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Review Article

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Photodynamic Diagnosis and Therapy for Peritoneal Carcinomatosis from Gastrointestinal Cancers: Status, Opportunities, and Challenges

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ABSTRACT

Selective accumulation of a photosensitizer and the subsequent response in only the light-irradiated target are advantages of photodynamic diagnosis and therapy. The limited depth of the therapeutic effect is a positive characteristic when treating surface malignancies, such as peritoneal carcinomatosis. For photodynamic diagnosis (PDD), adjunctive use of aminolevulinic acid- protoporphyrin IX-guided fluorescence imaging detects cancer nodules, which would have been missed during assessment using white light visualization only. Furthermore, since few side effects have been reported, this has the potential to become a vital component of diagnostic laparoscopy. A variety of photosensitizers have been examined for photodynamic therapy (PDT), and treatment protocols are heterogeneous in terms of photosensitizer type and dose, photosensitizer-light time interval, and light source wavelength, dose, and dose rate. Although several studies have suggested that PDT has favorable effects in peritoneal carcinomatosis, clinical trials in more homogenous patient groups are required to identify the true benefits. In addition, major complications, such as bowel perforation and capillary leak syndrome, need to be reduced. In the long term, PDD and PDT are likely to be successful therapeutic options for patients with peritoneal carcinomatosis, with several options to optimize the photosensitizer and light delivery parameters to improve safety and efficacy.

Keywords: Surgical guidance; Photodynamic diagnosis; Photodynamic therapy; Photosensitizer; Carcinomatosis

INTRODUCTION

Fluorescence-guided surgical resection is emerging as a valuable clinical approach to improve tumor margin identification and enable maximal safe reductive surgery [1]. Several fluorescent agents are currently used routinely in clinical practice for surgical guidance, such as indocyanine green (ICG) [2] and fluorescein [3]. Additionally, various novel fluorophores are in development, including molecules or nanoparticles that are specifically targeted to tumors through conjugation to antibodies or peptides [4,5]. A further option

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Conflict of Interest

No potential conflict of interest relevant to this article was reported.

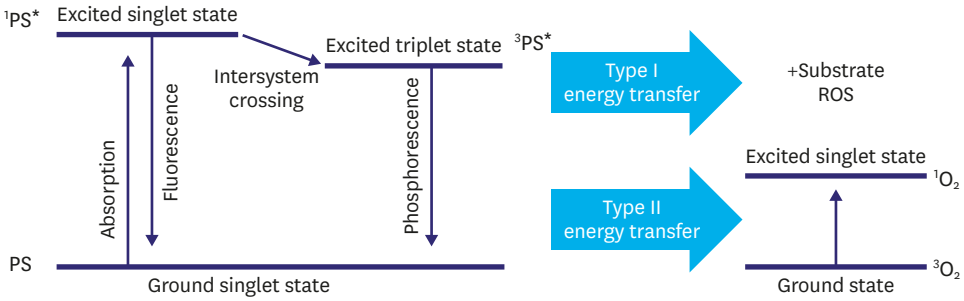

Fig. 1. Photophysical pathways (energy-level diagram) in PDD and PDT.
PDD = photodynamic diagnosis; PDT = photodynamic therapy; PS = photosensitizer; ROS = reactive oxygen species.

is to use fluorophores that are also photodynamic sensitizers, and in this case, the term "photodynamic diagnosis (PDD)" is often used. Photodynamic therapy (PDT) utilizes high doses of photosensitizer and light to destroy malignant tissue, often via the generation of cytotoxic reactive oxygen species (ROS), such as singlet oxygen. Tumor cell death may occur directly via necrotic and/or apoptotic pathways or by shutting down the tumor microvasculature via endothelial cell death when light is applied while the photosensitizer remains in circulation [6]. Historically, many developments in PDD and PDT have been closely linked, although not all fluorophores (materials that emit longer-wavelength light upon photoexcitation) are photosensitizers (molecules producing biochemical changes through photophysical and photochemical processes) and *vice versa*. Indeed, fluorescence and ROS generation are competing processes, as illustrated in **Fig. 1**. Singlet oxygen-mediated PDT occurs only when a photosensitizer, oxygen, and light are present in sufficient amounts (**Fig. 2**). Ideally, the photosensitizer should also have a degree of selectivity for tumor tissue over normal tissue selectivity, either through higher uptake in malignant cells/tissues and/or through differential sensitivity to ROS-mediated damage. The advantages of PDT as a clinical modality include its low systemic toxicity (apart from skin photosensitivity, reported with some earlier photosensitizers) and excellent tissue healing, since the lack of heat means that collagen is not destroyed during PDT and the normal tissue architecture is preserved. More recently, preclinical and clinical evidence have shown that immune upregulation contributes to the tumor response [7,8].

While many potential PDD/PDT agents can be used in the management of peritoneal carcinomatosis (PC), 5-aminolevulinic acid (5-ALA)-induced protoporphyrin IX (PpIX) is of special interest. 5-ALA is a small agent that is administered orally and is involved in the

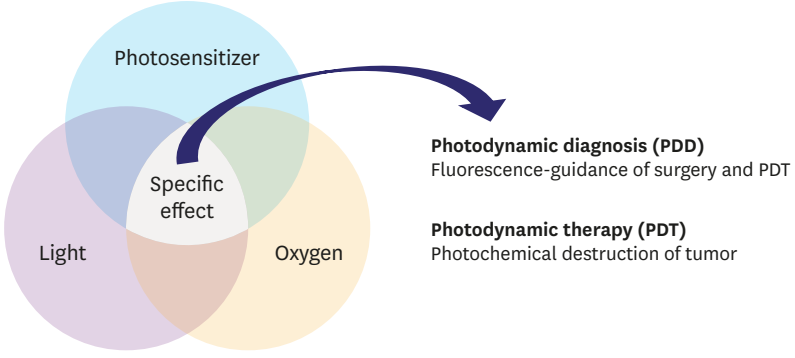

Fig. 2. Schematic showing the interactions between the main elements required in PDT.

