An Evidence Scoping Review of Photodynamic Therapy (PDT) in the Treatment of Cancers

Devidas Menon and Tania Stafinski
Department of Public Health Sciences, School of Public Health, University of Alberta, 3032 Research Transition Facility, 8308 114 Street, Edmonton, Alberta T6G 2V2
780-492-9080, Canada

Abstract

In this invited paper, we applied standard methods of evidence synthesis and critical appraisal to summarize the current state of clinical evidence on PDT for the treatment of different types of cancers. A total of 266 studies spanning 11,427 patients and 34 different types of cancer were reviewed. Forty-four were comparative and 222 were non-comparative. The majority of comparative studies did not assess PDT versus conventional therapy. Therefore, it was not possible to determine the incremental benefit of treatment with PDT. Most of the non-comparative studies involved small, mixed patient populations and short follow-up periods. Consequently, the quality of evidence accumulated to date was considered to be low. Well-defined, prospective, comparative trials of PDT, alone, versus conventional therapies are needed in order to determine its clinical effectiveness.

Introduction

The past two decades have seen significant investment in the development of new treatments for cancer. However, few have led to substantial improvements in health outcomes. As a result, interest in existing treatments and ways of modifying them to either optimize their effectiveness in the original indication or expand their use to include additional indications has grown. One such treatment is photodynamic therapy (PDT). PDT was first applied to cancer in the 1970s. Forty years later, it remains an ‘experimental technology’ for many cancer indications, with studies of clinical effectiveness only recently accumulating. Given the increased adoption of evidence-based decision-making processes for determining the coverage/funding of health technologies and services by most healthcare systems, adequate data demonstrating the effectiveness of PDT will likely be required before its benefits to patient populations beyond those in research settings can be realized. In this invited paper, we apply standard methods of evidence synthesis and critical appraisal to summarize the current state of clinical evidence on PDT for the treatment of different types of cancers.

Materials and Methods

The following methods, which comply with internationally recognized, published guidelines for conducting systematic reviews of clinical evidence, were used.

Literature search

A comprehensive search for relevant clinical studies of PDT published in English between January 1997 and June 2011 was conducted using a structured search strategy. The search strategy combined MeSH terms (e.g., ‘neoplasm’, ‘photosensitizing agents’, ‘photochemotherapy’, etc.) with free text terms and their synonyms (e.g., cancer, oncology, malignant, tumour, photodynamic therapy, PDT, etc.) identified through an analysis of keywords used to index known references (the full search strategy is available from the authors). The strategy was then applied to the following bibliographic databases: PubMed, The Cochrane Library, EMBASE, CINAHL, Web of Science (Science Citation Index only), and the UK Centre for Reviews and Dissemination databases (HTA, DARE and NHS EED). In addition, ClinicalTrials.gov was searched to identify recent clinical trials.

Data abstraction

Data from included studies and ongoing clinical trials were independently extracted by two researchers using a standard data abstraction form. The form contained the following elements: cancer type and stage, type and dose of photosensitizing agent, light source, study design, sample size, patient inclusion/exclusion criteria, outcomes measured, comparator (where relevant), co-interventions, results, and study/trial funding organization. The quality of each study was also appraised by two researchers, each using a simplified version of the Oxford Centre for Evidence-Based Medicine Levels of Evidence and Grades of Recommendation[1].

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Level of evidence

1. RCTs
2. Cohort studies and non-randomized controlled trials
3. Case-control studies
4. Case-series and single arm clinical trials
5. Expert opinion without explicit critical appraisal, or based on physiologic, bench research or “first principles”

*Corresponding author: Devidas Menon, Professor and Interim Chair, Department of Public Health Sciences, School of Public Health, University of Alberta, 3032 Research Transition Facility, 8308 114 Street, Edmonton, Alberta T6G 2V2 780-492-9080, Canada, E-mail: menon@ualberta.ca

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Data synthesis

Extracted information was tabulated by cancer type to facilitate a qualitative analysis of trends or patterns across studies. Where possible, pooled effect estimates were calculated (e.g., weighted mean differences).

