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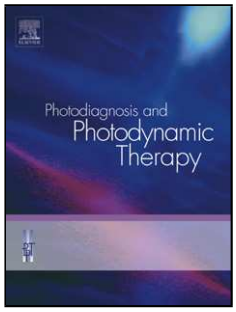

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Title:

Treatment of peritoneal carcinomatosis with photodynamic therapy: systematic review of current evidence

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Highlights:

- Peritoneal carcinomatosis pathological features make it suitable cancer for PDT
- PDT in animal studies showed significant survival increase and tumour regression
- Intraperitoneal PDT was feasible in human but limited by narrow therapeutic window
- Poor tolerance of PDT was mainly due to photosensitisers' low tumour-selectivity
- Photoimmunoconjugation improved PDT's efficacy and tolerance in animal studies

Abstract:

Background:

Peritoneal carcinomatosis results when tumour cells implant and grow within the peritoneal cavity. Treatment and prognosis vary based on the primary cancer. Although therapy with intention-to-cure is offered to selective patients using cytoreductive surgery with chemotherapy, the prognosis remains poor for most of the patients. Photodynamic therapy (PDT) is a cancer-therapeutic modality where a photosensitiser is administered to patients and exerts a cytotoxic effect on cancer cells when excited by light of a specific wavelength. It has potential application in the treatment of peritoneal carcinomatosis.

Methods:

We systematically reviewed the evidence of using PDT to treat peritoneal carcinomatosis in both animals and humans (Medline/EMBASE searched in June 2017).

Results:

Three human and 25 animal studies were included. Phase I and II human trials using first-generation photosensitisers showed that applying PDT after surgical debulking in patients with peritoneal carcinomatosis is feasible with some clinical benefits. The low tumour-selectivity of the photosensitisers led to significant toxicities mainly capillary leak syndrome and bowel perforation. In animal studies, PDT improved survival by 15-300%, compared to control groups. PDT led to higher tumour necrosis values (categorical values 0-4 [4=highest]: PDT 3.4±1.0 vs. control 0.4±0.6, $p<0.05$) and reduced tumour size (residual tumour size is 10% of untreated controls, $p<0.001$).

Conclusion:

PDT has potential in treating peritoneal carcinomatosis, but is limited by its narrow therapeutic window and possible serious side effects. Recent improvement in tumour-selectivity and light delivery systems is promising, but further development is needed before PDT can be routinely applied for peritoneal carcinomatosis.

Keywords: Photochemotherapy; neoplasms; photosensitizing agents; peritoneum; photodynamic therapy; peritoneal carcinomatosis

Words count: 5,509 (without abstract)

Introduction

Peritoneal carcinomatosis describes the dissemination and growth of cancer deposits within the peritoneal cavity. These most commonly represent secondary metastases from colorectal, ovarian, urogenital, gastric and pancreatic cancers. Less commonly, cancer deposits metastasise from melanomas or malignancies of distant organs such as the breast. Primary tumours originating from the peritoneum (e.g., peritoneal mesothelioma and primary peritoneal carcinoma) are rare[1,2].

The peritoneum has a complex anatomy with a large surface area equivalent to that of the external body[3]. Peritoneal cancer deposits can be extensive[4] and cover vital intra-abdominal structures (e.g., small bowels, liver and great vessels)[3]. Peritoneal carcinomatosis can occur in the absence of haematogenous or lymphatic metastases[5], causing local complications, including ascites and bowel obstruction[4].

The therapeutic modalities and prognosis vary widely depending on the origin of the primary cancer. Whilst some patients are treated with intention to cure, most patients have a poor prognosis and therapies are aimed at palliative symptom control.

Patients with pseudomyxoma peritonei or appendiceal neoplasia with peritoneal metastases can be treated with cytoreductive surgery and heated intraperitoneal chemotherapy with reasonable outcomes (median survival 196 months)[6]. Peritoneal carcinomatosis of ovarian origin can be treated with intention to cure in selected patients who are fit for major surgery with acceptable perioperative morbidity.[7,8] For selected patients, cytoreduction surgery, which aims to resect all macroscopic disease, is performed before or after chemotherapy (median survival 22-64 months)[9]. Peritoneal carcinomatosis secondary to gastrointestinal cancers (e.g. gastric or colorectal) have a poor prognosis even in the selected patients where cytoreductive surgery and heated intraperitoneal chemotherapy is attempted (median survival 8 and 7-19 months for gastric and colorectal, respectively)[10-12]

Photodynamic therapy is a therapeutic anti-cancer modality that has been used to treat many cancers, including oesophageal, skin and lung cancers[13]. A photosensitiser is administered that more rapidly accumulates in malignant compared to non-malignant tissue. A ground state photosensitiser is activated to a higher energy active triplet state when exposed to light of a particular wavelength. Decay of the active triplet state releases energy in the form of electrons to generate toxic singlet oxygen ($^1O_2$) and reactive oxygen species.

These products mediate tumour cell toxicity, microvascular damage[14] and anti-tumour immune responses[13,15-17].

In 1986, Tochner *et al* investigated the use of photodynamic therapy in a peritoneal carcinomatosis murine model. They reported a high cure rate of 85%[18]. This encouraged further research into the use of photodynamic therapy in peritoneal carcinomatosis over the next three decades[13]. Preliminary evidence suggests that photodynamic therapy might improve the outcomes of peritoneal carcinomatosis management and provide an effective modality alongside other therapeutic options.

This article is the first attempt to systematically review all existing evidence concerning the use of photodynamic therapy in treating peritoneal carcinomatosis. Given the limited evidence in human disease, we included animal studies to create an overview of the entire knowledge base.

Methods

Criteria for study inclusion

Studies

All original peer-reviewed comparative and non-comparative studies of any type were included. Conference proceedings were excluded.

Participants:

Patients or animal models with peritoneal carcinomatosis of any origin were included. Peritoneal carcinomatosis was defined by having more than one intraperitoneal nodule (disseminated model). Animal models where only one solid mass was obtained and those where seeding was performed outside the peritoneal cavity (e.g., flanks) were excluded.

Interventions

All studies that used any type of photodynamic therapy, with or without other modalities, to treat cancerous nodules within the peritoneum were considered. *In vitro* studies were excluded.

