Photodynamic Therapy For Cancer Treatment – An Update

HEALTH TECHNOLOGY ASSESSMENT SECTION
MEDICAL DEVELOPMENT DIVISION
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Please contact: htamalaysia@moh.gov.my, if you would like further information.

Health Technology Assessment Section (MaHTAS),
Medical Development Division
Ministry of Health Malaysia
Level 4, Block E1, Precinct 1
Government Office Complex
62590 Putrajaya

Tel: 603 88831246

Fax: 603 8883 1230

Available at the following website: http://www.moh.gov.my

Prepared by:
Noormah Mohd Darus, B.Pharm (Hons), MSc. Clinical Epid
Senior Principal Assisstant Director
Health Technology Assessment Section (MaHTAS)
Ministry of Health Malaysia

Reviewed by:
Dr Izzuna Mudla Mohamed Ghazali, MBBS, MPH (Epidemiology)
Public Health Physician
Senior Principal Assisstant Director
Health Technology Assessment Section (MaHTAS)
Ministry of Health Malaysia

DISCLOSURE

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EXECUTIVE SUMMARY

Introduction

Phototodynamic therapy (PDT) is claimed to be a promising new modality to combat cancer. PDT uses a light-sensitive drug, in combination with light of a visible wavelength, to destroy target cells. PDT consists of using a tumor specific photosensitizer and laser irradiation to induce production of reactive oxygen species in cancer cells. It can be defined as the administration of a non-toxic drug or dye known as a photosensitizer (PS) either systemically, locally, or topically to a patient with a lesion/tumour. After an incubation period, the lesion/tumour is targeted with a visible light of specific wavelength determined by the PS used. In the presence of oxygen, this leads to the generation of reactive oxygen species (ROS), cell death and tumour tissue destruction. The $^1O_2$ species is highly active in biological systems and can only diffuse less than 0.02 μm in a cell before deactivation during its very short lifetime. The use of PDT as a cancer therapy is particularly attractive owing to its specificity and selectivity as the PS concentrates specifically within the malignant tissue.[1-4] One considerable advantage is the fact that PDT is minimally invasive, much cheaper and has less harmful side-effects than conventional chemotherapy, radiotherapy or surgery.

NGPDT stands for Next Generation PhotoDynamic Therapy. The photosynthesising agent approved by the FDA in 1993 (Photofrin) has been referred to as “first Generation” agent. Subsequent discoveries have led to a dramatically advanced and greatly improved generation of photosynthesising agents and medicines: ‘Next Generation PDT’. NGPDT photosensitizing agent is chlorophyll. It was claimed by the vendor that with NGPDT every individual cancer cell will be treated, even developing cells that may not be detected at the time of treatment. Often the light is delivered externally and it is claimed that this reaches the tumour but light penetration to internal cancers is insufficient for effective PDT

This review was requested by Dr. Myralini Santhira Thesan, Medical Advisor from AIA Employee Benefits, AIA Bhd., following a case where a policy holder / a patient diagnosed with Nasopharyngeal Carcinoma with multiple metastases in lung, liver, lymph nodes & bone had sought treatment using Next Generation Photodynamic Therapy (NGPDT) for cancer therapy in China.

Objective/aim

To assess the effectiveness, safety and cost-effectiveness of photodynamic therapy especially Next Generation Photodynamic Therapy (NGPDT) for the treatment of cancer.

Results and conclusions

Sixteen articles were included that consists of a systematic review, two randomised controlled trial, a non-randomised clinical trial, 8 single arm prospective studies, a pre and post interventional study, two retrospective studies and a case report.

There was no retrievable scientific evidence on the effectiveness, safety and cost effectiveness on the Next Generation Photodynamic Therapy (NGPDT).

However, the retrieved evidence showed that there was limited, adequately powered RCT's on PDT. From the above review it was found that:

- There was insufficient evidence on the use of PDT in oesophageal cancer, lung cancer, brain cancer and cancers of the head and neck. Hence, further research into the role of PDT in these areas is needed.
- PDT has the potential and may be effective in the treatment of actinic keratosis (AK), nodular basal cell carcinoma (BCC) and possibly for treating Barrett's oesophagus.
- For cholangiocarcinoma, PDT may improve survival when compared with stenting alone.
- For advanced and/or recurrent tongue base carcinoma, treatment was well tolerated by patients and has potential in shrinking tumour and controlling further progression. Evidence suggests that 5-ALA-PDT and/or mTHPC-PDT may offer an effective alternative treatment for oral potentially malignant disorders.
- A wide variety of photosensitisers were used and, overall, no serious adverse effects were linked to PDT. However caution should be taken on signs for Bruguda syndrome and buried neoplasms after PDT.

The effectiveness of PDT and NGPDT in relation to other treatments is not yet apparent. High quality trials are warranted for PDT and NGPDT to establish their effectiveness and safety.

Methods

Literatures were searched through electronic databases specifically PubMed/Medline, Cochrane, OVID, INAHTA and also in general databases. Google was used to search as additional web-based information. In addition websites for existing HTA agency, society websites and cross-referencing of the articles retrieved were also carried out accordingly to the topic.

A critical appraisal of the retrieved papers was performed and the evidence level was graded according to the US/Canadian Preventive Services Task Force.

Photodynamic Therapy – An Update

1. INTRODUCTION

Phototodynamic therapy (PDT) is claimed to be a promising new modality to combat cancer. PDT use a light-sensitive drug, in combination with light of a visible wavelength, to destroy target cells. PDT consists of using a tumor specific photosensitizer and laser irradiation to induce production of reactive oxygen species in cancer cells. It can be defined as the administration of a non-toxic drug or dye known as a photosensitizer (PS) either systemically, locally, or topically to a patient with a lesion/tumour. After an incubation period, the lesion/tumour is targeted with a visible light of specific wavelength determined by the PS used. In the presence of oxygen, this leads to the generation of reactive oxygen species (ROS), cell death and tumour tissue destruction. The $^1O_2$ species is highly active in biological systems and can only diffuse less than 0.02 μm in a cell before deactivation during its very short lifetime. The use of PDT as a cancer therapy is particularly attractive owing to its specificity and selectivity as the PS concentrates specifically within the malignant tissue.[1-4] For this reason, PDT is becoming a major subject of intense investigation as a possible treatment modality for various forms of cancer. One considerable advantage is the fact that PDT is minimally invasive, much cheaper and has less harmful side-effects than conventional chemotherapy, radiotherapy or surgery.[1-4]

A report was done in 2006 on photodynamic therapy whereby there was limited evidence for the treatment of lung cancers, bladder cancers, superficial oral, oral/pharyngeal, or nasal cavity tumours, cancer of the larynx as well as superficial oesophageal cancers and it was suggested that PDT should be used only for clinical research purposes and as yet, should not be authorized for public coverage.

This review was requested by Dr. Myralini Santhira Thesan, Medical Advisor from AIA Employee Benefits, AIA Bhd., following a case where a policy holder / a patient diagnosed with Nasopharyngeal Carcinoma with multiple metastases in lung, liver, lymph nodes & bone had sought treatment using Next Generation Photodynamic Therapy for cancer therapy in China.

2. OBJECTIVE/AIM

To assess the effectiveness, safety and cost-effectiveness of photodynamic therapy for the treatment of cancer.

3. TECHNICAL FEATURES

Photodynamic therapy requires the presence and interaction of three key elements: light, a photosensitizer and oxygen. A basic law of photobiology is that the longer the wavelength of light the deeper the penetration through biological tissues. Three mechanisms are known to contribute to the observed reduction and often disappearance of tumours treated with PDT (Fig 1).[1-5] First, PDT induces generation of ROS which kill tumour cells directly by apoptosis and/or necrosis. Second, it induces destruction of tumour-associated vasculature, which can lead to tumour death via lack of oxygen and nutrients. Lastly, PDT triggers the recruitment of inflammatory and immune mediators causing an invasion of leukocytes that can both contribute to tumour destruction as well

as stimulate the immune system to recognize and destroy tumour cells even at isolated locations. [1, 6, 7] Direct induction of tumour cell death potentiated by ischaemia is responsible for early tumour ablation. However, accumulating evidence indicates that these early events trigger inflammatory responses that are important in achieving long-term tumour control.

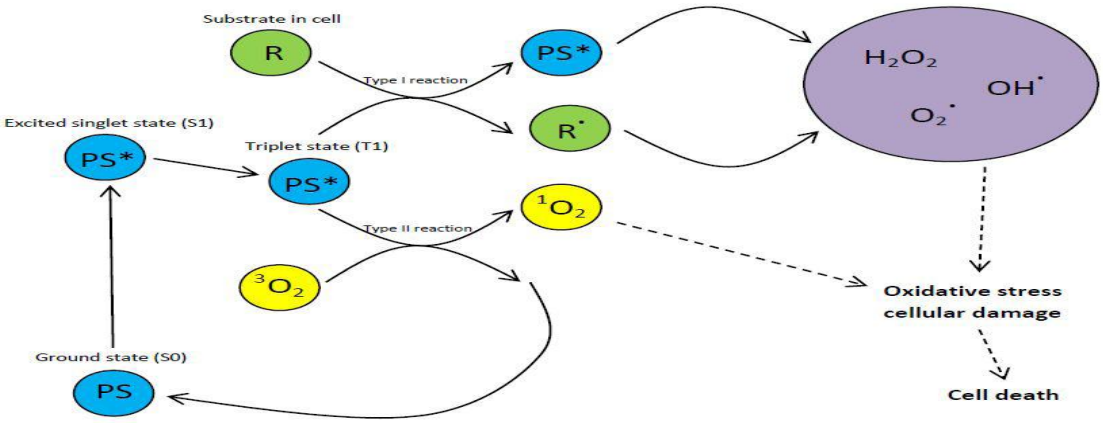

Fig. 1 : A basic principle of PDT: When PS in cells is exposed to specific wavelengths of light, the PS in its singlet ground state (S0) transforms to an excited singlet state (S1), which is followed by intersystem crossing to an excited triplet state (T1). Transfer energy from T1 to biological substrates and molecular oxygen, via type I and II reactions, generates ROS (1O2, H2O2, O2•, OH•). This causes cellular damage which can lead to tumour cell death [1,2,3,5] The $^1O_2$ species is highly active in biological systems and can only diffuse less than 0.02 μm in a cell before deactivation during its very short lifetime. However; there are several limitations and side effects associated with PDT treatment using photosensitizers such as Photofrin mainly owing to their prolonged phototoxicity.

