientific Director of the  
Centre for Magnetic Resonance  
Investigations and YCR  
Professor of Radiology, Hull  
Royal Infirmary

Dr Alan J Williams,  
Consultant in General  
Medicine, Department of  
Thoracic Medicine, The Royal  
Bournemouth Hospital

### Observers

Dr Tim Elliott,  
Team Leader, Cancer  
Screening, Department of  
Health

Dr Catherine Moody,  
Programme Manager,  
Neuroscience and Mental  
Health Board

Dr Ursula Wells,  
Principal Research Officer,  
Department of Health

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**Dr Edmund Jessop,**  
Medical Adviser, National  
Specialist Commissioning  
Advisory Group (NSCAG),  
Department of Health

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**Professor Margaret  
Thorogood,**  
Professor of Epidemiology,  
University of Warwick Medical  
School, Coventry

Dr Robert Cook  
Clinical Programmes Director,  
Bazian Ltd, London

Dr Elizabeth Fellow-Smith,  
Medical Director, West London  
Mental Health Trust, Middlesex

Dr Colin Greaves  
Senior Research Fellow,  
Peninsular Medical School  
(Primary Care)

Dr John Jackson,  
General Practitioner, Parkway  
Medical Centre, Newcastle  
upon Tyne

Dr Russell Jago,  
Senior Lecturer in Exercise,  
Nutrition and Health, Centre  
for Sport, Exercise and Health,  
University of Bristol

Dr Chris McCall,  
General Practitioner, The  
Hadleigh Practice, Corfe  
Mullen, Dorset

Miss Nicky Mullany,  
Service User Representative

Dr Julie Mytton,  
Locum Consultant in Public  
Health Medicine, Bristol  
Primary Care Trust

Professor Irwin Nazareth,  
Professor of Primary Care  
and Director, Department of  
Primary Care and Population  
Sciences, University College  
London

Professor Ian Roberts,  
Professor of Epidemiology and  
Public Health, London School  
of Hygiene & Tropical Medicine

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Glasgow Centre for Population  
Health

Mrs Jean Thurston,  
Service User Representative

Professor David Weller,  
Head, School of Clinical  
Science and Community  
Health, University of  
Edinburgh

### Observers

Ms Christine McGuire,  
Research & Development,  
Department of Health

Ms Kay Pattison  
Senior NIHR Programme  
Manager, Department of  
Health

Dr Caroline Stone,  
Programme Manager, Medical  
Research Council

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| Professor Nicholas Clarke,<br>Consultant Orthopaedic<br>Surgeon, Southampton<br>University Hospitals NHS Trust                         | Dr John Holden,<br>General Practitioner, Garswood<br>Surgery, Wigan                                       | Dr Simon Padley,<br>Consultant Radiologist, Chelsea<br>& Westminster Hospital  | Professor Yit Chiun Yang,<br>Consultant Ophthalmologist,<br>Royal Wolverhampton Hospitals<br>NHS Trust |
|  |   |  | Mrs Isabel Boyer,<br>Service User Representative,<br>London  |

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Professor in Child Health,  
University of Nottingham

#### Deputy Chair,

**Dr Lesley Wise**,  
Unit Manager,  
Pharmacoepidemiology  
Research Unit, VRMM,  
Medicines & Healthcare  
Products Regulatory Agency

Mrs Nicola Carey,  
Senior Research Fellow,  
School of Health and Social  
Care, The University of  
Reading

Mr John Chapman,  
Service User Representative

Dr Peter Elton,  
Director of Public Health,  
Bury Primary Care Trust

Professor Robin Ferner,  
Consultant Physician and  
Director, West Midlands Centre  
for Adverse Drug Reactions,  
City Hospital NHS Trust,  
Birmingham

Dr Ben Goldacre,  
Research Fellow, Division of  
Psychological Medicine and  
Psychiatry, King's College  
London

Dr Bill Gutteridge,  
Medical Adviser, London  
Strategic Health Authority

Dr Dyfrig Hughes,  
Reader in Pharmacoeconomics  
and Deputy Director, Centre  
for Economics and Policy in  
Health, IMSCaR, Bangor  
University

Dr Yoon K Loke,  
Senior Lecturer in Clinical  
Pharmacology, University of  
East Anglia

Professor Femi Oyeboode,  
Consultant Psychiatrist  
and Head of Department,  
University of Birmingham

Dr Andrew Prentice,  
Senior Lecturer and Consultant  
Obstetrician and Gynaecologist,  
The Rosie Hospital, University  
of Cambridge

Dr Martin Shelly,  
General Practitioner, Leeds,  
and Associate Director, NHS  
Clinical Governance Support  
Team, Leicester

Dr Gillian Shepherd,  
Director, Health and Clinical  
Excellence, Merck Serono Ltd

Mrs Katrina Simister,  
Assistant Director New  
Medicines, National Prescribing  
Centre, Liverpool