Primary outcomes:

- Survival
- Adverse effects

Secondary outcomes:

These outcomes measured the local pathological tumour response to the treatment:

- *Nodule necrosis*: this represents the proportion of tumour mass which is found to be necrotic. A= mild (<1/3 of the tumour mass), B= moderate (1/3 - 2/3 of the tumour mass), C= strong (>2/3 of the tumour mass).
- *Tumour size*: in order to estimate the tumour size, some studies used bioluminescence imaging which assesses the luciferase activity in cancer cells that stably express luciferase. Other studies tagged cancer cells with green florescent protein before seeding them into animal models. The fluorescence intensity was used to estimate tumour size.
- *Mean percentage of tumour burden*: this equals the mean tumour burden of the treatment group divided by the mean tumour burden of the control group (mean tumour burden per group was calculated by subtracting the weight of organs in a third group of healthy animal from the weight of organs in the tumour animal model).
- *Experimental peritoneal cancer index*: this index divides the abdominal cavity into four quadrants and each quadrant is given a score of 0 to 5 based on the size of tumour in it (0: no tumour is visible, 1: tumour is 0 to 0.5 cm, 2: tumour is 0.5 to 1 cm, 3: tumour is 1 to 2 cm, 4: tumour is 2 to 3 cm, 5: tumour > 3 cm). The results of all four quadrants are summated giving an experimental peritoneal cancer index score of 0 to 20.
- *Necrosis value*: this is determined by the depth of the necrotic area in the specimen in relation to the full tumour thickness (score= 0: no necrosis, score= 1: necrosis up to 33 %, score= 2: necrosis is 33-66 %, score= 3: necrosis is 66-99 %, score=4: necrosis is 100%) for each sample of the illuminated peritoneum[19]. 'Response' is defined as having a necrosis value of 3 or 4. 'Insufficient response' is defined as having a necrosis value of 0 to 2.

Search strategy:

Literature searches were performed in both MEDLINE and EMBASES databases (June 2017) to identify both animal and human studies investigating the use of photodynamic therapy in peritoneal carcinomatosis of any origin. The used search terms were ("photodynamic" OR "photochemotherapy" OR "phototherapy" OR "photoradiation" OR "photoimmunotherapy" OR "fluorescen*") AND "peritone*", in any field. The search was restricted to articles written in English.

Study selection:

The selection process was divided into two phases. In the initial phase, the titles and abstracts of all citations located through the electronic search were scanned to identify potentially relevant articles to the eligibility criteria. The full texts of the relevant articles were obtained in the second phase and assessed for inclusion or exclusion. The selection process was performed independently by two authors (MQA and GG). Only studies that fulfilled the eligibility criteria were included. In cases of disagreement, a consensual decision was made following discussion of the full manuscript. The references of the 'relevant articles' were checked for any additional relevant articles.

Risk of bias assessment:

The risk of bias in the included studies was determined using an assessment tool modified from the Cochrane Collaboration assessment tool for interventional studies [20,21]. This included 10 elements (i. randomisation, ii. concealment of allocation, iii. blinding of assessors, iv. sample size calculation, v. statistical model description, vi. description of subjects, vii. disclosing financial support, viii. incomplete outcome data, ix. detailed description of intervention and x. description of housing and nutrition conditions for animals in preclinical studies). The answers to the above elements were either 'yes' if the area was well covered in the article or 'no' if the element was not reported.

Results

Description of studies

Figure 1 summarises the process for identifying studies. Twenty eight studies were included in this review: three human studies (11 citations)[3,22-29] and 25 animal studies[18,19,30-52].

Twenty seven studies were excluded. Reasons for exclusion were: non-tumour bearing animal model[27,53-58], no disseminated peritoneal carcinomatosis model (tumour cells injected in the flanks[59] or subcutaneously[60,61] or only a single intraperitoneal tumour[62]), no photodynamic therapy given (photosensitiser only[53,63] or light only[64]), no useful clinical outcomes[64-70], conference abstracts (no full texts)[71-76] and mixed populations and interventions (results are not broken down by intervention)[77].

Clinical data (human):

Three clinical studies investigated the use photodynamic therapy in human patients with peritoneal carcinomatosis (Table 1).

Phase I:

In a 'phase I trial', DeLaney (1993)[3,24,27] assessed the feasibility and maximum tolerated dose of photodynamic therapy in patients with refractory or recurrent disseminated peritoneal carcinomatosis. Fifty four patients underwent debulking surgery with 39 having successful cytoreduction (i.e. tumour residual < 5 mm) and additional photodynamic therapy using a first generation photosensitiser (dihematoporphyrin ethers). Photodynamic therapy was modified, starting with a low dose of photosensitisers and escalating the dose from 1.5 to 2.5 mg/kg, shortening the injection-to-surgery intervals from 72 to 48 h, and increasing the light dose.

Initially, red light (630 nm) at increasing dose of 0.2-3.0 J/cm^2 was used alone to illuminate the bowel and mesentery. However, due to the observed small bowel oedema and perforation, the light source was switched to green light (514 nm; dose 2.5-9.0 J/cm^2). Additional boosts of red light (dose up to 10-15 J/cm^2) or green light (dose up to 5.0-7.5 J/cm^2) were delivered to sites of gross disease on the peritoneum. Dilute lipid emulsion was sued to help light scattering within the peritoneal cavity the light. Four photodiodes were used to measure the real time dosimetry; three of them were sewn into the parietal peritoneum and a fourth one was left as a mobile one. The maximum tolerated dose of photodynamic therapy given 48 h after intravenous administration of dihematoporphyrin ethers (2.5 mg/kg) was 3.75 J/cm^2 of green light with boosts of green light (5.0 to 7.5 J/cm^2) or red light (10-15 J/cm^2) to the sites of gross disease.

No operative or post-operative (within 30 days) mortality was reported. The major complications were small bowel perforation (n=3), gastric perforation (n=1) and colo-cutaneous fistula (n=1). Twenty three patients (59%) developed a pleural effusion, of whom six patients needed thoracocentesis. Mild adverse effects included transient mild thrombocytopenia (63%), transient insignificant elevated liver enzymes (AST 89%, ALT 86%) and phototoxicity (15%).

Thirty one patients (80%) had no evidence of disease recurrence at 2-3 months follow up. At 3-27 months follow up, 9 patients (23%) were disease-free, 21 patients (54%) had recurrent tumour and 9 patients (23%) died of progressive disease. The median survival of patients who received photodynamic therapy was 30 months.

Phase II:

Using the tolerated doses revealed by the phase I trial, Hahn *et al* (2006) [22,23,25,26,29,78,79] examined the efficacy and toxicities of using photodynamic therapy in a 'phase II trial'. One

hundred patients with refractory peritoneal carcinomatosis or sarcomatosis, in the absence of distant metastases, were recruited.

Photofrin (2.5 mg/kg) was given intravenously to all patients 48h before undergoing a debulking surgery. After surgery, patients with residual nodules of <5mm received light therapy (n=71). Illumination was with green light for the mesentery and the bowel at a dose of 2.5 J/cm^2 whilst red light was used to treat the rest of the peritoneal surfaces. Sites of gross disease received extra-boost treatment of red light up to 15 J/cm^2. Patients were instructed to avoid direct light exposure for 30 to 60 days after the operation.

Two patients died post-operatively (n=1 myocardial infarction, n=1 sepsis). The most common adverse effect related to photodynamic therapy was 'capillary leak syndrome' with massive fluid shifts into the abdominal cavity. The average fluid requirement in the first 48h after operation was 29.3± 12.4 L. Twenty patients developed grade I or 2 skin photosensitisation. Other complications included bowel fistulae and anastomotic leaks (n=4), poor wound healing (n=4), and prolonged intubation > 1 day (n=24).