The ideal optimum light dose for PDT should cause adequate lethal effects over the targeted tumour area while minimizing damage to the adjacent normal tissues. Overtreatment causes side effects, whereas undertreatment leads to treatment failure. However, identifying the optimum dose is a much more complex issue owing to the complexity of the PDT mechanism itself, which in addition to the light dose, needs to consider the amount of photosensitizer and availability of oxygen.[8, 9]

NGPDT stands for Next Generation PhotoDynamic Therapy. The photosynthesising agent approved by the FDA in 1993 (Photofrin) has been referred to as “first Generation” agent.[8, 9] The most recently approved photosensitizer for cancer is mTHPC (temorforfin, Foscan) approved for the palliative treatment of head and neck cancer in 2001 in the EU.[10, 11] Subsequent discoveries have led to a dramatically advanced and greatly improved generation of photosynthesising agents and medicines: ‘Next Generation PDT’. NGPDT photosensitizing agent is chlorophyll. It was claimed by the vendor that with NGPDT every individual cancer cell will be treated, even developing cells that may not be detected at the time of treatment. Often the light is delivered externally and it is claimed that this reaches the tumour but light penetration to internal cancers is insufficient for effective PDT

4. METHODS

4.1. Searching

Electronic databases searched through the Ovid interface (examples);

- MEDLINE(R) In-process and other Non-Indexed Citations and Ovid MEDLINE(R) 1948 to present
- EBM Reviews - Cochrane Central Register of Controlled Trials-2nd Quarter 2013
- EBM Reviews – Database of Abstracts of Review of Effects (2rd Quarter 2013)
- EBM Reviews - Cochrane database of systematic reviews - 2005 to July 2013
- EBM Reviews - Health Technology Assessment – 2nd Quarter 2013
- NHS economic evaluation database – 2nd Quarter 2013

Other databases (example);

- PubMed
- Horizon Scanning database (National Horizon Scanning Centre, Australia and New Zealand Horizon Scanning Network, National Horizon Scanning Birmingham)
- FDA website
- INAHTA
- MHRA

Google was used to search for additional web-based materials and information.

Appendix 1 showed the detailed search strategies. Last search was conducted on 21st Jun 2013.

4.2. Selection

A reviewer screened the titles and abstracts against the inclusion and exclusion criteria and then evaluated the selected full-text articles for final article selection.

The inclusion and exclusion criteria were:

Inclusion criteria

Population	Patients who had cancer
Interventions	Photodynamic therapy
Comparators	Chemotherapy, radiotherapy, surgery
Outcomes	a) Curative rates of treatment b) Palliative treatment c) Survival rates d) Recurrence of tumours e) Mortality
Study design	Clinical trials, interventional studies, systematic reviews for efficacy and effectiveness. Case series, case reports for adverse events

Exclusion criteria

Study design	surveys, anecdotal, animal studies

Relevant articles were critically appraised using Critical Appraisal Skills Programme (CASP) and evidence graded according to the US / Canadian Preventive Services Task Force (Appendix 2). Data was extracted and summarised in evidence table (see Appendix 3).

5. RESULTS AND DISCUSSION

The search strategy yielded a total of 84 relevant titles and 53 abstracts were screened using the inclusion and exclusion criteria. After screening, 37 abstracts were found to be irrelevant. In total fifteen full text articles which met the inclusion/exclusion criteria and quality of studies were included in this systematic review.

5. 1. EEFICACY/ EFFECTIVENESS

Twelve articles included consists of a systematic review, one randomised controlled trial, a non-randomised clinical trial, seven single arm prospective studies and two retrospective studies.

Fayter D, et al did a systematic review to study 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 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.[12] Overall, 88 trials reported in 141 publications were included, with some trials covering more than one condition.

- For actinic keratosis (AK), there was evidence of effectiveness 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 (BE), 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.

The author mentioned that this study had several limitations. There were few well-conducted, adequately powered RCTs, and quality of life (QoL) and resource outcomes were under-reported. Evidence of effectiveness was found for PDT in the treatment of

actinic keratosis (AK) and nodular basal cell carcinoma (BCC) in relation to placebo, and possibly for treating Barrett's oesophagus.

Jerjes W et al reported, in a prospective study, on the use of PDT as a minimally-invasive surgical intervention for advanced and/or recurrent tongue base carcinoma. [13] Twenty-one patients with stage IV advanced and/or recurrent tongue base from University College London Hospital (UCLH) were subjected to mTHPC-US-guided using mTHPC as the photosensitizing agent, (0.15 mg/kg was administered into the mid-cubital vein 96 hours prior to treatment interstitial PDT). The group was followed-up for a mean of 36 months. The result showed that:

- The majority of the patients (11/14) reported improvement of breathing ($P<0.001$), with one patient reporting worsening of symptoms.
- An improvement of swallowing was reported by 28/33 patients ($P<0.001$); while speech improvement was evident in 15/18 patients ($P<0.001$).
- Clinical assessment showed that two-thirds of the patients had "good response" to the treatment and a third reported "moderate response".
- Radiological assessment comparing imaging 6-week post-PDT to the baseline showed stable pathology with no change in size in six patients, minimal response (<25% reduction) in seven patients, moderate response (<50% reduction) in 12 patients and significant response (50-75% reduction) in eight patients.
- Unfortunately, due to the extended duration of skin photosensitization following treatment, skin burn was reported by six of the patients; while two patients had skin necrosis caused by treating pathologies very close to the surface.

Hence, the results showed that the treatment was well tolerated by all patients, effective in shrinking tumour and controlling further progression.

Jerjes W et al in 2011 reported that in a prospective study carried out at the UCLH, Head and Neck Centre, a total of 147 consecutive patients with potentially malignant oral disorders were treated with surface illumination PDT, using 5-ALA or mTHPC as the photosensitiser.[14] Comparisons with the clinical and histopathological features and rate of recurrence as well as malignant transformation were made. The patients were followed-up for a mean of 7.3 years. The result showed that:

- Homogenous leukoplakias were identified in 55 patients, non-homogenous leukoplakias in 73 patients, whereas 19 patients had erythroplakias.
- Moderate dysplasia was identified in 33 patients while 63 patients had severe dysplasias; and 32 patients had a histopathological diagnosis of carcinoma in situ.
- The rate of recurrence in laser surgery was approximately 11.6%. Malignant transformation was observed in 11 patients (7.5%), in the tongue, floor of mouth and retromolar area.
- Recurrence and malignant transformation was mainly identified in erythroplakias and non-homogenous leukoplakias. The final outcome showed that 11/147 (7.5%) suffered from progressive disease, 5 /147 (3.4%) had stable disease, 12/147 (8.2%) were considered partially responsive to the therapy. Complete response was identified in 119/147 patients (81%).

The above study suggested that 5-ALA-PDT and/or mTHPC-PDT may offer an effective alternative treatment for potentially malignant oral disorders.

Jerjes W et al in 2011 reported another prospective clinical study carried out at the UCLH, Head and Neck Centre, on thirty-eight patients with clinical presentation such as an ulcer mainly identified in the tongue, floor of mouth (FOM), or buccal mucosa.[15] The

study assessed the oncological outcomes following surface illumination mTHPC-photodynamic therapy of early tumour (TNM stage T1/T2 N0) of oral squamous cell carcinoma (OSCC) patients. T1/T2 is commonly referred to as low risk tumours and T3/T4 commonly referred to as high risk. Clinically, nine patients had T1 disease while 29 had T2 disease. Pathological analysis revealed that 12 patients had well differentiated SCC, 16 moderately differentiated and 10 had poorly-differentiated cancer. All patients underwent mTHPC-PDT. PDT was repeated in 6- to 7-month period following the first round when residual tumor was identified in the treated site. The result showed that:

- At last clinic review post-PDT, 26/38 patients showed complete normal clinical appearance of their oral mucosa in the primary tumor site.
- Later, surgical biopsies from the study cohort showed that 17 had normal mucosa, five with hyperkeratinization, 10 with dysplastic changes and six showed recurrent squamous cell carcinoma (SCC).
- The overall recurrence was 6/38 (15.8%). Most common presentation was an ulcer involving the buccal mucosa or retromolar area, identified in current or ex-smokers and current drinkers.
- The 5-year survival was 84.2%.
- Death from loco-regional and distant disease spread was identified in three patients.

The above study suggests that mTHPC-photodynamic therapy (up to three rounds) is a comparable modality to other traditional interventions in the management of low-risk tumors of the oral cavity. Although, sometimes, multiple rounds of the treatment are required, morbidity following PDT is far less when compared to the three conventional modalities: surgery, radiotherapy, and chemotherapy.