Mr David Symes,  
Service User Representative

### Observers

Ms Kay Pattison  
Senior NIHR Programme  
Manager, Department of  
Health

Mr Simon Reeve,  
Head of Clinical and Cost-  
Effectiveness, Medicines,  
Pharmacy and Industry Group,  
Department of Health

Dr Heike Weber,  
Programme Manager,  
Medical Research Council

Dr Ursula Wells,  
Principal Research Officer,  
Department of Health

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### Members

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**Professor Scott Weich**,  
Professor of Psychiatry,  
University of Warwick

Professor Jane Barlow,  
Professor of Public Health in  
the Early Years, Health Sciences  
Research Institute, Warwick  
Medical School

Dr Sabyasachi Bhaumik,  
Consultant Psychiatrist,  
Leicestershire Partnership NHS  
Trust

Mrs Val Carlill,  
Service User Representative,  
Gloucestershire

Dr Steve Cunningham,  
Consultant Respiratory  
Paediatrician, Lothian Health  
Board

Dr Anne Hesketh,  
Senior Clinical Lecturer in  
Speech and Language Therapy,  
University of Manchester

Dr Yann Lefevre,  
GP Partner, Burrage Road  
Surgery, London

Dr Jeremy J Murphy,  
Consultant Physician &  
Cardiologist, County Durham &  
Darlington Foundation Trust

Mr John Needham,  
Service User, Buckinghamshire

Ms Mary Nettle,  
Mental Health User Consultant,  
Gloucestershire

Professor John Potter,  
Professor of Ageing and Stroke  
Medicine, University of East  
Anglia

Dr Greta Rait,  
Senior Clinical Lecturer and  
General Practitioner, University  
College London

Dr Paul Ramchandani,  
Senior Research Fellow/Cons.  
Child Psychiatrist, University of  
Oxford

Dr Howard Ring,  
Consultant & University  
Lecturer in Psychiatry,  
University of Cambridge

Dr Karen Roberts,  
Nurse/Consultant, Dunston Hill  
Hospital, Tyne and Wear

Dr Karim Saad,  
Consultant in Old Age  
Psychiatry, Coventry &  
Warwickshire Partnership Trust

Dr Alastair Sutcliffe,  
Senior Lecturer, University  
College London

Dr Simon Wright,  
GP Partner, Walkden Medical  
Centre, Manchester

### Observers

Ms Kay Pattison  
Senior NIHR Programme  
Manager, Department of  
Health

Dr Morven Roberts,  
Clinical Trials Manager, MRC,  
London

Professor Tom Walley,  
HTA Programme Director,  
Liverpool

Dr Ursula Wells,  
Policy Research Programme,  
DH, London



## Expert Advisory Network

### Members

Professor Douglas Altman,  
Professor of Statistics in  
Medicine, Centre for Statistics  
in Medicine, University of  
Oxford

Professor John Bond,  
Professor of Social Gerontology  
& Health Services Research,  
University of Newcastle upon  
Tyne

Professor Andrew Bradbury,  
Professor of Vascular Surgery,  
Solihull Hospital, Birmingham

Mr Shaun Brogan,  
Chief Executive, Ridgeway  
Primary Care Group, Aylesbury

Mrs Stella Burnside OBE,  
Chief Executive, Regulation  
and Improvement Authority,  
Belfast

Ms Tracy Bury,  
Project Manager, World  
Confederation for Physical  
Therapy, London

Professor Iain T Cameron,  
Professor of Obstetrics and  
Gynaecology and Head of the  
School of Medicine, University  
of Southampton

Dr Christine Clark,  
Medical Writer and Consultant  
Pharmacist, Rossendale

Professor Collette Clifford,  
Professor of Nursing and  
Head of Research, The  
Medical School, University of  
Birmingham

Professor Barry Cookson,  
Director, Laboratory of Hospital  
Infection, Public Health  
Laboratory Service, London

Dr Carl Counsel, Clinical Senior Lecturer in  
Neurology, University of  
Aberdeen

Professor Howard Cuckle,  
Professor of Reproductive  
Epidemiology, Department  
of Paediatrics, Obstetrics &  
Gynaecology, University of  
Leeds

Dr Katherine Darton,  
Information Unit, MIND – The  
Mental Health Charity, London

Professor Carol Dezateux,  
Professor of Paediatric  
Epidemiology, Institute of Child  
Health, London

Mr John Dunning,  
Consultant Cardiothoracic  
Surgeon, Papworth Hospital  
NHS Trust, Cambridge

Mr Jonothan Earnshaw,  
Consultant Vascular Surgeon,  
Gloucestershire Royal Hospital,  
Gloucester

Professor Martin Eccles,  
Professor of Clinical  
Effectiveness, Centre for Health  
Services Research, University of  
Newcastle upon Tyne

Professor Pam Enderby,  
Dean of Faculty of Medicine,  
Institute of General Practice  
and Primary Care, University of  
Sheffield