Patients had a median follow up of 51 months. The median disease-free survival and overall survival for the patients who underwent photodynamic therapy with cytoreductive surgery (n=71) were 3.0 and 22.0 months for ovarian cancer patients (n=23), 3.3 and 13.2 months for gastrointestinal cancer patients (n=22) and 4.0 and 21.9 months for sarcoma patients (n=26). When all enrolled patients were included (n=100), the results were 2.1 and 20.1 months for ovarian cancer, 1.8 and 11.1 months for gastrointestinal cancer and 3.7 and 21.9 months for sarcoma. In patients who only had locoregional recurrence, most of the recurrence areas were not previously involved in the gross disease[29].

Other trials:

Wierrani (1997)[28] investigated the use of photodynamic therapy in eight patients with recurrent gynaecological cancer that metastasised to the peritoneum. All patients had previous surgery combined with either chemotherapy (n=6) or radiotherapy (n=2). Six patients had cytoreductive surgery combined with photodynamic therapy while two patients underwent photodynamic therapy alone. Mesotetrahydroxyphenylchlorin (*Foscan*®) was used as the photosensitiser at an intravenous dose of 0.15 mg/kg 96 h before the operation. KTP:YAG pumped laser (652 nm, red light) was delivered at a fluence of 5 J/cm^2 using a cylindrical diffusing fibre.

One patient died 2 days post-operatively with multiple organ failure secondary to cardiac insufficiency. Reported adverse effects included grade 1 and 2 cutaneous burns (3 patients) and prolonged ileus. Disease-free survival was 17.6 (0-32) months.

Preclinical data (animal models)

1. Photodynamic therapy versus control:

1.1 Survival

Eleven animal studies [18,31,32,34-36,42,45,47,49,80] compared the overall survival of animals treated with photodynamic therapy with those left untreated (table 2). The studies used different animal models, photosensitisers and light doses. They all found a significant prolongation of survival of animals treated with photodynamic therapy (between 15% and 300%) in comparison with those left untreated (figure 2).

Song *et al*[36] combined cytoreductive surgery with photodynamic therapy and compared this with cytoreductive surgery alone in a rat ovarian cancer model. Adding photodynamic therapy to cytoreductive surgery led to significant improvement in animal survival in comparison with cytoreductive surgery alone (cytoreduction surgery + photodynamic therapy 45 days vs. cytoreductive surgery alone 15 days, $p<0.01$). Similar results were shown by Yokoyama *et al*[49] although the difference did not reach statistical significance (cytoreductive surgery + photodynamic therapy 46 days vs. cytoreductive alone 36 days, $p=0.08$).

1.2 Toxicity

Mroz *et al* [42] used Fullerene BB4 (5mg/kg intraperitoneally) in mice with colonic cancer peritoneal carcinomatosis. A fluence of 100 J/cm^2 was used when illuminating the peritoneum with either of three lights (white, green or red). The authors reported death in all mice in the photodynamic therapy group illuminated with red light. No mortality occurred when red light was used without the photosensitiser. The other photodynamic therapy groups illuminated with white or green light experienced no adverse effects.

Kishi *et al* [39] used Talaporfin (10 mg/kg intraperitoneally) in mice with gastric cancer peritoneal carcinomatosis. The authors compared different illumination regimens using fluences of 2, 5 or 10 J/cm^2 either 2 or 4 h after injecting the photosensitiser. There was increasing oedema formation in the small bowel wall as the dose increased from 2 to 10 J/cm^2 irrespective of whether the illumination occurred 2 or 4 h after the photosensitiser's injection. Intestinal ischaemic changes were noted in both the 5 and 10 J/cm^2 groups which

were illuminated 2 h post injection, but not in the groups illuminated 4 h post injection. All mice (n=5) treated with 2 J/cm^2 at 2 h interval died 3 days post photodynamic therapy (due to intestinal perforation) whilst all those treated with 2 J/cm^2 4 h post injection survived with no complications until 30 days after the photodynamic therapy. The authors concluded that laser dose of 2 J/cm^2 and a 4 h interval between Talaporfin administration and laser treatment is the optimal safest treatment.

1.3 Pathological response:

Seventeen animal studies [32-35,37-41,43-48,52,81] investigated the peritoneal tumour response when treated with photodynamic therapy as compared to controls (table 3).

The studies show significant pathological response of the tumour in response to photodynamic therapy. Animal groups treated with photodynamic therapy had more necrosis in the tumour area (70% ± 13% versus 33% ± 8%)[40], less weight of the residual carcinoma (34 ± 14 µg versus 379 ± 65 µg, p <0.001)[32], and higher necrosis values (3.4 ± 1.0 versus 0.4 ± 0.6, p <0.05)[37] in comparison to controls. The 'mean percentage of tumour burden' in the photodynamic therapy group was almost a third that of the control group (38%, 95% confidence interval 29%-47%, p <0.001)[35].

2. Synergistic effect of combined therapy:

2.1 Anti-epidermal growth factor receptor

Epidermal growth factor receptor is a receptor that promotes disproportionate cell proliferation and is associated with poor prognosis of a variety of cancers[82]. Cell cycle arrest is induced by competitive binding of the monoclonal antibody Cetuximab with native ligand epidermal growth factor for epidermal growth factor receptor binding sites[83,84].

Del Carmen *et al* [35] examined the efficacy of combining immunotherapy with photodynamic therapy. Human epithelial ovarian cancer cells were seeded into the peritoneum of mice. The anti-epidermal growth factor receptor group received 0.5 mg of Cetuximab intraperitoneally on days 11, 14, 17 and 19 after tumour inoculation (2 mg per mouse). The photodynamic therapy group received 0.25 mg/kg of liposomal benzoporphyrin derivative monoacid intraperitoneally. Ninety minutes after injecting the photosensitiser, the peritoneum of the mouse was illuminated with red light (690 nm) at a fluence of 20 J/cm^2. The combination group received both treatments (cetuximab and photodynamic therapy).

The median survival for the combined group was 80 days, which was double the median survival in photodynamic therapy group (38 days). Both the combined group and the photodynamic therapy group showed significant improvement in survival in comparison with the no-treatment group (28 days), p <0.001 and p= 0.01, respectively. Survival in the cetuximab group was 26 days and not different from the no-treatment group. The mean percentage of tumour burden when using the combined therapy was significantly lower than that reported in the individual treatment groups (combined modality: 10%, 95% confidence interval 2-17%, photodynamic therapy: 38%, 95% confidence interval 29-47%, cetuximab: 67%, 95% confidence interval 59-74%, p <0.001).

2.2 Photoimmunoconjugate:

Many investigators have tried to improve the selectivity of photosensitisers by conjugating them with antibodies directed against antigens specific to cancer cells forming photoimmunoconjugates.

In 1996, Molpus *et al* [34] conjugated the photosensitiser Chlorine$_{e6}$ with OC125. OC125 is a monoclonal antibody that recognises CA-125, a cell surface antigen highly expressed by ovarian cancer cells [85]. The resulting photoimmunoconjugate could be produced with either a cationic or anionic charge. A mouse model of peritoneal carcinomatosis from human ovarian cancer was used. Mice were injected intraperitoneally with either chlorine$_{e6}$ (n=10), anionic photoimmunoconjugate (n=16), cationic photoimmunoconjugate (n=19) or left untreated (n=12). Illumination using red light (650nm, dose 25 J/mice) was 3 h after injecting the photosensitiser or its functionalised form.