Yoon HY et al did a non-randomized study to determine the role of PDT as an adjuvant therapy for the palliation of advanced esophageal carcinoma in order to reduce dysphagia and to maintain nutrition and occlusion of tracheoesophageal fistula so as to improve the quality of life of the patient.[16] Surgical oesophagectomy, while an effective means of palliating dysphagia, is accompanied by marked morbidity and mortality. Twenty consecutive patients with obstructing oesophageal cancer were enrolled in this study at the Konkuk University Medical Centre, Seoul, Korea. Each subject had dysphagia, and nine could not swallow fluid. None were eligible for surgical resection due to tumor involvement into the adjacent tissue, distant lymph node metastasis, poor performance status plus inoperable status due to co-morbidity, refusal of surgical intervention, or a combination of these reasons. External beam radiotherapy or a self-expandable metal stent was used following PDT for dysphagia due to recurrence of the malignancy. The results were as shown below:

- At 4 weeks post-PDT, a significant improvement in the dysphagia score was observed in 90% of patients, from 2.75 ± 0.91 to 1.05 ± 0.83 ($p < 0.05$).
- Patients with recurrent dysphagia underwent stent insertion at an average of 63 days (range, 37 to 90 days). The rate of major complications was 10%.
- Two esophageal strictures occurred, which were treated by placement of a modified expandable stent across the stricture.
- The median survival in these cases was 7.0 ± 0.6 months.
- One patient that was treated with PDT and radiotherapy was alive and showed a complete tumor response.
- Eighteen patients (90%) died from their disease.

The study showed that PDT as a multimodality treatment that may be safe and effective for relieving malignant oesophageal obstruction with minimal complications.

Nava HR et al did a non-randomised study to examine the toxicity and optimal drug and light dose with endoscopic (2-[1-hexyloxyethyl]-2-devinyl pyropheophorbide-a); HPPH-PDT at Roswell Park Cancer Institute.[17] Thirty six patients referred with a diagnosis of Barrett's esophagus (BE) with high grade dysplasia (HGD) were enrolled and had to meet the following criteria: biopsy-proven HGD or early intramucosal adenocarcinoma. Two nonrandomized dose escalation studies were performed (18 patients each) with biopsy-proven high grade dysplasia or early intramucosal adenocarcinoma of oesophagus. HPPH doses ranged from 3 to 6 mg/m2. At 24 or 48 hours after HPPH administration the lesions received one endoscopic exposure to 150, 175 or 200 J/cm of 665 nm light. The results were as follows:

HPPH dose escalation study responses (18 patients)

- In the drug dose ranging study (light dose of 150 J/cm at 48 h), 3 and 4 mg/m^2 of HPPH emerged as most effective.
- After one patient was treated at 3 mg/m^2 HPPH, the study was amended to change the starting dose to 4 mg/m2 because the patient treated with 3 mg/m^2 did not respond as rapidly
- Eleven patients were treated with 4 mg/m^2 of HPPH. The 1-year complete response (CR) rate for the combined 3 and 4 mg/m^2 treatments (7 patients) was 39%.
- There were no complete responses with HPPH doses of 5 and 6 mg/ m^2. Eight patients experienced good responses with significant decreases in length of BM, but because some residual HGD was found in biopsies, these patients were placed in the "no response" category as per study criteria.

Light dose escalation study responses (18 patients)

- In the light dose ranging study (3 or 4 mg/m2 HPPH, light at 24 h), complete response rates (disappearance of high grade dysplasia and early carcinoma) of 13/18 (72%) were achieved at 1 year, with all patients treated with 3 mg/m^2 HPPH plus 175 J/cm and 4 mg/m^2 HPPH plus 150 J/cm showing complete responses at 1 year.
- Of 13 patients with CR, seven (54%) patients did not show any recurrence of the disease on follow-up at 5 years, with one patient lost to follow up

PPH-PDT for precancerous lesions in Barrett's oesophagus appears to be safe and showing promising efficacy. Further clinical studies are required to establish the use of HPPH-PDT.

Höblinger A et al did a retrospective analysis of 10 patients with unresectable extrahepatic cholangiocarcinoma (CC) in the department of Internal Medicine of the University Hospital Bonn, Germany between 10/2005 and 08/2010.[18] All patients underwent endoscopic biliary drainage. Nine patients received metallic stents and one patient received a plastic stent. PDT was performed and patients received intravenous Photofrin at a dose of 2 mg/kg bodyweight 48 hours before laser activation. One patient received after 7th PDT-procedure, Photofrin at the reduced dose of 1 mg/kg bodyweight because of the phototoxic skin reaction on the hands. In two patients the photodynamic therapy was combined with chemotherapy. Results were as follows:

- Eight patients had elevated bilirubin levels with a mean bilirubin at admission of 9.9 ± 11.3 mg/dl, which had decreased to an average minimum of 1.2 ± 0.9 mg/dl after 3 months.
- No severe toxicity was noted.
- Four patients died during the follow-up because of tumor progression.

- The estimated survival of all patients was 47.6 months, 95% CI; 25.9 – 48.1 months.

The study suggests that long-term PDT in patients with extra hepatic CC is feasible, may be effective and is accompanied – at least in this cohort- by a survival time of more than two years.

Usuda J et al did a single arm prospective study at the Tokyo Medical University Hospital, between June 2004 and December 2008 on 75 patients with centrally located early lung cancers (CLELC).[19] NPe6-PDT was used to treat patients who met the criteria for NPe6-PDT after obtaining their informed consent in accordance with institutional guidelines. NPe6 is a second-generation photosensitizer, and it has a longer absorption band (664 nm) than Photofrin (630 nm). The photosensitizer Photofrin has been applied to the treatment of many kinds of cancers, and it has been approved by the U.S. Food and Drug Administration for the treatment of centrally located early lung cancer (CLELC) as well as advanced lung cancer. PDT allows lung function to be preserved and is recommended for CLELCs in the evidence-based clinical practice guidelines of the American College of Chest Physicians. The second-generation photosensitizer mono-L-aspartyl chlorine e6 (talaporfin sodium, NPe6), which has a major absorption band at 664 nm, was recently approved for the treatment of CLELC by the Japanese Ministry of Health, Labour and Welfare. Results of the study were as shown below:

- Seventy cancer lesions ≤1.0 cm in diameter and 21 lesions >1.0 cm in diameter were identified, and the complete response rate was 94.0% (66 of 70) and 90.4% (19 of 21), respectively.
- After the mass of large tumors and deeply invasive tumors had been reduced by electrocautery, NPe6-PDT was capable of destroying the residual cancer lesions.

The study showed that NPe6-PDT has a strong antitumour effect against CLELCs >1.0 cm in diameter that have invaded beyond the bronchial cartilage, thereby enabling the destruction of residual cancer lesions after mass reduction of large nodular- or polypoid-type lung cancers by electrocautery.

Downie GH did a single arm prospective study whereby seven patients ages 28 to 76, with typical endobronchial carcinoid tumors with comorbid conditions or contraindication to surgery from Roswell Park Cancer Institute and Brody School of Medicine, USA were included.[20] The patients were treated with PDT using porfimer sodium 2 mg/kg and 630nm laser at 200 J/cm. Patients were followed up for 5 years. Results were as shown below:

- Six of seven patients (86%) had complete recovery (CR), with two patients had two years CR, two patients with three years CR, and two patients with five years CR post-PDT.
- One CR patient required balloon dilatations for bronchial stenosis with success; no other significant side effects were seen.
- The sole partial response (PR) had visualized distal margins in the anterior subsegment of the right upper lobe but had an unsuspected origin in the posterior subsegment and was unable to be completely treated with any local ablation technique.

Employing selection criteria, CR in six out of seven (86%) patients were observed. There were no sustained significant side effects. Endobronchial treatments with PDT may be effective, safe, and surgery sparing in selected patients.

De Vijlder HC et al. did a study to compare the five-year lesion (complete) response rates of superficial basal cell carcinoma (sBCC) treated with topical aminolaevulinic acid (ALA)-PDT using a single illumination versus ALA-PDT using a 2-fold illumination scheme within the department of dermatology of Erasmus MC in Rotterdam, The Netherlands. [21] A prospective, randomized study was performed, in which 91 patients with 299 lesions were treated with a two-fold illumination scheme, and 106 patients with 274 lesions were treated with a single illumination. A 12-month interim analysis of these two groups of patients resulted in a statistically significant increase in CR rate in the group receiving the two-fold illumination. Given this result, a third group of 50 additional patients with 172 lesions that received only the two-fold illumination were included between November 2004 and August 2005. All patients were followed for a period of five years.

- The CR rate was significantly greater following the two-fold illumination than the single illumination ($p = 0.0002$, log-rank test). Five years after therapy the CR rate after two-fold illumination was 88%, whereas the CR rate after single illumination was 75%.
- The CR rate in the third group of lesions, treated with two-fold illumination was 97% and 88% at 12 months and five years after therapy, respectively.

Long-term follow-up indicates superior efficacy in sBCC of ALA-PDT with two-fold illumination compared with ALA-PDT with single illumination.

Basal cell carcinoma (BCC) is the most common cancer affecting Caucasians and due to its large size or to the poor condition of the patient, it can be difficult to treat it with conventional therapies: in these cases photodynamic therapy with methyl aminolevulinate (MAL-PDT) may represent a good option. Eibenschutz L et al did a retrospective non-comparative follow-up study which was performed to test the response of giant and large BCC to MAL-PDT.[22] From February 2003 to February 2007 the authors treated twelve patients with 14 giant BCC (≥ 5 cm) and five patients with five large BCC (4-5 cm) with MAL-PDT at the S Gallicano Dermatological Institute, Rome, Italy. They were evaluated 6 months after the end of the treatment to define the initial cure rate, and then at 12 and 36 months for the follow-up.