Results

Over 3,000 studies were identified through the literature search, of which 266 met the selection criteria and were included in the review. The 266 studies, which spanned 33 different cancers, comprised 44 comparative (Table 1) and 222 non-comparative studies (Table 2), and involved a total of 11,427 patients.

Comparative studies

Cancer indications with the greatest number of comparative studies were lung (9 studies) and basal cell carcinoma (BCC) (9 studies). All of the BCC studies were randomized controlled trials (RCTs). In contrast, the vast majority of lung cancer studies were cohort studies. Of the BCC RCTs, most were: 1) single-blinded (patients were unaware of the treatment received), 2) compared PDT with aminolevulinic acid (ALA) to surgery, and 3) followed patients for approximately one year. Although all 7 cohort studies of lung cancer employed the same photosensitizing agent (porfimer sodium), they were retrospective in design and typically included patients with different types of lung cancer. Further, findings were presented for the sample in its entirety, rather than by lung cancer sub-type.

Among the remaining cancers with comparative studies available, all were associated with 3 or fewer RCTs. Moreover, the RCTs were often non-blinded, involved small sample sizes, and had follow-up periods of less than 1 year. Also, in several cases, the comparator was not ‘active’ conventional treatment (e.g., in the case of breast cancer and mesothelioma). Therefore, despite the availability of RCTs, the quality of the evidence was limited.

Non-comparative studies

Of the non-comparative studies, the majority were small retrospective case series, a study design near the bottom of the strength/level of evidence scale. Despite the large number of studies found for esophageal cancer and non-melanoma skin cancers, patient inclusion criteria (e.g., cell line involved, stage of cancer, previous treatments, etc.) frequently varied across studies, as did the PDT protocol (e.g., photosensitizing agents and light sources). Finally, for 20% of the cancer indications, the evidence base comprised a single study.

Against this backdrop, the following section provides a brief summary of the findings of studies conducted to date for each cancer.

Anal or perianal cutaneous

The 4 non-comparative studies collectively included 19 patients with different types of cancer in the perianal or anal region, and used 3 different photosensitizing agents: oral ALA, topical ALA, and porfimer sodium [2-5]. While ‘pain at the treatment site’ comprised the only adverse event reported across the 4 studies, it was experienced by almost all of the patients. The percentage of patients who achieved and maintained a complete response (i.e., initial eradication of the lesion) ranged from 40% to 100%, based on follow-up periods from less than 6 months to 8 years.

Bile duct

Twelve of the 17 studies were non-comparative [6-17]. Of the 5 comparative studies, 2 were small RCTs involving patients with advanced or unresectable disease [18-22]. Typically, the studies compared stenting alone to stenting plus PDT. Among comparative studies, the most commonly reported serious adverse event was bacterial infection, which affected patients in both the PDT and non-PDT treatment groups. Almost all of the studies reported skin photosensitivity in some patients receiving PDT. In general, the main outcome measured was survival. Findings were consistent

<table>
<thead>
<tr>
<th>Type of cancer</th>
<th>Comparative studies (N)</th>
<th>Type of comparative study</th>
<th>Total number of patients in comparative studies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Randomized Controlled Trial</td>
<td>Non-randomized controlled trial</td>
</tr>
<tr>
<td>Bile duct [18-22]</td>
<td>5</td>
<td>2</td>
<td>0</td>
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<tr>
<td>Breast [35]</td>
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<td>Cervical [41-43]</td>
<td>3</td>
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<td>0</td>
</tr>
<tr>
<td>Esophageal - early [50]</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Esophageal – advanced/ inoperable [51,74,75]</td>
<td>3</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Gastrointestinal [95]</td>
<td>1</td>
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<td>1</td>
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<tr>
<td>Head and neck – nasopharyngeal [101]</td>
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<tr>
<td>Lung [133-141]</td>
<td>9</td>
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</tr>
<tr>
<td>Mesothelioma [160,161]</td>
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<td>Skin – basal cell [175-183]</td>
<td>9</td>
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<td>0</td>
</tr>
<tr>
<td>Skin – squamous [184-186]</td>
<td>3</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Skin – Bowen [187-189]</td>
<td>3</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Skin – multiple (non-melanoma) [190]</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Vulval [257,258]</td>
<td>2</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>44</td>
<td>23</td>
<td>7</td>
</tr>
</tbody>
</table>

*Number of patients not reported for one study (reported number of lesions instead)

Table 1: Number of comparative studies according to cancer type.
Table 2: Number of non-comparative studies according to cancer type.