The median survival was found to be higher in the cationic photoimmunoconjugate group (41 days) in comparison with the anionic photoimmunoconjugate group (37 days, p <0.05), the chlorine$_{e6}$ group (34.5 days, p <0.05) and the control group (35 days, p <0.01). A highly significant decrease in the residual intraperitoneal tumour was seen in all three treatment groups in comparison with the control group; the greatest effect was found in the cationic photoimmunoconjugate group (cationic photoimmunoconjugate 33± 20mg, anionic photoimmunoconjugate 73 ± 29 mg, chlorine $_{e6}$ 59 ± 18 mg, control 330 ± 109 mg, p <0.0001).

Goff *et al* (1996) [31] investigated the use of photoimmunoconjugate (chlorine $_{e6}$ + OC125) in a murine disseminated ovarian cancer model. Mice in the photoimmunoconjugate group survived significantly longer than those in the control group (p<0.001). However, there was

no 'Chlorine$_{e6}$-mediated photodynamic therapy only' group to assess the additive-effect of photoimmunoconjugation.

More recently, Sato (2014)[44] and (2015)[46] used a photoimmunoconjugate (tra-IR700) which comprised a photosensitising agent (IR-700) conjugated to Trastuzumab (a monoclonal antibody against HER2 receptors). A HER2-expressing cancer cell line (N87-GFP[44], SKOV-Luc[46]) was used to establish a disseminated peritoneal carcinomatosis mouse model. Significant reduction in the tumour size was reported following photoimmunoconjugate-mediated photodynamic therapy in comparison with the no-treatment group[44,46,47]. Harada (2016)[48] conjugated IR-700 with galactosyl serum albumin, which binds to β-D-galactose receptors. An ovarian cancer cell line (SHIN3), which overexpresses D-galactose receptors, was used. A significant reduction in tumour size was reported in the photoimmunoconjugate group in comparison with control groups ($p<0.05$).

Ishida (2016)[47] investigated improving the effect of tra-IR700 mediated photodynamic therapy by increasing the expression of the antigen (HER-2) in the ovarian cancer cells. A HER-2 negative cancer cell line (MKN45-Luc) was used in their animal model. Adenoviral vector, which carries the HER2-extracellular domain gene, was used to induce exogenous HER2-extracellular domain overexpression on the HER2-negative cancer cell membranes and sensitise them to Trastuzumab. Adding the adenoviral vector to the photoimmunoconjugate led to a significant reduction in the residual tumour weight (HER-2 adenovirus vector + photoimmunoconjugate-mediated photodynamic therapy: 0.50± 0.06 g, photoimmunoconjugate-mediate photodynamic therapy alone: 1.10± 0.29 g, no treatment: 1.32± 0.58 g, $p<0.05$).

2.3 Anti-angiogenesis

Piatrouskaya *et al* [40] argued that the release of pro-angiogenic mediators, particularly vascular endothelial growth factor, following photodynamic therapy could compromise its cytotoxic effect by allowing the tumour to restore its microvasculature. They assessed the early tumour response after combining photodynamic therapy with an anti-angiogenesis treatment (Bevacizumab) in a peritoneal sarcomatosis rat model. Animals were divided into four groups: the photodynamic therapy group (n=5) which received Fotolon (intravenous 2.5 mg/kg) and were illuminated with a laser (670 nm) via a laparotomy approach (5 J/cm^2 with boost treatment up to 100 J/cm^2 for gross disease sites); the anti-angiogenesis group (n=5) which received Bevacizumab (intravenous 15 mg/kg); the combined treatment group (n=5) which received both modalities; and the control group (n=3) which received no treatment.

Four days after the intervention, there was a significant increase in the 'necrosis to tumour percentage' in the combined treatment group (90% ± 7%) in comparison with the photodynamic therapy group (70% ± 13%), the anti-angiogenesis group (42 % ± 11 %) and the control group (33 % ± 8 %), $p = 0.000$.

3. **Photodynamic therapy versus chemotherapy:**

Raue *et al* [41] compared different regimens of chemotherapy and photodynamic therapy in a rat model with peritoneal malignancy of colonic origin. Animals were randomly divided into six groups of 15 animals. Group 1 received no treatment, Group 2 had cytoreductive surgery, Groups 3 to 6 had cytoreductive surgery followed by either hyperthermic intraoperative peritoneal chemotherapy with mitomycin 15 mg/m^2 (Groups 3), intraperitoneal taurolin 0.5% (Group 4), hyperthermic intraoperative peritoneal chemotherapy with gemcitabine 24 mg/kg (Group 5), or protoporphyrin IX-mediated photodynamic therapy (intravenous 5-aminolevulinic acid 150mg/kg 6 h pre-operatively, illumination with red light (630 nm), power 3 watts, duration 2 x 10 min) (Group 6).

All treatment groups (Groups 2 - 6) had significantly lower tumour weight and experimental peritoneal cancer index in comparison with the control group. The experimental peritoneal cancer index was lower in the mitomycin group (median 4, range 0-14) in comparison with the photodynamic therapy group at the parameters used (median 6, range 0-20) (p =0.03). However, no significant difference was found in the residual tumour weight between these two groups. Applying protoporphyrin IX-mediated photodynamic therapy at this same dose and timing with cytoreductive surgery did not lead to significant decrease in tumour weight when compared with cytoreductive surgery alone (median 0.3, range 0-20 versus median 1.4, range 0- 21.5).

4. Continuous versus fractionated illumination for photodynamic therapy:

Ascencio *et al*[51] compared two methods of illumination for photodynamic therapy: continuous and fractionated. The authors injected hexaminolaevulinate intraperitoneally at a dose of 100 mg/kg in rats with peritoneal carcinomatosis of ovarian origin. Illumination using green light (532 nm, 30mW/cm^2) was performed 4 h after the photosensitiser's injection. The rats were divided into two groups: the continuous-1 group (n=20), which received a continuous illumination of a total fluence of 45 J/cm^2, and the fractionated group (n=16), which received a fractionated illumination (on for 120 sec then off for 60 sec) until reaching a fluence of 30

J/cm^2 (i.e., total illumination duration equals that of the continuous group). Biopsies were taken 24 h after treatment to assess the pathological response. The mean necrosis value was significantly higher in the fractionated light group (3.7 ± 0.7) in comparison to the continuously applied light group (3.1 ± 0.9), $p < 0.05$.

In another experiment by the same group[50], a similar protocol was used but with the addition of a third group (continuous-2) which received continuous illumination at a reduced fluence of 30 J/cm^2 (similar overall dose to the fractionated group). Tumour destruction assessed by the depth of necrosis was higher using the fractionated illumination in comparison with continuous illumination applications (fractionated: 213 ± 113 µm vs. continuous-1: 154 ± 133 µm versus continuous-2: 171 ± 155 µm, $p<0.05$). Although no significant difference was found in the mean necrosis value between the three different methods of illumination, the full necrosis (necrosis value of 4) rate was significantly higher in the fractionated group (fractionated: 50 % versus continuous-1: 30 % versus continuous-2: 10 %, $p < 0.0001$).