- At 6 months the initial cure rate for the 19 BCCs was 18/19 (95%)
- The cure rate was 13/19 (68.4%) at 12 months and 10/19 (52.7%) at 36 months with an overall long-term cure rate of 66%, ranging from 39% for giant BCC to 100% for lesions sized 4-5 cm
- In total, eight out of 18 successfully treated lesions recurred after MAL-PDT, 5/18 (28%) at 12 months and 3/18 (17%) at 36 months, all giant BCC
- The degree of pain and discomfort referred by the patients during the treatment was mild in 45% and severe in 55% of the cases. No patients discontinued the treatment, nor asked for anaesthesia as, after cooling the lesions with a water spray or by pausing the light for a few minutes, the pain could be sufficiently soothed.

Hence, the above study suggests that MAL-PDT may be a valid option for the treatment of giant and large BCC.

Surrenti T et al did an open label trial to evaluate efficacy, safety, tolerability and cosmetic outcome of methyl aminolevulinate (MAL-PDT) in selected patients with superficial and nodular BCCs who attended the out-patient clinic of the Department of Dermatology, University of L'Aquila, Italy, from February 2004 to March 2005.[23] Patients aged ≥ 18 years were included in the study if they satisfied at least one of the following

criteria: i) contraindication to surgical excision due to bleeding abnormalities or cardiac risk; ii) multiple or recurrent BCCs; iii) patient's request for alternative treatment due to needle/surgery phobia. Ninety-four superficial and 24 nodular BCCs in 69 patients were treated with two to eight MAL-PDT sessions. Efficacy, safety, tolerability and cosmetic outcome were evaluated at months 1, 3, 6 and 12 after the last MAL-PDT treatment and then every three months. Efficacy was rated as i) complete response, corresponding to clinical disappearance of BCC; ii) partial response, clinically corresponding to ≥40% and < 100% reduction in tumour size; iii) no response, defined as < 40% reduction in tumour size as compared to initial clinical examination and iv) worsening, defined as an increase in tumour size from baseline. The results of the study were:

- Complete clinical regression was detected in 84/94 (89.4%) superficial BCCs including three pigmented BCC lesions, and 12/23 (52.2%) nodular BCCs one month after two MAL-PDT sessions.
- A partial response was observed in 10/94 (10.6%) superficial BCCs and in 11/23 (47.8%) nodular BCCs, one month after two MAL-PDT sessions
- No further clinical improvement was observed in either superficial or nodular BCCs with treatment continuation up to a maximum of eight MAL-PDT sessions.
- Adverse effects were limited to mild local skin reactions,
- Cosmetic outcome was rated as excellent or good.
- Recurrence was observed in 2/84 (2.4%) successfully treated superficial BCCs at 6 and 12 months after treatment discontinuation.

Based on the efficacy, tolerability, a cosmetic outcome and recurrence rate of this study, the results suggests that MAL-PDT for treatment of superficial BCC and for selected cases of nodular BCC may be used.

There was no retrievable evidence on the Next Generation PhotoDynamic Therapy (NGPDT). There is no convincing data that shows that treatment carried out as reported is effective in the treatment of primary tumour and multiple metastases.

5. 2 SAFETY

The first generation photosensitizer is Porfirmer sodium which had received the United States of America Food and Drug Administration (U.S. FDA) approval since 1993 for use in PDT to treat or relieve the symptoms of certain cancers.[8, 9] It has also been used in Canada, Denmark, Finland, France, Germany, Ireland, Japan, Netherlands, UK, Norway, and Iceland.[9] The second generation photosensitizer ALA (Levulan) received approval for the treatment of cancerous lesions in 1999. The methyl esters ALA (Metvix) was approved in the European Union (EU) in 2001 for the treatment of actinic keratosis and basal cell carcinoma (BBC). The most recently approved photosensitizer for cancer is mTHPC (temorforfin, Foscan) approved for the palliative treatment of head and neck cancer in 2001 in the EU.[10, 11]

Five studies; a non randomised study, a retrospective study, a prospective study, a pre and post interventional study as well as a case report were included that reported on the adverse events after treatment with photodynamic therapy (Three of the studies had reported on effectiveness above).

The restoration of squamous epithelium after photodynamic therapy (PDT) for Barrett esophagus (BE) and its related neoplasms has been noted. It may result in the development of buried neoplasms and/or BE underneath restored squamous epithelium

which maintain their potential for malignant transformation. Mino-Kenudson M did a study to evaluate the prevalence, endoscopic, and histologic characteristics and also response to further treatment of buried neoplastic epithelium developing after PDT.[24] Fifty-two BE patients with high-grade dysplasia (n=19), intramucosal adenocarcinoma (n=28), and invasive adenocarcinoma (n=5) were treated with porfimer PDT. They were either considered noncandidates for oesophagectomy or refused surgery. Pre-PDT endoscopies were performed once in 41 patients, twice in nine patients, three times and four times in a patient each; all within four months of treatment. Mean follow-up after PDT was 29.3 months. Each patient had an average of seven endoscopies. Areas of mucosal abnormality were also sampled. In addition, the neoplastic sites recorded in prior biopsies were also systematically rebiopsied. The presence of buried neoplasms was correlated with endoscopic findings, neoplastic grade, diffuseness, and location of neoplasia, as well as outcome. The results of the study were as follows:

- After the first PDT, BE was eradicated in eight patients but recurred in seven. At the end of follow-up, BE was eradicated in 32 patients (61.5%). The neoplastic lesions were eradicated by a single course of PDT with or without fulguration in 15/52 patients (28.8%). Ultimately, the neoplastic lesions were eradicated in 40/52 patients (76.9%) and persisted or recurred in twelve patients.
- Before treatment, only one patient showed a completely buried neoplasm, which responded to one course of PDT. After PDT, completely buried neoplasms were noted in 19 levels from 13 patients The prevalence of completely buried neoplasms was 0.6% (1/173) and 7.4% (19/258) in pre and post-PDT positive biopsy levels, respectively (P=0.001)
- Completely buried lesions represented the highest grade of residual neoplasm in a series of 11 post-PDT endoscopies (7.1% of 155 post-PDT endoscopies with neoplastic diagnoses) from 8 patients

Buried neoplasms are not uncommon after PDT. Hence, thorough endoscopic surveillance with extensive biopsies, especially of the sites previously positive for neoplasia is important to avoid overlooking buried neoplasms that may progress.

Brugada syndrome is typified by an electrocardiographic (ECG) pattern of elevated ST-segments in the right precordial leads (V1–V3), morphology similar to that seen in right bundle branch block, an absence of structural heart disease, and a high risk of ventricular fibrillation and sudden death. Bang DW, et al reported a case of Brugada syndrome developing after photodynamic therapy (PDT) in a patient diagnosed with cholangiocarcinoma.[25] A previously healthy 62-year-old man was admitted to the hospital for PDT following a diagnosis of cholangiocarcinoma (Klatskin tumor, type IV) made one month prior to admission. His only complaint upon admission was mild abdominal pain. An endoscopic retrograde biliary catheter for draining bile was already in place. The electrocardiogram was normal. There was no prior family history of ventricular arrhythmias or sudden cardiac death. For scheduled PDT, the patient was injected intravenously for over 5 minutes with a hematoporphyrin derivative- type photosensitizer, Photogem, 2 mg/kg. After 40 to 50 hours of PDT, light at a release power of 150 J/cm2 was applied. The patient was stable until 7 hours following the light application, at which time he began to complain of feeling febrile and having chills. His body temperature was 38.4°C. Emergency laboratory tests revealed hepatic biochemical abnormalities: an aspartate transaminase (AST) level of 247 U/L, alanine transaminase (ALT) of 140 U/L, and direct bilirubin of 0.8 mg/dL. One hour following the injection of antipyretics, the patient's condition stabilized. His only complaint was general weakness, but he went into

cardiac arrest 10 hours later. The ECG performed during the cardiopulmonary resuscitation revealed polymorphic ventricular tachycardia. After electrical cardioversions (300 J × 3), the cardiac rhythm recovered to a sinus rhythm. The 12-lead ECG showed a right bundle branch block and a pronounced ST segment elevation in the precordial leads (V1, V2) consistent with Brugada syndrome. On the sixth day post-attack, the patient died of fulminant hepatic failure and sepsis due to obstruction of the biliary tract.

Nava HR et al did a non-randomised study to examine the toxicity and optimal drug and light dose with endoscopic (2-[1-hexyloxyethyl]-2-devinyl pyropheophorbide-a); HPPH- at Roswell Park Cancer Institute.[17] The author reported some adverse events whereby:

- Most patients experienced mild to moderate chest pain requiring symptomatic treatment only.
- Six patients experienced Grade 3 & 4 adverse events (16.6%). Three esophageal strictures were treated with dilatation.
- No clear pattern of dose dependence of toxicities emerged.
- Four unexpected events (diabetic acidosis grade 4, bradycardia grade 2, shortness of breath grade 2 and respiratory depression grade 2) were unrelated to PDT and were attributable to underlying disease and surgery (anesthesia) respectively.
- Two photosensitivity reactions (6% of patients) were observed; one patient experienced mild photophobia and another patient experienced grade 1 sunburn due to HPPH.