<table>
<thead>
<tr>
<th>Type of cancer</th>
<th>Non-comparative studies</th>
<th>Type of non-comparative study</th>
<th>Total number of patients in non-comparative studies</th>
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<tr>
<td></td>
<td></td>
<td>Single arm trial</td>
<td>Prospective case series</td>
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<tr>
<td>Anal [2-5]</td>
<td>4</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Bile duct [6-17]</td>
<td>12</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Bladder [23-29]</td>
<td>7</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Brain [30-34]</td>
<td>5</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Breast [36-40]</td>
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<td>0</td>
</tr>
<tr>
<td>Cervical [44-49]</td>
<td>6</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Esophageal - early [51-73]</td>
<td>23</td>
<td>0</td>
<td>14</td>
</tr>
<tr>
<td>Esophageal - advanced/inoperable [62,76-83]</td>
<td>9</td>
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<td>3</td>
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<tr>
<td>Eye [84-94]</td>
<td>11</td>
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<td>1</td>
</tr>
<tr>
<td>Gastrointestinal [96-100]</td>
<td>5</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Head and neck – nasopharyngeal [102]</td>
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<td>0</td>
<td>0</td>
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<tr>
<td>Head and neck – oral and laryngeal [103,104,261]</td>
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<td>0</td>
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<tr>
<td>Head and neck – oral and laryngeal [108-116,262]</td>
<td>10</td>
<td>3</td>
<td>1</td>
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<tr>
<td>Head and neck – laryngeal [263,264]</td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Head and neck – oral and pharyngeal [118-120]</td>
<td>3</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Head and neck [121-128,265,266]</td>
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<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Intrapertoneal carcinomatosis and sarcomatosis [130,131]</td>
<td>2</td>
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<td>0</td>
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<tr>
<td>Colorectal – metastatic (liver) [132,267]</td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Lung [142-159]</td>
<td>18</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Mesothelioma [162,163,268]</td>
<td>3</td>
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<td>0</td>
</tr>
<tr>
<td>Ovarian [165]</td>
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<tr>
<td>Pancreatic [269]</td>
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<tr>
<td>Pituitary [167]</td>
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<td>0</td>
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<tr>
<td>Prostate [168-173]</td>
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<td>5</td>
<td>0</td>
</tr>
<tr>
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<td>Skin – basal cell [191-213]</td>
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<td>14</td>
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<tr>
<td>Skin – Bowen’s [237,238]</td>
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<td>1</td>
</tr>
<tr>
<td>Skin – multiple (non-melanoma) [214-236]</td>
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<td>3</td>
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</tr>
<tr>
<td>Skin – cutaneous T-cell lymphoma [243-249]</td>
<td>7</td>
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<td>0</td>
</tr>
<tr>
<td>Skin – Kaposi’s sarcoma [241,242]</td>
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<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Skin – melanoma [239,240]</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Skin – Paget’s disease, extramammary [4,220,222,250-256]</td>
<td>10</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Vulval [259,260]</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>222</td>
<td>61</td>
<td>52</td>
</tr>
</tbody>
</table>

*Number of patients not reported for one study (reported number of lesions instead).

Across comparative studies, with median survival in patients treated with stenting and PDT statistically significantly greater (2 to 3 times longer) than in those receiving stenting alone. In contrast, some studies reported complete elimination of bile duct stenosis in patients who underwent PDT and stenting, while others reported only partial clearance in such patients. Across studies that assessed quality of life, scores either remained stable or improved following PDT treatment. Therefore, despite the lack of ‘level 1’ evidence, given the severity of the disease and magnitude of the effect observed, PDT appears to be a promising treatment for this indication.