Discussion

Residual peritoneal metastases after cytoreductive surgery remain a surgical challenge and a significant contributor to cancer recurrence[86]. The pathophysiological characteristics of peritoneal carcinomatosis, namely disseminated nodules localised to the peritoneum with little penetration of the underlying structures[87], make it an ideal form of cancer to treat with photodynamic therapy. The effects of photodynamic therapy are limited by tissue light penetration, making it most effective for surface malignancies. Visible light is needed to activate photosensitisers that are taken up or are in close proximity to cells[14]. Therefore, the depth of the therapy can be controlled by using different wavelengths[79]. This facilitates treating cancerous nodules that have spread over the large area of the peritoneum with limited toxicity to deeper structures, such as the intestines[3,78].

Summary of results:

In this systemic review, we explored the use of photodynamic therapy for the treatment of peritoneal carcinomatosis highlighting the pros and cons of its use in isolation and as a combined therapy. This review includes three human and twenty five animal studies. Animal studies have shown promising results with treated animals surviving 15 - 300% longer than control groups. Photodynamic therapy was shown to double the extent of tumour necrosis and reduce tumour size by up to 90%.

Phase I and II human trials have shown that applying photodynamic therapy after surgical debulking of peritoneal carcinomatosis is feasible[3,78]. Some benefit in terms of slightly prolonged survival have been described, but did not lead to long-term tumour control. The toxicity induced by intraperitoneal photodynamic therapy was also significant. Post-therapy capillary leak syndrome characterised by excessive fluid shifts and bowel perforation were the main adverse effects[23,78].

Interpretation of the findings of these Phase I and II clinical trials, including the efficacy and toxicity profiles of photodynamic therapy, is limited by certain drawbacks. Firstly, the authors included a heterogeneous population of patients with peritoneal sarcomatosis and carcinomatosis of different origin. Secondly, all the included patients had poor prognosis and failed to respond to first line treatments including surgical debulking and chemotherapy. Future trials should ideally focus on selected populations with intention to cure. Thirdly, the included patients received a suboptimal incomplete macroscopic cytoreductive surgery (gross residual disease < 5mm). Current practice emphasises the importance of complete gross disease debulking which has been found to lead to significant improvement in patient's prognosis in comparison with incomplete resection.[1] Fourthly, nonspecific first generation photosensitizers were used in the studies causing significant toxicities. Newer, more cancer-specific photosensitisers have since been developed.

Current challenges of photodynamic therapy and future directions:

A photosensitiser, molecular oxygen, and activating light are needed for photodynamic therapy. Controlling the adverse effects might be managed by manipulating the activating light, the available molecular oxygen and/or the tumour selectivity of the photosensitiser and photosensitising agents. The use of the less penetrating green light appears to reduce the risk of bowel perforation in comparison to more penetrating red light[3,42]. However, the trade-off is that green light is less effective for more invasive cancers, with greater risk of incomplete cancer treatment and recurrence.

Only first generation photosensitisers have been evaluated in patients with peritoneal carcinomatosis in phase I and II clinical trials[3,28,78]. One Phase II trial, which was undertaken more than a decade ago, showed low tumour-to-normal tissue selectivity ratios for the photosensitiser (*Photofrin*) (tumour-to-normal ratio =0.9 and 0.5 for the small and large bowels)[25]. This low tumour selectivity of *Photofrin* is attributed to its significant toxicities. In addition, *Photofrin*'s prolonged retention in tissues, such as the skin, causes skin phototoxicity.[25]

Since Hahn *et al* (2006) report their phase II clinical trial[25], significant pre-clinical research has been undertaken to improve the tumour-selectivity photosensitisers. Second-generation photosensitisers (e.g., meta-tetrahydroxyphenyl chlorin) have been tested in peritoneal carcinomatosis animal models and shown to have better tumour-selectivity and shorter *in vivo* retention time. This has improved the therapeutic window and reduced the associated phototoxicity[33-35,41,43]. Integrating targeted molecular therapy into photodynamic therapy holds strong clinical potential and has attracted recent attention[13]. Photosensitisers have been functionalised by conjugating them to tumour-specific antibodies, forming photoimmunoconjugates. This review suggests that efficacy can be improved by using photoimmunoconjugates in comparison with photodynamic therapy only in animal models[31,34,44,48,69]. This strategy warrants further investigation.

Another area for further study is the potential synergistic effect between photodynamic therapy and other anti-cancer treatments. This might allow the doses of photodynamic therapy to be reduced whilst retaining the same anti-cancer efficacy. Animal studies have shown an improved effect of photodynamic therapy when combined with anti-epidermal growth factor receptor [34,35] and anti-angiogenesis [40] agents.

Although a significant decrease in tumour burden has been noted following intraperitoneal photodynamic therapy in animals, survival advantage was limited[32]. This suggests regrowth of tumour nodules that escaped photodynamic therapy or were incompletely treated.

Delivering the activating light to allow photodynamic therapy to uniformly treat all potential peritoneal surfaces is challenging[3,78]. The peritoneal surface is a large and complex structure. Light delivery to hidden surfaces (e.g., mesentery surface, subhepatic, subdiaphragmatic and inter-loop surfaces) is difficult and necessitates moving organs to ensure adequate light exposure. Lipid emulsion (Intralipid) was used by Hahn *et al* and placed in the abdominal cavity to help scatter light, reduce shadowing and permit more homogenous light delivery to the intra-abdominal organs.[88] There is currently no commercially available hardware to deliver light within the abdomen.

Interestingly, repeating photodynamic therapy might reduce the risk of tumour recurrence with no accumulative toxicity, hypersensitivity or resistance[17]. This requires repeat access to the peritoneal cavity, which might not be practical. Implantable intra-abdominal light sources and light scattering solutions could potentially allow repeat photodynamic therapy.

As efforts to develop this promising therapeutic modality continue, one of the main challenges is the numerous variables which need to be controlled. The studies included in this review have used different photosensitisers, drug concentrations, drug-to-light intervals, light sources, wavelengths, light fluences and illumination times. This, in addition to the different outcomes used to report the results, made it difficult to draw clear conclusions.

Limitations and risk of bias assessment:

This review is limited by the type of studies included. Whilst the review included a reasonable number of studies (n=28), the average sample size was relatively small and none of the sample sizes were based on pre-study power calculation. In addition, animal models do not always replicate the human experience because of the biological differences and any extrapolation from the animal literature needs to be with caution.

There were no concerns about the delivery of the 3 clinical trials. However, the grade of evidence was low considering their non-comparative design. Animal studies were scored medium in the quality assessment tool (average score= 5.7/10). The main drawback with most study designs was the absence of a pre-defined power calculation and the presence of selection and performance biases (e.g. randomisation, concealment of allocation and blinding of assessors).

Conclusion:

Photodynamic therapy has efficacy and translational applicability for the treatment of peritoneal carcinomatosis. Animal studies of photodynamic therapy have shown promising results, but human trials have revealed a narrow therapeutic index that limits its present clinical application.