Höblinger A et al did a retrospective analysis of 10 patients with unresectable extrahepatic cholangiocarcinoma (CC) in the department of Internal Medicine of the University Hospital Bonn, Germany between 10/2005 and 08/2010.[18] The authors found that there were some adverse events whereby:

- The primary adverse event after intervention was cholangitis in 2 patients (20%), which was treated with antibiotics alone. In one patient, the authors performed subsequent PDT procedures without using a biliary contrast with no cholangitis episodes thereafter.
- One patient experienced skin phototoxicity World Health Organization grade I after the seventh PDT procedure. He was managed with topical therapy, no hospital readmission was required. PDT treatment was continued with 50% dose reduction of Photofrin and no phototoxicity reaction was observed after subsequent procedures.

Annemans L et al. did a prospective, observational, one arm study to evaluate the effectiveness of photodynamic therapy using methyl aminolevulinate (MAL-PDT) in the treatment of actinic keratosis (AK), nodular and superficial basal cell carcinoma (nBCC and sBCC). The authrs found that there some adverse events such as:

- Two patients withdrew for adverse events. Skin discomfort was experienced by 139 (56%) patients in total (62% of AK patients and 51% of BCC patients). Other adverse events were reported by 18 (7%) patients, and included pain (3%), oedema and erythema (1%), skin necrosis with severe crust forming (1%).

5.3 COST/COST-EFFECTIVENESS

Annemans L et al. did a prospective, observational, one arm study to evaluate the effectiveness of photodynamic therapy using methyl aminolevulinate (MAL-PDT) in the treatment of actinic keratosis (AK), nodular and superficial basal cell carcinoma (nBCC and sBCC) and to calculate the real-life cost of treatment as well as validate predictions from an economic evaluation model.[26] Patients with AK and/or BCC were selected according to Belgian reimbursement criteria for treatment with MAL-PDT. Clinical response, cosmetic outcome and tolerability were assessed. MAL-PDT cost was calculated and compared to published model cost data. Data were collected from 247 patients (117 AK, 130 BCC). The results were as follows:

- A complete clinical response was obtained for 83% of AK (85/102) and 83% of BCC (97/116) patients (85.2% of sBCC patients and 77.8% of nBCC patients).
- A good or excellent cosmetic outcome was obtained for 95% of AK patients and 93% of BCC patients (94% of the patients with sBCC and 89% of the patients with nBCC).
- Tolerability was good: only two patients withdrew for adverse events. Skin discomfort was experienced by 139 (56%) patients in total (62% of AK patients and 51% of BCC patients). Other adverse events were reported by 18 (7%) patients, and included pain (3%), oedema and erythema (1%), skin necrosis with severe crust forming (1%).
- Total cost of care per patient was €381 for AK, €318 for nBCC, and €298 for sBCC. Total cost per lesion was €58 for AK (identical to model prediction), €316 for nBCC and €178 for sBCC (both within 20% of model prediction).

The clinical results of MAL-PDT in this real-life practice study confirmed those demonstrated in previous clinical trials. Costs calculated from this study confirmed predicted cost-effectiveness in the original model for MAL-PDT in the management of AK and BCC.

5.4 LIMITATIONS

Our study has several limitations. The selection of the studies and appraisal was done by one reviewer. Although there was no restriction in language during the search, only English full text articles were included in the report.

6. CONCLUSION

There was no retrievable scientific evidence on the effectiveness, safety and cost effectiveness on the Next Generation Photodynamic Therapy (NGPDT).

However, the retrieved evidence showed that there was limited, adequately powered RCT's on PDT. From the above review it was found that:

- There was insufficient evidence on the use of PDT in oesophageal cancer, lung cancer, brain cancer and cancers of the head and neck. Hence, further research into the role of PDT in these areas is needed.
- PDT has the potential and may be effective in the treatment of actinic keratosis (AK), nodular basal cell carcinoma (BCC) and possibly for treating Barrett's oesophagus.
- For cholangiocarcinoma, PDT may improve survival when compared with stenting alone.

- For advanced and/or recurrent tongue base carcinoma, treatment was well tolerated by patients and has potential in shrinking tumour and controlling further progression. Evidence suggests that 5-ALA-PDT and/or mTHPC-PDT may offer an effective alternative treatment for oral potentially malignant disorders.
- A wide variety of photosensitisers were used and, overall, no serious adverse effects were linked to PDT. However caution should be taken on signs for Bruguda syndrome and buried neoplasms after PDT.

The effectiveness of PDT and NGPDT in relation to other treatments is not yet apparent. High quality trials are warranted for PDT and NGPDT to establish their effectiveness and safety.

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9. APPENDIX

9.1. Appendix 1: LITERATURE SEARCH STRATEGY

Ovid MEDLINE® In-process & other Non-Indexed citations and OvidMEDLINE® 1948 to present

1. exp photodynamic therapy/
2. (photodynamic adj 1 therapy).tw
3. photodynamic therapy.tw
4. photodynamic therapy.mp
5. light-sensitive drug$.tw
6. Photosensitizer$.tw
7. Non-toxic drug or dye or Photosensitizer$.tw
8. Neoplasm$.tw
9. Cancer$.tw
10. Tumour$.tw
11. Lesion$.tw
12. (Photodynamic therapy adj 1 cancer).tw

13 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12

13. Photodynamic$ therapy.mp. And Neoplasm$.twcancer$.tw.tumour$.twlesion$.tw

[mp=protocol supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier]

OTHER DATABASES	
EBM Reviews - Cochrane Central Register of Controlled Trials	Same MeSH, keywords, limits used as per MEDLINE search
EBM Reviews - Database of Abstracts of Review of Effects	
EBM Reviews - Cochrane database of systematic reviews	
EBM Reviews - Health Technology Assessment	
PubMed	
NHS economic evaluation database	
INAHTA	
FDA	

9.2. Appendix 2

HIERARCHY OF EVIDENCE FOR EFFECTIVENESS STUDIES

DESIGNATION OF LEVELS OF EVIDENCE

I Evidence obtained from at least one properly designed randomized controlled trial.

II-I Evidence obtained from well-designed controlled trials without randomization.

II-2 Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one centre or research group.

II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.

III Opinions or respected authorities, based on clinical experience; descriptive studies and case reports; or reports of expert committees.

SOURCE: US/CANADIAN PREVENTIVE SERVICES TASK FORCE (Harris 2001)

Evidence Table: Efficacy / Effectiveness
Question: Is Photodynamic therapy effective for management and treatment of cancer.

Bibliographic citation	Study Type / Methodology	LE	Number of patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures/ Effect size
1. Fayter D, Corbett M, Heirs M,Fox D and A Eastwood. A systematic review of photodynamic therapy in the treatment of precancerous skin conditions, Barrett's oesophagus and cancers of the biliary tract, brain, head and neck, lung, oesophagus and skin. *Health Technology Assessment* 2010; 14(37).	Systematic review	1	People with Barrett's oesophagus, precancerous skin conditions or primary cancer in the following sites: biliary tract, brain, head and neck, lung, oesophageal and skin.	Any type of PDT for either curative or palliative treatment.	Any comparator including differing applications of PDT treatments (relevant comparators varied according to the condition).		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. The author mentioned that this study had several 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 uncertain. Evidence of effectiveness was found for PDT in the treatment of actinic keratosis (AK) and nodular basal cell carcinoma (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 quality of life (QoL) and adverse effects. Further research is also needed on patient experience of PDT, as well as on the cost effectiveness of PDT.

Evidence Table: Efficacy / Effectiveness
Question: Is Photodynamic therapy effective for management and treatment of cancer.

Bibliographic citation	Study Type / Methodology	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up	Outcome measures/ Effect size
2. Jerjes W, Upile T, Radhi H and Hopper C, Photodynamic therapy and end-stage tongue base cancer: short communication. Head & Neck Oncology 2011, 3:49. doi:10.1186/1758-3284-3-49. http://www.Head and neck oncology.org /content /3/1/49	a prospective study, on the use of PDT as a minimally-invasive surgical intervention for advanced and/or recurrent tongue base carcinoma,	II-3	Twenty-one patients with stage IV advanced and/or recurrent tongue base from University College London Hospital (UCLH)	mTHPC-US-guided using mTHPC as the photosensitizing agent. (0.15 mg/kg was administered into the mid-cubital vein 96 hours prior to treatment interstitial PDT), t		followed-up for a mean of 36 months	The result showed that: • The majority of the patients (11/14) reported improvement of breathing (P<0.001), with one patient reporting worsening of symptoms. • An improvement of swallowing was reported by 28/33 patients (P<0.001); while speech improvement was evident in 15/18 patients (P<0.001). • Clinical assessment showed that two-thirds of the patients had “good response” to the treatment and a third reported “moderate response”. • Radiological assessment comparing imaging 6-week post-PDT to the baseline showed stable pathology with no change in size in 6 patients, minimal response (<25% reduction) in 7 patients, moderate response (<50% reduction) in 12 patients and significant response (50-75% reduction) in 8 patients. • Unfortunately, due to the extended duration of skin photosensitization following treatment, skin burn was reported by six of our patients; while two patients had skin necrosis caused by treating pathologies very close to the surface. Here the results showed that the treatment was well tolerated by all patients and very effective in shrinking tumour and controlling further progression.

Evidence Table: Efficacy / Effectiveness
Question: Is Photodynamic therapy effective for management and treatment of cancer.