Bladder

All 7 studies were either case series (2) or single arm phase I/II clinical trials (5), and the majority used 5-ALA as the photosensitizing agent [23-29]. While they involved similar patients, sample sizes were small. Further, patients in over half of the studies had received additional therapies immediately prior to treatment or during the follow-up period, making it difficult to assess the effect of PDT. Across studies, commonly reported adverse events included hematuria (13% to 100%) and dysuria (13% to 100%), both of which resolved within 3 weeks. More serious adverse events, such as vesicoureteral reflux (14% of patients), bladder contracture (39% of patients), and bladder spasm (29% of patients) were associated with higher doses of photosensitizing agents. Although the main outcomes assessed in studies were typically ‘complete response’ (total eradication of the lesion(s)) and ‘recurrence’, the time points at which they were measured varied. Based on findings for the most frequently used points, the percentage of patients who achieved a complete response at 3 months follow-up ranged from 44% to 100% across studies. The percentage of those patients who...
subsequently experienced a recurrence within 2 years ranged from 46% to 79%.

Brain

The 5 studies found represented 3 single arm clinical trials and 2 retrospective case series, which collectively involved 292 patients [30-34]. Studies typically involved patients with different types of brain tumours who were also receiving concurrent surgical resection and/or chemotherapy. Therefore, it was not possible to isolate the effect of PDT on disease progression or survival in patients with specific tumour types. Similarly, although 3 treatment-related deaths and a series of other non-fatal adverse events were reported across the 5 studies, any cause-effect relationship to PDT could not be determined. The most commonly experienced adverse events were cerebral edema and temporary neurological deficits (including facial weakness and partial paralysis), both occurring in less than 6% of patients. Median survival following PDT varied by tumour type, and ranged from 6 months to 77 months.

Breast

Six small studies, all published between 1998 and 2005, were identified - 5 non-comparative and 1 comparative (RCT) [35-40]. Combined, they represented 116 patients who were followed for a maximum of 6 months post treatment with PDT. The single RCT, which compared PDT to no treatment in patients who had failed salvage external beam radiation, was non-blinded and multi-centered. Five of the 6 studies reported on adverse events. Approximately 40% of patients experienced chest wall pain within the first few weeks of treatment. In addition, 14% to 40% (depending on the study) developed redness and inflammation in light exposed areas. Across studies, ‘complete response’ measured at 6 months comprised the main outcome. The percentage of patients in whom lesions were totally eradicated ranged from 43% to 100%. None of the studies presented information on recurrence within the 6 month follow-up period. In those that reported healing time, the period was 2 to 3 months.

Cervical

One double-blind, placebo controlled RCT, 2 non-RCTs, 5 single arm clinical trials, and 1 retrospective case series, all published between 1999 and 2004, were found [41-49]. While the 3 comparative trials recruited similar patient populations, comparators, PDT protocol (including photosensitizing agent, route of administration, and light source), and follow-up time differed. This was also the case with the non-comparative studies. Nonetheless, with one exception, similar adverse events were reported. They included vaginal discomfort, vaginal discharge, pelvic pain, vaginal bleeding, and mild cramping. The exception was skin photosensitivity and cervical stenosis, which was only experienced by patients who had received porfimer sodium or hematoporphyrin derivative. Across all studies, complete response ranged from 0% to 97%. Importantly, among comparative studies, no statistically significant difference in the proportion of patients achieving a complete response between treatment and control groups was observed. Further, there was no difference in recurrence or the likelihood of eradicating signs of HPV between groups.