Developing more tumour-selective photosensitisers, combining photodynamic therapy with targeting agents and improving light delivery techniques could enhance its therapeutic potential. These issues need to be addressed before photodynamic therapy can be established within the current management strategy of peritoneal carcinomatosis.

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Authors Contribution:

MQA: Study concept, study design, data acquisition, data analysis and interpretation, manuscript preparation, final manuscript.

GG: Data acquisition, data analysis and interpretation, editing of manuscript.

KEW: Data analysis and interpretation, editing of manuscript

DGJ: Study concept, study design, data analysis and interpretation, editing of manuscript.

Conflict of interest

None to be declared

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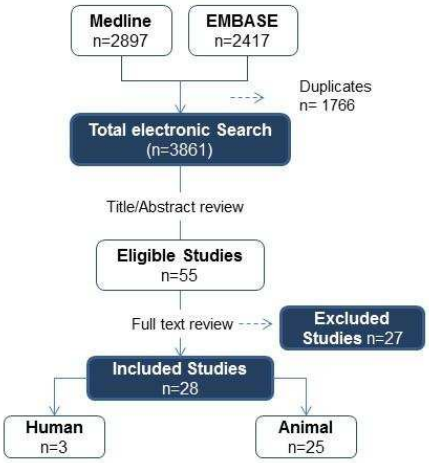
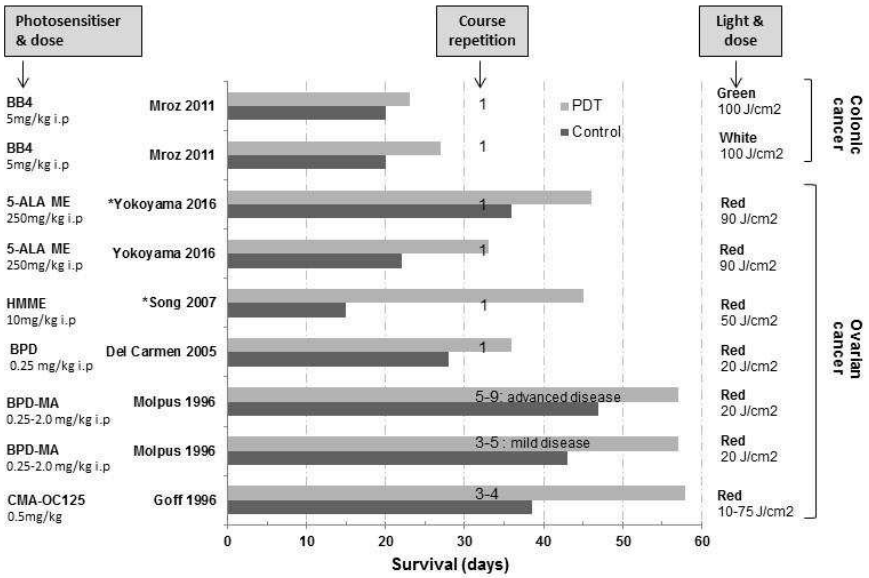
Figures:

Figure 1. Chart flow of search strategy and identification of studies

Figure 2. Photodynamic therapy versus control in animal models (outcome: survival/days)

*Both arms had cytoreductive surgery. IP= intra-peritoneal, BB4= N-methylpyrrolidinium-fullerene, HMME= hematoporphyrin monomethyl ether, BPD-MA= benzoporphyrin derivative-mono acid, CMA-OC125= Chlorin e6 monoethylendiamine monamide conjugated with OC125.





Tables:

Table 1. Photodynamic therapy for peritoneal carcinomatosis: human clinical trials

Study	Participants	Intervention	Survival	Toxicity
Phase I Delaney 1993[1-3] USA	39 patients with refractory disease, no metastases outside peritoneum	DHE iv. 1.5- 2.5 mg/kg 48-72 h before CS. If PC residual ≤ 5mm, light therapy given (red ± green light).	At potential follow up of 3.8-43.1 months (median 22.1) 30/39 (77%) of patients were alive and 9/39 (23%) were disease-free.	Small bowel and gastric perforations, prolonged intubation (7-9 days), colo-cutaneous fistula, pleural effusion, cutaneous phototoxicity, transient deranged liver function.
Phase II Hahn 2006 [4-10] USA	100 patients with refractory disease, no metastases outside peritoneum	Photofrin (DHE) 2.5 mg/kg i.v 48h before CS. If PC residual ≤ 5mm, light therapy given (red ± green light).	Median disease-free survival and overall survival by strata were ovarian (n=33) 2.1 and 20.1 months; GI (n=37) 1.8 and 11.1 months, sarcoma (n=30) 3.7 and 21.9 months.	Capillary leak syndrome, ARDS, fistulae or anastomotic leak, prolonged ileus and phototoxicity
Wierrani 1997[11] Austria	8 patients with recurrent gynaecological cancer	m-THPC i.v 96 h pre-CS (0.15 mg/kg), red light.	Disease-free survival: 17.6 months (range 0-32 months)	1 death post operative (heart failure). Cutaneous burns and ileus

Table 2. Photodynamic therapy for peritoneal carcinomatosis: animal studies (primary outcomes: survival & toxicity)

Study	Animal, Cancer type (cells)	Photosensitiser, Other interventions	Energy fluence	Interval (hour)	Light type	Survival	Improved survival	Toxicity

DHE= dihematoporphyrin ethers, *m-THPC*= Mesotetrahydroxyphenylchlorin, *CS*= cytoreductive surgery, *PC*= peritoneal carcinomatosis, *GI*= gastrointestinal

<table>
<tr>
<td>Ishida 2016 [1] USA</td>
<td>Mice, Gastric (MKN45-*Luc), HER-2 negative</td>
<td>Tra-IR700 (80 µg i.p) AD= Ad/HER2-ECD (1x10^8 pfu) injected i.p 5 days post MKN45-Luc injection.</td>
<td>50 J/cm^2</td>
<td>24 h

Single or repeated courses</td>
<td>NIR 690 nm</td>
<td>Survival, n=5 each group:
[AD+PDT]> Other groups, (p <0.05, log-rank test)

Survival at 50 days:
[AD+PDT] once = 60%,
[AD+PDT] treatment repeated x3= 60%
[PDT] once= 20%
[PDT] treatment repeated x3= 25%
[no treatment]= 0%</td>
<td></td>
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<tr>
<td>Yokoyama 2016[2] Japan</td>
<td>Rats, Ovarian (DISS)</td>
<td>5-ALA methyl ester 250mg/kg i.p
CA= Clofibric acid. 9,000 ppm orally daily.
DS= Debulking surgery</td>
<td>90 J/cm^2</td>
<td></td>
<td>600 nm</td>
<td>Survival, n=5 each group:
Control= 22 days, PDT alone= 33 days, DS alone= 36 days, DS+PDT= 46 days, DS+PDT+CA= 53 days.
<table>
<tr><th>P value</th><th>DS</th><th>PDT</th><th>DS+PDT</th><th>DS+PDT+CA</th></tr>
<tr><td>Control</td><td>p< 0.05</td><td>P< 0.01</td><td>-</td><td>-</td></tr>
<tr><td>DS</td><td>-</td><td>-</td><td>p= 0.08</td><td>p<0.05</td></tr>
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<tr>
<td>Tsujimoto 2014[3] Japan</td>
<td>Mice, Gastric (MKN45-*Luc)</td>
<td>ICGm: 100µL (281µmol).