Bibliographic citation	Study Type / Methodology	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up	Outcome measures/ Effect size
3. Jerjes W, Upile T, Hamdoon Z, Mosse CA et al. Photodynamic therapy outcome for oral dysplasia. Lasers Surg Med. 2011 Mar;43(3):192-9. doi: 10.1002/lsm.21036.	prospective study	II-3	carried out at the UCLH, Head and Neck Centre, a total of 147 consecutive patients with oral potentially malignant oral disorders	surface illumination PDT, using 5-ALA or mTHPC as the photosensitiser		mean of 7.3 years	The result showed that: • Homogenous leukoplakias were identified in 55 patients, non-homogenous leukoplakias in 73 patients, whereas 19 patients had erythroplakias. • Moderate dysplasia was identified in 33 patients while 63 patients had severe dysplasias; and 32 patients had a histopathological diagnosis of carcinoma in situ. • The rate of recurrence in laser surgery was approximately 11.6%. • Malignant transformation was observed in 11 patients (7.5%), in the tongue, floor of mouth and retromolar area. • Recurrence and malignant transformation was mainly identified in erythroplakias and non-homogenous leukoplakias. • The final outcome showed that 11/147 (7.5%) suffered from progressive disease, 5 /147 (3.4%) had stable disease, 12/147 (8.2%) were considered partially responsive to the therapy. • Complete response was identified in 119/147 patients (81%). The above study suggests that 5-ALA-PDT and/or mTHPC-PDT may offer an effective alternative treatment for oral potentially malignant disorders.

Evidence Table: Efficacy / Effectiveness
Question: Is Photodynamic therapy effective for management and treatment of cancer.

Bibliographic citation	Study Type / Methodology	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up	Outcome measures/ Effect size
4. Jerjes W, Upile T, Hamdoon Z, Alexander Mosse C, et al. Photodynamic therapy outcome for T1/T2 N0 oral squamous cell carcinoma. Lasers Surg Med. 2011 Aug;43(6):463-9. doi: 10.1002/lsm.21071.	Single arm study prospective study	II-3	thirty-eight patients with clinical presentation such as an ulcer mainly identified in the tongue, floor of mouth (FOM), or buccal mucosa, at the UCLH, Head and Neck Centre,	surface illumination mTHPC-photodynamic therapy			The result showed that: • At last clinic review post-PDT, 26/38 patients showed complete normal clinical appearance of their oral mucosa in the primary tumor site. • Later, surgical biopsies from the study cohort showed that 17 had normal mucosa, five with hyperkeratinization, 10 with dysplastic changes and six showed recurrent squamous cell carcinoma (SCC). • The overall recurrence was 6/38 (15.8%). Most common presentation was an ulcer involving the buccal mucosa or retromolar area, identified in current or ex-smokers and current drinkers. • The 5-year survival was 84.2%. • Death from loco-regional and distant disease spread was identified in three patients. The above study suggests that mTHPC-photodynamic therapy (up to three rounds) is a comparable modality to other traditional interventions in the management of low-risk tumors of the oral cavity. Although, sometimes, multiple rounds of the treatment are required, morbidity following PDT is far less when compared to the three conventional modalities: surgery, radiotherapy, and chemotherapy.

Evidence Table: Efficacy / Effectiveness
Question: Is Photodynamic therapy effective for management and treatment of cancer.

Bibliographic citation	Study Type / Methodology	LE	Number of patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures/ Effect size
5. Yoon HY, Cheon YK, Choi HJ, and Shim CS. Role of Photodynamic Therapy in the Palliation of Obstructing Esophageal Cancer. Korean J Intern Med 2012; 27:278-284. http://dx.doi.org /10.3904/kjim. 2012.27.3.278	Non-randomized, prospective study to determine the role of photodynamic therapy (PDT) in a multimodal approach for the palliation of advanced esophageal carcinoma to reduce dysphagia and to maintain nutrition and occlusion of tracheoesophageal fistula so as to improve the quality of life.	II-3	Twenty consecutive patients with obstructing esophageal cancer were enrolled in this study at the Konkuk University Medical Centre, Seoul, Korea. Each subject had dysphagia, and nine could not swallow fluid. None were eligible for surgical resection due to tumor involvement into the adjacent tissue, distant lymph node metastasis, poor performance status plus inoperable status due to co-morbidity, refusal of surgical intervention, or a combination of these reasons. External beam radiotherapy or a self-expandable metal stent was used following PDT for dysphagia due to recurrence of the malignancy.	photodynamic therapy (PDT)			The results were as shown below: • At 4 weeks post-PDT, a significant improvement in the dysphagia score was observed in 90% of patients, from 2.75 ± 0.91 to 1.05 ± 0.83 ($p < 0.05$). • Patients with recurrent dysphagia underwent stent insertion at an average of 63 days (range, 37 to 90 days). The rate of major complications was 10%. • Two esophageal strictures occurred, which were treated by placement of a modified expandable stent across the stricture. • The median survival in these cases was 7.0 ± 0.6 months. • One patient that was treated with PDT and radiotherapy was alive and showed a complete tumor response. • Eighteen patients (90%) died from their disease. The study showed that PDT as a multimodality treatment that may be safe and effective for relieving malignant esophageal obstruction with minimal complications.

Evidence Table: Efficacy / Effectiveness
Question: Is Photodynamic therapy effective for management and treatment of cancer.

Bibliographic citation	Study Type / Methodology	LE	Number of patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures/ Effect size
6. Nava HR, Allamaneni SS, Dougherty TJ, Cooper MT. Photodynamic therapy (PDT) using HPPH for the Treatment of precancerous lesions associated With Barrett's Esophagus. Lasers Surg Med. 2011; 43(7): 705–712. doi:10.1002/lsm.21112.	Non-randomised prospective study. Examine the toxicity and optimal drug and light dose with endoscopic (2-[1-hexyloxyethyl]-2-devinyl pyropheophorbide-a); HPPH-PDT at Roswell Park Cancer Institute.	II-3	36 patients referred with a diagnosis of Barrett's esophagus (BE)with high grade dysplasia (HGD) were enrolled and had to meet the following criteria: biopsy-proven HGD or early intramucosal adenocarcinoma	HPPH (2-[1-hexyloxyethyl]-2-devinyl pyropheophorbide-a) ranged from 3 to 6 mg/m2. At 24 or 48 hours after HPPH administration the lesions received one endoscopic exposure to 150, 175 or 200 J/cm of 665 nm light			Results— Adverse events: • Most patients experienced mild to moderate chest pain requiring symptomatic treatment only. • Six patients experienced Grade 3 & 4 adverse events (16.6%). Three esophageal strictures were treated with dilatation. No clear pattern of dose dependence of toxicities emerged. • Four unexpected events (diabetic acidosis grade 4, bradycardia grade 2, shortness of breath grade 2 and respiratory depression grade 2) were unrelated to PDT and were attributable to underlying disease and surgery (anesthesia) respectively. • Two photosensitivity reactions (6% of patients) were observed; one patient experienced mild photophobia and another patient experienced grade 1 sunburn due to HPPH. HPPH dose escalation study responses (18 patients) • In the drug dose ranging study (light dose of 150 J/cm at 48 h), 3 and 4 mg/m2 of HPPH emerged as most effective. • After one patient was treated at 3 mg/m2 HPPH, the study was amended to change the starting dose to 4 mg/m2 because the patient treated with 3 mg/m2 did not respond as rapidly • Eleven patients were treated with 4 mg/ m2 of HPPH. The 1-year CR rate for the combined 3 and 4 mg/m2 treatments (7 patients) was 39%. • There were no complete responses with HPPH doses of 5 and 6 mg/ m2. Eight patients experienced good responses with significant decreases in length of BM, but because some residual HGD was found in biopsies, these patients were placed in the "no response" category as per study criteria. Light dose escalation study responses • In the light dose ranging study (3 or 4 mg/m2 HPPH, light at 24 h), complete response rates (disappearance of high grade dysplasia and early carcinoma) of 13/18 (72%) were achieved at 1 year, with all patients treated with 3 mg/m2 HPPH plus 175 J/cm and 4 mg/m2 HPPH plus 150 J/cm showing complete responses at 1 year. • Of 13 patients with CR, 7 (54%) patients did not show any recurrence of the disease on follow-up at 5 years, with one patient lost to followup PPH-PDT for precancerous lesions in Barrett's esophagus appears to be safe and showing promising efficacy. Further clinical studies are required to establish the use of HPPH-PDT.

Evidence Table: Efficacy / Effectiveness
Question: Is Photodynamic therapy effective for management and treatment of cancer.

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Bibliographic citation	Study Type / Methodology	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up	Outcome measures/ Effect size
7. Höblinger A, Gerhardt T, González-Carmona MA, Hüneburg R et al. Feasibility and safety of long-term photodynamic therapy (PDT) in the palliative treatment of patients with Hilar cholangiocarcinoma. Eur J Med Res (2011) 16: 391-395	Retrospective analysis of 10 patients with unresectable extrahepatic cholangiocarcinoma (cc)	II-3	ten patients with unresectable extrahepatic cholangiocarcinoma (cc) in the department of Internal Medicine of the University Hospital bonn between 10/2005 and 08/2010. all patients underwent endoscopic biliary drainage. nine patients received metallic stents and one patient a plastic stent. .	treated with at least 4 PDT procedures		the mean follow-up time was 27.98 ± 11 months	Results: Eight patients had elevated bilirubin levels with a mean bilirubin at admission of 9.9 ± 11.3 mg/dl, which had decreased to an average minimum of 1.2 ± 0.9 mg/dl after 3 months. No severe toxicity was noted. two patients Four patients died during the follow-up because of tumor progression. The estimated survival of all patients was 47.6 months, 95% CI; 25.9 – 48.1months. Safety: The primary adverse event after intervention was cholangitis in 2 patients (20%), which was treated with antibiotics alone. In one patient, the authors performed subsequent Pdt procedures without using a biliary contrast with no cholangitis episodes thereafter. one patient experienced skin phototoxicity world Health organization grade I after the seventh PDT procedure. He was managed with topical therapy, no hospital readmission was required. PDT treatment was continued with 50% dose reduction of Photofrin and no phototoxicity reaction was observed after subsequent procedures. Long-term PDT in patients with extra hepatic CC is feasible, may be effective and is accompanied – at least in this cohort- by a survival time of more than 2 years.