Esophageal – early

Of the 24 studies found, all but one was non-comparative [50-73]. In general, patients had T1 tumours or stage I disease. Published in 2003, the single comparative study was a small, retrospective cohort study (88 patients) that compared endomucosal resection and PDT to esophagectomy in 2 groups of patients who were followed for approximately 12 months [50]. Regardless of study type, the most commonly reported adverse events associated with PDT included esophageal stricture, redness, and skin photosensitivity, occurring in up to about half of patients. From the results of the single comparative study, strictures were more common following esophagectomy than after PDT (16% of patients vs. 8% of patients). Also, anastomotic leaks and infections were reported in 8% of patients, and 3% developed severe bleeding requiring a transfusion or atrial fibrillation. Moreover, treatment-related deaths were reported in 2% of patients who underwent surgery, but in none of the patients who received PDT. Combining findings from all of the studies, the percentage of patients achieving a complete response appeared to vary with cell type. For esophageal adenocarcinoma (ACC) and squamous cell esophageal carcinoma (SCC), the pooled mean complete response was 54% and 71%, respectively. Across studies of SCC, recurrence was reported in 19% of patients after an average follow-up of 18 months. In contrast, only 3% of the ACC patients relapsed after an average follow-up of 24 months. In the ACC studies, recurrence did not appear to vary with photosensitizing agent. Although 6 of the studies reported 5 year survival (cause-specific or overall), it was not possible to accurately estimate the survival benefit attributable to PDT because patients who relapsed typically received other treatments, the details of which were not presented.

Esophageal – advanced or inoperable

Between 1999 and 2009, twelve studies were published – 3 comparative and 9 non-comparative [51,62,74-83]. The 3 comparative studies comprised 1 RCT, 1 prospective cohort study, and 1 comparative case series. Of the non-comparative studies, there were 8 retrospective case series and 1 case report. Neither the RCT nor the cohort study compared PDT to non-PDT interventions. Rather, the RCT used PDT plus chemotherapy with 5-flourouracil as the comparator, and the cohort compared two different photosensitizing agents. In the comparative case series, only patients who failed PDT received the comparator treatment (radiotherapy). Therefore, from the comparative studies, it was not possible to assess the incremental benefits and risks of PDT to existing treatments. Regarding adverse events, among the most commonly reported were chest pain (10% to 17%), fistulae (2% to 17%), stricture (2% to 11%), stenosis (7% to 25%), pain on swallowing (33% to 64%), and skin photosensitivity (4% to 100%). Across studies, dysphagia improved after PDT in almost all patients (87% to 100%). This improvement was maintained for approximately 2 months. No survival information was presented for the RCT. However, based on findings from the cohort study, survival did not statistically significantly vary with type of photosensitizing agent (ALA: 8 months vs. Polyhematoporphyrin: 9 months).

Eye

All 11 studies found, published between 2004 and 2009, were non-comparative [84-94]. Collectively, they involved 97 patients with different types of cancer (in many cases, metastases from other organs), almost all of whom were treated with the same photosensitizing agent. Adverse events, presented in less than half of the studies, included retinal haemorrhage and edema, retinal detachment, cytokid macular edema, and epiretinal membrane formation. In all studies, complete eradication of or significant reduction in tumour mass following PDT was demonstrated. In addition, most reported slight improvements in visual acuity.
**Gastrointestinal**

The 6 studies (1 non-RCT, 3 single arm clinical trials, and 2 case series) were all published between 1998 and 2002 [95-100]. Of the collective 107 patients treated, the majority had early gastric carcinoma. The remaining patients were those with intraperitoneal tumours which had spread from gastrointestinal malignancies. The single non-RCT examined PDT with and without the use of a device for marking the area to be irradiated prior to treatment. Therefore, no information regarding the relative effectiveness of PDT (i.e., PDT compared to existing treatment(s)) appears to be available. In patients with early gastric carcinoma, adverse events included skin photosensitivity (8% to 86%) and temporary epigastric pain (55%). In patients with intraperitoneal tumours, more serious adverse events, such as capillary leak syndrome (100%) and intra-abdominal abscesses (7%) were reported. The percentage of patients with early gastric cancer who achieved a complete response ranged from 67% to 100%. Tumour eradication was not reported for patients with intraperitoneal tumours. In patients with early gastric cancer, survival following PDT ranged from 3 years to over 13 years. In patients with intraperitoneal tumours, survival was significantly shorter, averaging 21 months.