ICGs: 100µL (281µmol)</td>
<td>500 mW/cm^2 for 1,000 sec (500 J/cm^2)</td>
<td></td>
<td>808 nm laser diode</td>
<td>Survival (n=8 each group)
ICGm vs. ICGs: 32 vs. 17 days (p < 0.05)</td>
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<td></td>
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</table>

Mroz 2011 [4] USA	Mice, Colon (CT26)	BB4†, 5mg/kg i.p	100 J/cm^2	24 h (single) 3 h (single)	Red White Green	PDT (n=10) vs. Control (n=10): White: 27 vs. 20 days, sig Green: 23 vs. 20 days, sig (p=0.02). White: 24 vs. 20 days, sig (p<0.01) Green: no significant difference.	35% 15% 20%	Red light led to death in 2-3 days,
Song 2007 [5] China	Rats Ovary (NuTu - 19)	HMME 10mg/kg i.p	50 J/cm^2	3h, (single)	Red	CS +PDT (n=9): 45 days (CI 95% 1-89) CS+ laser alone: 19 days (CI 95% 14-25) CS alone (n=8): 15 days (CI 95% 7-23), *p*< 0.01.	236% 300%	None
del Carmen 2005[6] USA	Mice Ovary (NIH:OVCAR-5)	BPD 0.25 mg/kg i.p	20 J/cm^2	1.5 h (single)	Red	PDT (n=10) vs. Control (n=10): 36 (IQR 32-90) vs. 28 (IQR 21-31), p= 0.01.	29%	None
Molpus 2000[7] USA	Mice Ovary (NIH:OVCAR-5)	*Ce6*-OC125 (PIC) 1mg/kg i.p	25 J/cm2	3 h (repeated x3)	Red	Cationic PIC (n=19) vs. anionic PIC (n=16) vs. free Ce6 (n=10) vs control (n=11): 41 vs. 37 vs. 34.5 vs. 35 days		
Molpus 1996[8] USA	Mice Ovary (NIH:OVCAR-5)	BPD-MA 0.25-2.0 mg/kg i.p	20 J/cm^2	1.5 h (repeated)	Red	*Advanced disease groups (5-9 courses):* PDT (n=11) vs. control (n=9): 57 vs. 47 days, *p* <0.05. *Minimal disease groups (3-5 courses):* PDT (n=?), vs. control (n=?): 57 vs. 43 days, *p* <0.05.	21% 33%	None
Goff 1996 [9] USA	Mice Ovary (NIH:OVCAR-3)	C_{e6}-OC125 (PIC) 0.5mg/kg	10-75 J/cm^2	24 h (repeated)	Red	*3-4 courses separated by 48h* PDT 4 courses (n=12) vs. PDT 3 courses (n=10), vs. control (n=18): 58 vs. 47.5 vs. 38.5 days, log-rank test p<0.001.	51%	None
Tochner 1986 [10] USA	Mice Malignant Teratoma	HPD (Photofrin) 10mg/kg i.p		2 h (repeated)	Green	*4 courses separated by 48h:* All controls died within 25 days. PDT group: 17/20 (85%) survival at 25 days. These were disease free at 11 months.		None

Tochner 1985 [11] USA	Mice Embryonal ovary carcinoma	HPD (Photofrin) 50 mg/kg i.p		2 h	Green	All controls died before day 23. **1 Course PDT** (day 9): 8/32 (25%) died before day 23, 25/32 (78%) died before day 34, 1/32 (3%) lived > 90 days (cured). **2 courses of PDT** (day 9 and 15): 6/15 (40%) lived > 90 days (cured)		Death due to bowel perforation

***Luc**= luciferases expressing cancer cells. ***Tra-IR700**= IR Dye 700 DX NHS ester conjugated to trastuzumab (anti-HER2), ***Ad/HER2-ECD**= adenovirus transduction of HER-2 extracellular domain gene into HER-2 negative gastric cancer cells. ***ICGm**= indocyanine green loaded lactosomes, ***ICGs**= indocyanine green solution. ***IP**= intra-peritoneal, ***CS**= cytoreductive surgery, ***IQR**= interquartile range, ***BB4**= N-methylpyrrolidinium-fullerene, ***HMME**= hematoporphyrin monomethyl ether, ***BPD-MA**= benzoporphyrin derivative-mono acid, ***Ce6*-OC125**= Chlorin e_6 conjugated with OC125, ***PIC**= Photoimmunoconjugate, ***HPD**= haematoporphyrin derivative. †In cremophor micelles.

Table 3. Photodynamic therapy for peritoneal carcinomatosis: animal studies (secondary outcomes: pathological local response)

Study	Animal & Cancer	Photosensitiser (PS)	Energy	Interval (h) from PS	Light type	Pathological response
Kato 2017[1] Japan	Mice, pancreatic (AsPC1/luc)	Mal_3-chlorin 1.25 mmol/kg i.p Talaporfin 1.25 mmol/kg i.p	13.9 J/cm2	Two courses (day 0, day 7)	660 nm	**Tumour size, indicated by BLI (n=7 each group):** Mal_3-chlorin vs. control (p= 0.036) Mal_3-chlorin vs talaporfin (p=0.074, ns) **Ascites volume (n=7 each group):** Mal_3-chlorin vs. control (p= 0.066, ns) Mal_3-chlorin vs talaporfin (p=0.159, ns)
Ishida 2016 [2] Japan	Mice, Gastric (MKN45-*Luc), HER-2 negative	Tra-IR700 (PIC) 80µg i.p AD= Ad/HER2-ECD injected i.p 5 days post MKN45-Luc injection.	50 J/cm^2	24 h Single course or repeated courses	NIR 690nm	**Tumour weight [g], n=4 each group:** [no treatment]= 1.32 ± 0.58 [PDT alone]= 1.10± 0.29 [AD+PDT] = 0.50± 0.06, p< 0.05
Harada 2016[3] USA	Mice, ovarian (SHIN3) overexpresses D-galactose receptors	GSA-IR700 (PIC) 25µg i.p	100 J/cm^2 (500 mW/cm^2, 200 sec)	Repeated daily for 3 days	NIR	**Tumour size, indicated by BLI (n=5 each group):** Significant reduction in PDT group in day 2 (p<0.01), day 3 (p=0.044), day 6 (p=0.049) and day 7 (0.042) in comparison with other control groups (no treatment, NIR light only; GSA-IR700 only). No significant therapeutic effect in control groups.
Sato 2015[4] USA	Mice, Ovarian (SKOV-*Luc)	Tra-IR700 (PIC) 100µg i.v	50J/cm^2 on day1 100J/cm^2 on day2		NIR	**Tumour size, indicated by BLI (n=6 each group): Day 7 post PDT** PDT vs. NIR light alone (p= 0.026) PDT vs. no treatment (p= 0.004) **Tumour size, indicated by BLI (n=6 each group): Day 14 post-PDT** PDT vs. NIR light alone (p= 0.033) PDT vs. no treatment (p= 0.017) PDT vs. tra-IR700 alone (p= 0.013)