Evidence Table: Efficacy / Effectiveness
Question: Is Photodynamic therapy effective for management and treatment of cancer.

Bibliographic citation	Study Type / Methodology	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up	Outcome measures/ Effect size
8. Usuda J, Ichinose S, Ishizumi T, Hayashi H et al. Outcome of Photodynamic Therapy Using NPe6 for Bronchogenic Carcinomas in Central Airways >1.0 cm in Diameter *Clin Cancer Res* 2010;16:2198-2204. DOI: 10.1158/1078-0432.CCR-09-2520	Single arm study prospective study	II-3	At the Tokyo Medical University Hospital, Between June 2004 and December 2008, 75 patients (91 lesions) with centrally located early lung cancers (CLELC)	NPe6-PDT. NPe6 is a second-generation photosensitizer, and because it has a longer absorption band (664 nm) than Photofrin (630 nm),			Results: • Seventy cancer lesions ≤1.0 cm in diameter and 21 lesions >1.0 cm in diameter were identified, and the complete response rate was 94.0% (66 of 70) and 90.4% (19 of 21), respectively. • After the mass of large tumors and deeply invasive tumors had been reduced by electrocautery, NPe6-PDT was capable of destroying the residual cancer lesions. NPe6-PDT has a strong antitumor effect against CLELCs >1.0 cm in diameter that have invaded beyond the bronchial cartilage, thereby enabling the destruction of residual cancer lesions after mass reduction of large nodular- or polypoid-type lung cancers by electrocautery.

Evidence Table: Efficacy / Effectiveness
Question: Is Photodynamic therapy effective for management and treatment of cancer.

Bibliographic citation	Study Type / Methodology	LE	Number of patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures/ Effect size
9. Downie GH, Qureshi A, Loewen G, Cuenca R, Endobronchial Ablation of Typical Carcinoid Tumor With Photodynamic Therapy. J Bronchol 2007;14:10–14	Single arm prospective study	II-3	Seven patients ages 28 to 76, with typical endobronchial carcinoid tumors with comorbid conditions or contraindication to surgery.	treated with PDT using porfimer sodium 2 mg/kg and 630nm laser at 200 J/cm		5 years	Results: • Six of 7 (86%) had complete recovery (CR), with 2 patients 2 years CR, 2 patients with 3 years CR, and 2 patiebnts with 5 years CR post-PDT. • One CR patient required balloon dilatations for bronchial stenosis with success; no other significant side effects were seen. • The sole partial response (PR) had visualized distal margins in the anterior subsegment of the right upper lobe but had an unsuspected origin in the posterior subsegment and was unable to be completely treated with any local ablation technique. • Employing selection criteria, CR in 6/7 86% of patients were observed. There were no sustained significant side effects. Endobronchial treatments with PDT may be effective, safe, and surgery sparing in selected patients.

Evidence Table: Efficacy / Effectiveness
Question: Is Photodynamic therapy effective for management and treatment of cancer.

Bibliographic citation	Study Type / Methodology	LE	Number of patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures/ Effect size
10. De Vijlder HC, Sterenborg HJCM, Neumann HAM et al. Light Fractionation Significantly Improves the Response of Superficial Basal Cell Carcinoma to Aminolaevulinic Acid Photodynamic Therapy: Five-year Follow-up of a Randomized, Prospective Trial. Acta Derm Venereol 2012; 92: 641-647.	RCT	1	all patients were diagnosed as having a sBCC within the department of dermatology of Erasmus MC in Rotterdam, The Netherlands	91 patients with a total of 299 lesions were treated using a 2-fold illumination scheme,	A total of 104 patients, who altogether had 274 lesions, were treated using a single illumination scheme		Results: • The CR rate was significantly greater following the 2-fold illumination than the single illumination (p = 0.0002, log-rank test). • Five years after therapy the CR rate after 2-fold illumination was 88%, whereas the CR rate after single illumination was 75%. • The CR rate in the third group of lesions, treated with 2-fold illumination was 97% and 88% at 12 months and 5 years after therapy, respectively. Long-term follow-up indicates superior efficacy in sBCC of ALA-PDT with 2-fold illumination compared with ALA-PDT with single illumination

Evidence Table: Efficacy / Effectiveness
Question: Is Photodynamic therapy effective for management and treatment of cancer.

Bibliographic citation	Study Type / Methodology	LE	Number of patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures/ Effect size
11. Eibenschutz L, Marenda S, Buccini P et al. Giant and large basal cell carcinoma treated with topical photodynamic therapy. Eur J Dermatol 2008; 18 (6): 663-6	A retrospective non-comparative follow-up study was performed to test the response of giant and large BCC to MAL-PDT.	II-3	From February 2003 to February 2007 the authors treated twelve patients with 14 giant BCC (≥ 5 cm) and 5 patients with 5 large BCC (4-5 cm) were treated with MAL-PDT at the S Gallicano Dermatological Institute, Rome, Italy	methyl aminolevulinate PDT(MAL-PDT)			The patients were evaluated 6 months after the end of the treatment to define the initial cure rate, and then at 12 and 36 months for the follow-up. • At 6 months the initial cure rate for the 19 BCCs was 18/19 (95%) • The cure rate was 13/19 (68.4%) at 12 months and in 10/19 (52.6%) at 36 months and at 36 months the overall long-term cure rate was 66%, 39% for giant BCC to 100% for lesions sized 4-5 cm. • In total, 8 out of 18 successfully treated lesions recurred after MAL-PDT, 5 of which (28%) at 12 months and 3 (23%) at 36 months, all giant BCC • The degree of pain and discomfort referred by the patients during the treatment was mild in 45% and severe in 55% of the cases no patients discontinued the treatment, nor asked for anaesthesia as, after cooling the lesions with a water spray or by pausing the light for a few minutes, the pain could be sufficiently soothed. Hence, the above study suggests that MAL-PDT may be a valid option for the treatment of giant and large BCC.

Evidence Table: Efficacy / Effectiveness
Question: Is Photodynamic therapy effective for management and treatment of cancer.

Bibliographic citation	Study Type / Methodology	LE	Number of patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures/ Effect size
12. Surrenti T, De Angelis L, Di Cesare A et al. Efficacy of photodynamic therapy with Methyl Aminolevulinate in the treatment of superficial and nodular basal cell carcinoma: an open-label Trial. Eur J Dermatol 2007; 17 (5): 412-5	Open label trial	1	Patients with superficial and nodular basal cell carcinomas (BCCs) who attended the out-patient clinic of the Department of Dermatology, University of L'Aquila, Italy, from February 2004 to March 2005. Patients aged ≥ 18 years were included in the study if they satisfied at least one of the following criteria: i) contraindication to surgical excision due to bleeding abnormalities or cardiac risk; ii) multiple or recurrent BCCs; iii) patient's request for alternative treatment due to needle/surgery phobia.	Methyl Aminolevulinate (MAL-PDT)	Surgery		Efficacy was rated as i) complete response, corresponding to clinical disappearance of BCC; ii) partial response, clinically corresponding to ≥40% and < 100% reduction in tumour size; iii) no response, defined as < 40% reduction in tumour size as compared to initial clinical examination and iv) worsening, defined as an increase in tumour size from baseline. The results of the study were: • Complete clinical regression was detected in 84/94 (89.4%) superficial BCCs including 3 pigmented BCC lesions, and 12/23 (52.2%) nodular BCCs one month after 2 MAL-PDT sessions. • A partial response was observed in 10/94 (10.6%) superficial BCCs and in 11/23 (47.8%) nodular BCCs, one month after 2 MAL-PDT sessions • No further clinical improvement was observed in either superficial or nodular BCCs with treatment continuation up to a maximum of 8 MAL-PDT sessions. • Adverse effects were limited to mild local skin reactions, Cosmetic outcome was rated as excellent or good. Recurrence was observed in 2/84 (2.4%) successfully treated superficial BCCs at 6 and 12 months after treatment discontinuation. Based on the efficacy, tolerability, a cosmetic outcome and recurrence rate of this study, the results suggests that MAL-PDT for treatment of superficial BCC and for selected cases of nodular BCC may be used.

Evidence Table : Safety
Question: Is photodynamic therapy safe for cancer treatment?