**Head and neck**

A total of 30 studies involving 1,323 patients were found [101-129]. Published between 1998 and 2010, all but 1 was non-comparative. Also, for many of the studies, information on patient demographics and the PDT protocol applied was not presented. Across studies in which such information was presented, cancer type and location, photosensitizing agents, and methods for determining treatment response differed. Further, in many of the studies, patients received therapies in addition to PDT during follow-up, precluding an assessment of the effect associated with PDT alone. Commonly reported adverse events included ‘pain at the treatment site’ (11% to 82%), edema (10% to 100%), and skin photosensitivity (2% to 25%). One death attributed to carotid blow out after erosion of the treated tumour in a patient with metastatic disease was reported. The percentage of patients in whom an initial complete response with PDT was reported ranged from 8% to 100%. However, disease recurrence was observed in 8% to 75% of patients across studies. In studies that assessed functional status, no significant detrimental changes in oral cavity functional status after PDT were found. In the single RCT, which compared PDT to chemotherapy, greater improvements in quality of life were demonstrated for PDT.

**Intraperitoneal carcinomatosis or sarcomatosis**

Two studies were found, one published in 2003 and the other in 2006 [130,131]. Both comprised small, single arm clinical trials that employed PDT as an adjunct to surgical debulking in 122 patients. The most common adverse event was capillary leak syndrome. There were 2 deaths, 1 from a myocardial infarction and 1 due to intra-abdominal bleeding. Minor adverse events, which occurred in 29% of patients, were primarily related to skin photosensitivity. In both studies, less than 25% of patients achieved a complete response with PDT. Median overall survival following treatment ranged from 13 months to 22 months.

**Colorectal with liver metastases**

Two single arm clinical trials involving a total of 31 patients were identified [14,132]. Published between 2005 and 2007, they employed different PDT protocols and followed patients for a maximum of 60 days. Serious adverse events included severe abdominal pain, bleeding from the treated tumour, and pancreatic injury. The main outcome measure in both trials was tumour response. None of the patients in either of the studies experienced complete tumour regression.

**Lung**

Twenty-seven studies published between 1997 and 2009 were found [133-159]. Collectively, they involved 1,751 patients, each of whom participated in 1 of 9 comparative and 18 non-comparative studies. The majority, including the 2 RCTs, involved patients with non-small cell lung cancer (NSCLC). Both RCTs and 2 of the 7 retrospective cohort studies compared PDT to laser therapy (ND:YAG). Of the remaining 5 retrospective cohort studies, 2 compared PDT alone to PDT combined with other non-surgical therapies, 1 compared PDT or laser therapy to surgery, 1 compared PDT to bronchoscopic electrocautery or laser therapy, and 1 compared PDT to stenting, laser therapy, or high dose brachytherapy, either alone or in combination with laser therapy. In general, the 18 non-comparative studies involved small patient populations with various types and stages of cancer who were followed over short periods. In addition, PDT was often applied in combination with other therapies. The most commonly reported adverse events were skin photosensitivity (3% to 91%) and pneumonia (2% to 9%). While several deaths were noted, they occurred in patients who had received PDT as an adjunct to brachytherapy or surgery. Based on findings from the multiple comparative studies of PDT versus laser therapy, no statistically significant differences in response rates at 1 month post treatment were found. Also, no differences in symptom improvement between treatment groups were demonstrated. However, the overall survival rate at 1 year following treatment was greater in patients treated with PDT compared to those who had received laser therapy. Equivalent information was not available for patients with other types of lung cancer.