Professor Gene Feder,  
Professor of Primary Care  
Research & Development,  
Centre for Health Sciences,  
Barts and The London School  
of Medicine and Dentistry

Mr Leonard R Fenwick,  
Chief Executive, Freeman  
Hospital, Newcastle upon Tyne

Mrs Gillian Fletcher,  
Antenatal Teacher and Tutor  
and President, National  
Childbirth Trust, Henfield

Professor Jayne Franklyn,  
Professor of Medicine,  
University of Birmingham

Mr Tam Fry,  
Honorary Chairman, Child  
Growth Foundation, London

Professor Fiona Gilbert,  
Consultant Radiologist and  
ACRN Member, University of  
Aberdeen

Professor Paul Gregg,  
Professor of Orthopaedic  
Surgical Science, South Tees  
Hospital NHS Trust

Bec Hanley,  
Co-director, TwoCan Associates,  
West Sussex

Dr Maryann L Hardy,  
Senior Lecturer, University of  
Bradford

Mrs Sharon Hart,  
Healthcare Management  
Consultant, Reading

Professor Robert E Hawkins,  
CRC Professor and Director  
of Medical Oncology, Christie  
CRC Research Centre,  
Christie Hospital NHS Trust,  
Manchester

Professor Richard Hobbs,  
Head of Department of Primary  
Care & General Practice,  
University of Birmingham

Professor Alan Horwich,  
Dean and Section Chairman,  
The Institute of Cancer  
Research, London

Professor Allen Hutchinson,  
Director of Public Health and  
Deputy Dean of ScHARR,  
University of Sheffield

Professor Peter Jones,  
Professor of Psychiatry,  
University of Cambridge,  
Cambridge

Professor Stan Kaye,  
Cancer Research UK Professor  
of Medical Oncology, Royal  
Marsden Hospital and Institute  
of Cancer Research, Surrey

Dr Duncan Keeley,  
General Practitioner (Dr Burch  
& Ptms), The Health Centre,  
Thame

Dr Donna Lamping,  
Research Degrees Programme  
Director and Reader in  
Psychology, Health Services  
Research Unit, London School  
of Hygiene and Tropical  
Medicine, London

Mr George Levy,  
Chief Executive, Motor  
Neurone Disease Association,  
Northampton

Professor James Lindesay,  
Professor of Psychiatry for the  
Elderly, University of Leicester

Professor Julian Little,  
Professor of Human Genome  
Epidemiology, University of  
Ottawa

Professor Alistaire McGuire,  
Professor of Health Economics,  
London School of Economics

Professor Rajan Madhok,  
Medical Director and Director  
of Public Health, Directorate  
of Clinical Strategy & Public  
Health, North & East Yorkshire  
& Northern Lincolnshire  
Health Authority, York

Professor Alexander Markham,  
Director, Molecular Medicine  
Unit, St James's University  
Hospital, Leeds

Dr Peter Moore,  
Freelance Science Writer,  
Ashted

Dr Andrew Mortimore,  
Public Health Director,  
Southampton City Primary  
Care Trust

Dr Sue Moss,  
Associate Director, Cancer  
Screening Evaluation Unit,  
Institute of Cancer Research,  
Sutton

Professor Miranda Mugford,  
Professor of Health Economics  
and Group Co-ordinator,  
University of East Anglia

Professor Jim Neilson,  
Head of School of Reproductive  
& Developmental Medicine  
and Professor of Obstetrics  
and Gynaecology, University of  
Liverpool

Mrs Julietta Patnick,  
National Co-ordinator, NHS  
Cancer Screening Programmes,  
Sheffield

Professor Robert Peveler,  
Professor of Liaison Psychiatry,  
Royal South Hants Hospital,  
Southampton

Professor Chris Price,  
Director of Clinical Research,  
Bayer Diagnostics Europe,  
Stoke Poges

Professor William Rosenberg,  
Professor of Hepatology  
and Consultant Physician,  
University of Southampton

Professor Peter Sandercock,  
Professor of Medical Neurology,  
Department of Clinical  
Neurosciences, University of  
Edinburgh

Dr Susan Schonfield,  
Consultant in Public Health,  
Hillingdon Primary Care Trust,  
Middlesex

Dr Eamonn Sheridan,  
Consultant in Clinical Genetics,  
St James's University Hospital,  
Leeds

Dr Margaret Somerville,  
Director of Public Health  
Learning, Peninsula Medical  
School, University of Plymouth

Professor Sarah Stewart-Brown,  
Professor of Public Health,  
Division of Health in the  
Community, University of  
Warwick, Coventry

Professor Ala Szczepura,  
Professor of Health Service  
Research, Centre for Health  
Services Studies, University of  
Warwick, Coventry

Mrs Joan Webster,  
Consumer Member, Southern  
Derbyshire Community Health  
Council

Professor Martin Whittle,  
Clinical Co-director, National  
Co-ordinating Centre for  
Women's and Children's  
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