Bibliographic citation	Study Type / Methodology	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up	Outcome measures/ Effect size
1.Mino-Kenudson M, Ban S, Ohana M, Puricelli W et al. Buried Dysplasia and Early Adenocarcinoma Arising in Barrett Esophagus After Porfimer-photodynamic Therapy. Am J Surg Pathol 2007; 31:403–409	Pre and post study on PDT	II-1	Fifty-two Barrett esophagus (BE)patients with high-grade dysplasia (n=19), intramucosal adenocarcinoma (n=28), and invasive adenocarcinoma (n=5) were treated with porfimer PDT.	porfimer PDT.		Mean follow-up after PDT was 29.3 months	Results showed that: • Not a single case of completely buried BE was noted pre-PDT. After PDT, completely buried BE was diagnosed in 12 biopsy levels (3.6%of 338 levels) of 9 patients (17.3%) • Before treatment, only 1 patient showed a completely buried neoplastic focus (HGD), which responded to 1 course of PDT. After PDT, completely buried neoplasms were noted in 19 levels from 13 patients The prevalence of completely buried neoplasms was 0.6% (1/173) and 7.4% (19/258) in pre and post-PDT positive biopsy levels, respectively (P=0.001) • Completely buried lesions represented the highest grade of residual neoplasm in a series of 11 post-PDT endoscopies (7.1% of 155 post-PDT endoscopies with neoplastic diagnoses) from 8 patients • Their occurrence after PDT was neither associated with the length of BE, the diffuseness of neoplasms nor the presence of buried lesions before treatment. There was no prevalent location for these lesions in relation to the original segment of BE, although the majority of both surface and buried neoplasms were found in the prior neoplastic sites. In conclusion, buried neoplasms are not uncommon after PDT. Thorough endoscopic surveillance with extensive biopsies, especially of the sites previously positive for neoplasia is important to avoid overlooking buried neoplasms that may progress

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Bibliographic citation	Study Type / Methodology	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up	Outcome measures/ Effect size
2. Bang DW, Hyon MS, Cho YD, Kim SK, and Kwon YJ. Development of Brugada Syndrome Following Photodynamic Therapy in a Patient with Cholangiocarcinoma. Korean J Intern Med 2012;27:95-97. http://dx.doi.org/10.3904/kjim.2012.27.1.95	Case report	II-3	A previously healthy 62-year-old man was admitted to the hospital for PDT following a diagnosis of cholangiocarcinoma (Klatskin tumor, type IV) made one month prior to admission.	photodynamic therapy (PDT)			Brugada syndrome can be unmasked by several conditions including a febrile state, marked leukocytosis, and electrolyte disturbances. For scheduled PDT, the patient was injected intravenously for over 5 minutes with a hematoporphyrin derivative- type photosensitizer, Photogem, 2 mg/kg. After 40 to 50 hours of PDT, light at a release power of 150 J/cm2 was applied. The patient was stable until 7 hours following the light application, at which time he began to complain of feeling febrile and having chills. His body temperature was 38.4°C. Emergency laboratory tests revealed hepatic biochemical abnormalities: an aspartate transaminase (AST) level of 247 U/L, alanine transaminase (ALT) of 140 U/L, and direct bilirubin of 0.8 mg/dL. One hour following the injection of antipyretics, the patient's condition stabilized. His only complaint was general weakness, but he went into cardiac arrest 10 hours later. The ECG performed during the cardiopulmonary resuscitation revealed polymorphic ventricular tachycardia. After electrical cardioversions (300 J × 3), the cardiac rhythm recovered to a sinus rhythm. The 12-lead ECG showed a right bundle branch block and a pronounced ST segment elevation in the precordial leads (V1, V2) consistent with Brugada syndrome. On the sixth day post-attack, the patient died of fulminant hepatic failure and sepsis due to obstruction of the biliary tract.

Evidence Table : Safety
Question: Is photodynamic therapy safe for cancer treatment?

Bibliographic citation	Study Type / Methodology	LE	Number of patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures/ Effect size
3. Nava HR, Allamaneni SS, Dougherty TJ, Cooper MT. Photodynamic therapy (PDT) using HPPH for the Treatment of precancerous lesions associated With Barrett's Esophagus. Lasers Surg Med. 2011; 43(7): 705–712. doi:10.1002/lsm.21112.	Non-randomised prospective study. Examine the toxicity and optimal drug and light dose with endoscopic (2-[1-hexyloxyethyl]-2-devinyl pyropheophorbide-a); HPPH-PDT at Roswell Park Cancer Institute.	II-3	36 patients referred with a diagnosis of Barrett's esophagus (BE)with high grade dysplasia (HGD) were enrolled and had to meet the following criteria: biopsy-proven HGD or early intramucosal adenocarcinoma	HPPH (2-[1-hexyloxyethyl]-2-devinyl pyropheophorbide-a) ranged from 3 to 6 mg/m2. At 24 or 48 hours after HPPH administration the lesions received one endoscopic exposure to 150, 175 or 200 J/cm of 665 nm light			Results— Adverse events: • Most patients experienced mild to moderate chest pain requiring symptomatic treatment only. • Six patients experienced Grade 3 & 4 adverse events (16.6%). Three esophageal strictures were treated with dilatation. No clear pattern of dose dependence of toxicities emerged. • Four unexpected events (diabetic acidosis grade 4, bradycardia grade 2, shortness of breath grade 2 and respiratory depression grade 2) were unrelated to PDT and were attributable to underlying disease and surgery (anesthesia) respectively. • Two photosensitivity reactions (6% of patients) were observed; one patient experienced mild photophobia and another patient experienced grade 1 sunburn due to HPPH.

Evidence Table : Safety
Question: Is photodynamic therapy safe for cancer treatment?

Bibliographic citation	Study Type / Methodology	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up	Outcome measures/ Effect size
4. Höblinger A, Gerhardt T, González-Carmona MA, Hüneburg R et al. Feasibility and safety of long-term photodynamic therapy (PDT) in the palliative treatment of patients with Hilar cholangiocarcinoma. Eur J Med Res (2011) 16: 391-395	Retrospective analysis of 10 patients with unresectable extrahepatic cholangiocarcinoma (cc)	II-3	ten patients with unresectable extrahepatic cholangiocarcinoma (cc) in the department of Internal Medicine of the University Hospital bonn between 10/2005 and 08/2010. all patients underwent endoscopic biliary drainage. nine patients received metallic stents and one patient a plastic stent.	treated with at least 4 PDT procedures		the mean follow-up time was 27.98 ± 11 months	Safety: The primary adverse event after intervention was cholangitis in 2 patients (20%), which was treated with antibiotics alone. In one patient, the authors performed subsequent Pdt procedures without using a biliary contrast with no cholangitis episodes thereafter. one patient experienced skin phototoxicity world Health organization grade I after the seventh PDT procedure. He was managed with topical therapy, no hospital readmission was required. PDT treatment was continued with 50% dose reduction of Photofrin and no phototoxicity reaction was observed after subsequent procedures.

Evidence Table : Safety
Question: Is photodynamic therapy safe for cancer treatment?

Bibliographic citation	Study Type / Methodology	LE	Number of patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures/ Effect size
5. Annemans L, Karin caekelbergh, Roelandts R et al. Real-life practice study of the clinical outcome and cost-effectiveness of photodynamic therapy using methyl aminolevulinate (MAL-PDT) in the management of actinic keratosis and basal cell carcinoma. Eur J Dermatol 2008; 18 (5): 539-46	prospective, observational, one arm study	II-1	Patients with actinic keratosis (AK), nodular and superficial basal cell carcinoma (nBCC and sBCC) were selected according to Belgian reimbursement criteria. Data were collected from 247 patients (117 AK, 130 BCC).	methyl aminolevulinate (MAL-PDT)		The follow up period was 6 months from the date of first application of Metvix	• 2 patients withdrew for adverse events. Skin discomfort was experienced by 139 (56%) patients in total (62% ofAK patients and 51% of BCC patients). • Other adverse events were reported by 18 (7%) patients, and included pain (3%), oedema and erythema (1%), skin necrosis with severe crust forming (1%).

Evidence Table: economic evaluation
Question: Is Photodynamic therapy cost effective for management and treatment of cancer.

Bibliographic citation	Study Type / Methodology	LE	Number of patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures/ Effect size
2. Annemans L, Karin caekelbergh, Roelandts R et al. Real-life practice study of the clinical outcome and cost-effectiveness of photodynamic therapy using methyl aminolevulinate (MAL-PDT) in the management of actinic keratosis and basal cell carcinoma. Eur J Dermatol 2008; 18 (5): 539-46	prospective, observational, one arm study	II-1	Patients with actinic keratosis (AK), nodular and superficial basal cell carcinoma (nBCC and sBCC) were selected according to Belgian reimbursement criteria. Data were collected from 247 patients (117 AK, 130 BCC).	methyl aminolevulinate (MAL-PDT)		The follow up period was 6 months from the date of first application of Metvix	The results were as follows: • A complete clinical response was obtained for 83% of AK (85/102) and 83% of BCC (97/116) patients (85.2% of sBCC patients and 77.8% of nBCC patients). • A good or excellent cosmetic outcome was obtained for 95% of AK patients and 93% of BCC patients (94% of the patients with sBCC and 89% of the patients with nBCC). • Tolerability was good: only 2 patients withdrew for adverse events. Skin discomfort was experienced by 139 (56%) patients in total (62% ofAK patients and 51% of BCC patients). • Other adverse events were reported by 18 (7%) patients, and included pain (3%), oedema and erythema (1%), skin necrosis with severe crust forming (1%). • Total cost of care per patient was €381 for AK, €318 for nBCC, and €298 for sBCC. Total cost per lesion was €58 for AK (identical to model prediction), €316 for nBCC and €178 for sBCC (both within 20% of model prediction). The clinical results of MAL-PDT in this real-life practice study confirmed those demonstrated in previous clinical trials. Costs calculated from this study confirmed predicted cost-effectiveness in the original model for MAL-PDT in the management of AK and BCC.