**Mesothelioma**

Five studies published between 1994 and 2004 and involving a total of 166 patients were identified [160-164]. They comprised 1 RCT, 1 non-RCT, and 3 single arm (phase I/II) clinical trials. In both the RCT and non-RCT, PDT plus conventional therapy (surgery without or without chemotherapy) was compared to conventional therapy. Similarly, across all 3 non-comparative studies, PDT was performed as an adjunct to surgery. Therefore, it was not possible to determine the effects of PDT alone. Neither comparative trial reported statistically significant differences in the type and frequency of adverse events between patients who received PDT plus conventional therapy and those who received just conventional therapy. Also, there were no statistically significant differences in time to disease recurrence between those treated with PDT plus conventional therapy and those treated with conventional therapy, alone. Across all studies, median survival ranged from 8 months to 15 months. However, based on findings from the single RCT, survival did not improve with the addition of PDT. Also, no statistically significant differences in relief from clinical symptoms or improvement in pulmonary function were found between patients who received PDT in addition to conventional therapy and those who just received conventional therapy.

**Ovarian**

Existing studies appear limited to 1 retrospective case series published in 1997 [165]. It included 131 patients in whom PDT was performed as an adjunct to surgical debulking by laparotomy or laparoscopy. Adverse events included skin photosensitivity and intestinal ileus (incidence not reported). Decreasing concentrations
of serum cancer markers reaching tumour free levels at 8 weeks were observed in 50% of patients. In addition, an improvement of 10% or greater in Karnofsky index scores were reported in 38% of patients.

**Pancreatic**

One single arm clinical trial of 16 patients who underwent PDT plus stenting was found [166]. Adverse events included hematoma (6 patients), duodenal bleeding requiring transfusion (2 patients), and duodenal stenosis (3 patients). Median survival post-PDT was 9.5 months. After 2 years of follow-up, overall survival was 13%.

**Pituitary**

The search identified 1 small single arm trial of PDT for pituitary gland cancer [167]. Twelve patients who had failed surgical treatment, radiotherapy, and chemotherapy underwent intra-operative PDT with porfimer sodium. Follow-up ranged from 10 days to 24 months. Adverse events were reported in one patient, who experienced temporary partial paralysis and skin photosensitivity. In the majority of patients, tumour volume decreased (mean reduction of 46%). All 12 patients demonstrated an improvement in visual acuity and field.

**Prostate**

All 6 studies identified, which involved a total of 111 patients, were non-comparative [168-173]. Five comprised single arm clinical trials published between 2002 and 2011. The remaining study was a retrospective case series published in 1998. Across studies, disease stage varied, as did the photosensitizing agent. Commonly reported adverse events included irritative urinary symptoms, reported in up to 46% of patients. The percentage of patients achieving a complete response with PDT ranged from 0% to 40%. Although PSA levels also decreased, they were not maintained over time. None of the studies reported on quality of life or survival.

**Sarcoma**

One small single arm trial of 10 patients followed for up to 51 months was found [174]. No adverse events were reported, and recovery of limb function to pre-operative levels was observed in 90% of patients. At the time of follow-up, overall survival among patients was 100%.

**Skin – non-melanoma**

Sixteen comparative studies [175-190] and 48 non-comparative studies [191-238] involving 1,349 patients and 3,189 patients, respectively, were identified. Nine of the 16 comparative studies were RCTs of patients with BCC. Of these 9 RCTs, 4 compared PDT to either surgical excision (2 trials) or cryotherapy (2 trials) and 5 compared different PDT protocols. The 7 remaining comparative studies included 3 trials in patients with squamous cell carcinoma - 1 single-blinded RCT comparing PDT to no treatment and 2 non-RCTs comparing PDT to placebo, cryotherapy, or topical 5-fluouracil and PDT with 2 different photosensitizing agents. It also included 3 RCTs of patients with Bowen’s disease. However, none compared PDT to other treatment modalities. Instead, different PDT protocols were examined. Commonly reported adverse events related to PDT were similar for comparative and non-comparative studies of different cell types, and included intra- and post-procedural pain that resolved within a few days, redness and swelling lasting less than 2 weeks, and hyper- or hypopigmentation lasting several months. Across the comparative studies, no statistically significant difference in pain following treatment with PDT compared to cryotherapy was found. However, where surgical resection was compared to PDT, PDT was associated with statistically significantly more pain. In contrast, among patients treated with 5-fluorouracil, post-procedural pain was statistically significantly greater than that reported in patients who underwent PDT. In almost all of the studies, the main outcomes measured were the proportions of patients achieving a ‘complete response’ and experiencing recurrence. Across all studies of basal cell carcinoma, a complete response was reported for 42% to 97% of lesions, and recurrence ranged from 0% to 45%. Among the comparative studies, 1 RCT reported a significantly higher complete response rate in patients who underwent surgery compared to those who received PDT. In trials of PDT compared to cryotherapy, no statistically significant differences were observed. Among the RCTs of various PDT protocols, 2 sessions of treatment (versus 1 session) were associated with higher complete response rates and less recurrence. Across comparative and non-comparative studies of squamous cell carcinoma, a complete response was reported for 25% to 100% of lesions treated with PDT. Recurrence ranged from 0% to 69%. With 1 exception, none of the comparative studies of PDT for squamous cell carcinoma presented information on the statistical significance of differences between treatment groups. The single study that did, an RCT of PDT versus no treatment in organ transplant recipients, found no difference in complete response rates between groups. For Bowen’s disease, the proportion of patients achieving a complete response in studies ranged from 25% to 100%. While 1 of the comparative trials assessed PDT relative to a different treatment modality, the statistical significance of the difference in complete response rates was not reported.