Sato 2014[5] USA	Mice Gastric (N87-GFP), HER2 +ve	Tra-IR700 (PIC) 100µg i.v	50J/cm^2 on day1 100J/cm^2 on day2		NIR	**Tumour size (indicated by GFP fluorescence intensity, n=5 each group):** PDT < no treatment (p= 0.049) PDT < NIR light alone (p= 0.030) PDT < tra-IR700 alone (p= 0.036)
Tsujimoto 2014[6] Japan	Mice, Gastric (MKN45-*Luc)	ICGm: 100µL (281µmol). ICGs: 100µL (281µmol)	500 mW/cm^2 for 1,000 sec (500 J/cm^2)		808 nm laser diode	**Total weight of tumour nodules (n=5 each group):** ICGm (1.5 g) vs. ICGs (1.0 g), p< 0.05 Total number of residual nodules: ICGm (26) vs. ICGs (30), non-significant
Hino 2013 [7] Japan	Mice Gastric (MKN-45)	5-ALA 250 mg/kg	4.5 J/cm^2	5	Violet Green Red	**Strong nodules' necrosis (necrosis >2/3):** 23% (violet**) vs. 17% (green**) vs. 7% (red*) vs. 1% (control), **p <0.01, *p <0.05.
Raue 2010[8] Germany	Rats Colonic (DHD/K12/ TRb)	5-ALA 150 mg/kg i.v	?	6 h	Red	**ePCI:** CS+PDT (n=15) vs. CS alone (n=15): 6 (0-20) vs. 9(0-20), non-sig difference.
Piatrouskaya 2010 [9] Belarus	Rats Sarcoma (M-1)	Fotolon 2.5 mg/kg i.v	?	?	?	**% of necrosis to tumour area:** PDT (n=5) vs. control (n=3): 70% ± 13% vs. 33% ± 8%
Kishi 2010[10] Japan	Mice GastricMKN-45	Talaporfin 10mg/kg i.p	 2, 5, 10 J/cm^2 2, 5, 10 J/cm^2	 2 h 4 h		**Strong nodule necrosis (necrosis > 2/3):** 2 J/cm^2 vs. 5J/cm^2 vs. 10 J/cm^2 53%, 43%, 64% 21%, 26%, 26%
Estevez 2010[11]	Rats Ovary (NuTu-19)	HAL 100mg/kg ip	Continuous (C1) 45J/cm^2 Continuous (C2): 30 J/cm^2 Fractionated (F) (2min on, 1min off) 30 J/cm^2	HAL 100mg/kg ip	Green	**F (n=16) vs. C1 (n=20) vs. C2 (n=20):** **Depth of necrosis (** µm) **thickness:** 213±113 vs.154±133 vs. 171±155, p <0.05 **Mean necrosis value (0-4):** 3.2±0.95 vs 2.2±1 vs. 2.55±1.19 **Responders (NV=3 or 4):** 75% (intermittent) vs. 40% (C1&C2) p<0.0001 **Full thickness necrosis (NV=4):** 50% vs. 10%, vs. 30%, p<0.0001
Zohng 2009 [12] USA	Mice, Ovarian (OVCAR5)	BPD-MA 0.25 mg/kg i.p	25 J/cm^2	Single, 90min	690nm	**Mean percentage tumour re-growth (day 5 post PDT):** PDT (n=3) < control (n=4): -58% reduction vs. +59% increase, p<0.05.
Ascencio 2008 b[13]	Rats Ovary (NuTu-19)	HAL 100mg/kg ip	Continuous (C2): 30 J/cm^2 Fractionated (F) (2min on, 1min off) 30 J/cm^2	HAL 100mg/kg ip	Green	**Necrosis value (0-4):** C2 (n=20) vs. F (n=16): 3.10±0.94 vs. 3.67±0.70, p < 0.05
Ascencio 2008a [14] France	Rats Ovary (NuTu-19)	HAL 100mg/kg ip	45 J/cm^2	4 h	Green	**Necrosis value (0-4):** PDT vs. control: 3.35±1.01 vs. 0.35±0.63, p<0.05. **Complete response (NV 3 or 4):** PDT vs. control: 77% vs. 0%
Ascencio 2007[15] France	Rats Ovary (NuTu-19)	5-ALA 60mg/kg i.p	100J/cm^2 150J/cm^2	4 h	 Red	**Necrosis value (0-4):** 1.89±1.05 2.67±1.00
			30 J/cm^2 45 J/cm^2		Green	3.22 ± 0.83 1.89 ±0.93 No necrosis in control (laser alone) group

del Carmen 2005 [16] USA	Mice Ovary (NIH:OVCA R-5)	BPD-MA 0.25 mg/kg i.p	20 J/cm^2	1.5	Red	**Mean % tumour burden:** PDT (n=16) vs. control (n=11) 38.2%, 95% CI 29.3%-47%, p< 0.001
Molpus 2000[17] USA	Mice Ovary (NIH:OVCA R-5)	*Ce6*-OC125 (PIC) 1mg/kg i.p	25 J/cm^2	3	Red	**Mean residual tumour (mg): Cationic PIC vs. anionic PIC vs. Ce6 vs. control:** 33±20 vs. 73±29 vs. 59±18 vs. 330±109 mg
Lilge 1998 [18] USA	Mice ovary (NIH:OVCA R-5)	BPD-MA 0.25 mg/kg i.p	15 J	1.25 (3 courses at 72 h interval)	Red	**Post PDT tumour burden:** PDT ($G_{1,2,3}$) vs. control: 138 vs.400 µg
Molpus 1996 [19] USA	Mice Ovary (NIH:OVCA R-5)	BPD-MA 0.25-2.0 mg/kg i.p	20 J/cm^2	1.5 (3 courses at 72 h interval)	Red	**Mean weight of residual carcinoma at necropsy:** PDT vs. control : 34.3±14 vs. 379±65 µg, p<0.001 **Animals with deposits >1mm at gross dissection:** PDT vs. control: 27% vs. 100%.

Luc= luciferases expressing cancer cells. ***Tra-IR700***= IR Dye 700 DX NHS ester conjugated to trastuzumab (anti-HER2), ***Ad/HER2-ECD***= adenovirus transducing HER-2 extracellular domain gene into HER-2 negative gastric cancer cells, ***GSA-IR700***= Galactosyl serum albumin binds to β-D-galactose receptors. ***BLI***= Bioluminescence Imaging assesses luciferase activity, ***NIR***= near infra-red, ***ICGm***= indocyanine green loaded lactosomes, ***ICGs***= indocyanine green solution, ***5-ALA***= aminolevulinic acid, ***HAL***= hexaminolaevulinate, ***BPD-MA***= benzoporphyrin derivative-mono acid, ***Ce6-OC125***= Chlorin e6 conjugated with OC125, ***PIC***= Photoimmunoconjugate, ***ePCI***= Experimental Peritoneal Cancer Index.