**Skin – melanoma**

Only 2 small retrospective case series, 1 published in 2002 and the other in 2004, were identified [239,240]. Collectively, they included 63 patients. Across studies, PDT protocols and follow-up times differed. One study reported no adverse events. In the other, pain lasting less than 5 days was observed in just over half of patients, and 15% developed a fever. While 93% of patients achieved a complete response in one of the studies, none responded completely in the other study. However, 84% experiences at least a 50% decrease in lesion size.

**Skin – Kaposi’s sarcoma**

Two small retrospective studies, 1 case report (published in 2006) and 1 retrospective case series of 26 patients (published in 1999), were found [241,242]. Only the case series presented information on adverse events, which consisted of skin photosensitivity in 28% of patients. The pooled proportion of patients achieving a complete response was 32%. No information on recurrence was presented.

**Skin – cutaneous T-cell lymphoma**

All 7 studies identified were non-comparative and published between 1997 and 2008 [243-249]. Involving a total of 22 patients, they comprised 3 retrospective case series, 3 case reports, and 1 single arm trial. All but 1 of the studies reported on adverse events, which frequently included pain, redness, and swelling. Across studies, the percentage of patients who experienced a complete response ranged from 78% to 100%. During follow-up periods of 4 to 34 months (depending on the study), no recurrence was observed.

**Skin – extra-mammary Paget’s disease**

Ten non-comparative studies published between 2000 and 2011 were found [4,220,222,250-256]. They included 52 patients, and represented 1 single arm clinical trial, 2 prospective case series,
2 retrospective case series, and 3 case reports. In almost half of the studies, no information related to adverse events was presented. Among those reporting on adverse events, the most common were pain and burning during and several hours following PDT. All studies assessed complete response, which was achieved in approximately half of the lesions treated.

**Vulval**

Of the 4 studies identified, 2 were comparative and 2 were non-comparative [257-260]. The 2 comparative studies, published in 2002 and 2006, included 1 non-RCT and 1 prospective cohort study, and collectively involved 226 patients. The 2 non-comparative studies, published in 2000 and 2004, comprised 1 single arm trial of 25 patients and 1 prospective case series of 6 patients. Both the non-RCT and cohort study compared PDT to laser therapy or surgical excision. Reporting of adverse events appeared to be limited to patients who underwent PDT. The most common was pain lasting up to 1 week. Across all studies, the proportion of patients experiencing a complete response with PDT ranged from 50% to 67%. Based on findings from the comparative studies, recurrence and disease free survival was similar among patients receiving PDT, laser, or surgery.

**Conclusion**

This review considered 44 comparative studies and 222 non-comparative studies of PDT for 33 different types of cancer. Despite the availability of double blind RCTs, few involved treatment and control groups that facilitated an assessment of the increment benefit of PDT alone.

**References**