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regulation of heme biosynthesis. Exogenous ALA increases heme synthesis; during the penultimate step, the fluorescent photosensitizer PpIX preferentially accumulates in tumor cells [9], most likely due to the low levels of ferrochelatase needed to convert PpIX into heme.

A variety of visible and near-infrared light sources (diode lasers, light-emitting diodes [LEDs]) and light delivery technologies, including fiberoptics and specialized light diffusers, are used [10-12] depending on the treatment site and clinical requirements. Both surface application and interstitial light delivery may be applied externally, intraoperatively, or endoscopically. PDT is particularly well suited for the treatment of surface malignancies, such as basal cell carcinomas and early-stage intraluminal lesions [13,14], where selective photosensitizer uptake in the tumor cells, targeted light irradiation, and, depending on the wavelength, limited light penetration in tissue can selectively destroy tumor or pre-malignant lesions (dysplasia) with minimal damage to underlying normal tissue. Combining PDD with laparoscopic guidance PDT treatment delivery using a minimally invasive approach is facilitated by the widespread use of endoscopic and laparoscopic tools.

Historically, PC was considered an incurable condition in patients with gastric, pancreatic, colorectal, or ovarian cancers. The discovery of one or more metastatic nodules during surgery changes the surgical plan from curative to palliative resection, or to no resection. Thus, early diagnosis of metastatic nodules has significant clinical implications. Despite improvements in computed tomography (CT) and magnetic resonance imaging (MRI), tumor nodules less than 5 mm are rarely detectable before surgery, and some are overlooked during surgery [15]. PDD addresses the latter; used as an adjunct to diagnostic laparoscopy, PDD with ALA-PpIX fluorescence contrast increases the rate of PC diagnosis by as much as 30% [16].

Aggressive treatments for peritoneal metastasis, such as cytoreductive surgery with hyperthermic intraperitoneal chemotherapy [17], intraperitoneal chemotherapy [18], or pressurized intraperitoneal aerosol chemotherapy [19], have shown positive outcomes in some patients. PDT has also been investigated as an adjunct to cytoreductive surgery [20-24]. In principle, PDT is an attractive option, since the treatment effect is confined to the irradiated area and to a few millimeters below the tissue surface, while high accumulation of photosensitizer in cancer cells may provide a further level of selectivity. However, clinical experience to date is limited, and serious treatment-related complications have been reported [25], as discussed below.

The aims of this paper are: 1) to briefly review the current status and limitations of PDD and PDT for the treatment of PC originating from gastrointestinal or gynecological cancers, and 2) to consider potential approaches to overcome these limitations so that the advantages of PDT can be achieved with an improved safety profile in clinical practice.

STATUS OF PDD IN PC

Preclinical studies

Ovarian, colorectal, and gastric cancer cell lines have been used in mouse and rat models of PC with induced metastatic nodules (**Table 1**). ALA-PpIX is the most widely studied agent under blue light (405 nm) excitation, with detection of red (≥600 nm) fluorescence. Considering that clinical laparoscopy systems were used for these studies, the smallest detectable tumor size of approximately 0.5 mm should be comparable between patients

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Table 1. PDD: preclinical studies

Year	Author	Host animal	Cancer cell line	No.	Lesions	PS	Dose (mg/kg)	Route of administration	Time Interval (hr)	Wavelength (nm)	Additional detection of tumor?	Dx count or % using white light only	Dx (%) using white light+fluorescence	Sens.	Spec.	Smallest detected tumor (mm)	TNR
2014	Kondo et al. [26]	Mice	CRC (HT-29-GFP)	NA	-	5-ALA	250	ip	6	405	-	-	-	-	-	-	-
2012	Kishi et al. [16]	Mice	GC (MKN-45-GFP)	8	726	5-ALA	250	Oral	4	375–445	Yes	39%	71.6	-	-	0.130	-
2012	Alexander et al. [27]	Mice	OC (SHIN3-RFP)	51	555	hGSA-NMP1	250	ip	6	405	-	-	91	91	92	-	-
2009	Zhong et al. [28]	Mice	OC (OVCAR5)	8	171	BPD-MA	1	ip	1.25	455	-	-	-	86	53	0.010	-
2007	Collinet et al. [29]	Rats	OC (NuTu-19)	21	-	5-ALA, He-ALA	100	ip	2	350–440	Yes	WL (20.7), WL (33.6)	5-ALA (32), He-ALA (42.9)	-	-	Lesion <10 mm	1.22 (He-ALA), 1.17 (5-ALA)
2007	Regis et al. [30]	Rats	OC (NuTu-19)	16	235 (5-ALA), 248 (He-ALA)	5-ALA, He-ALA	100	ip	2	380–440	Yes	WL (198), WL (199)	5-ALA (235), He-ALA (248)	21	-	Lesion <2 mm	1.55 (He-ALA), 1.45 (5-ALA)
2005	Till et al. [31]	Rats	HB (HuH6)	7	-	5-ALA	3%	ip	3	375–440	No	57.1%	57.1%	-	-	-	6.34
2003	Ludicke et al. [32]	Rats	OC (NuTu-19)	11	88	5-ALA, HAL	ALA 8 mM, HAL 4–12 mM in 2 mL	ip	2	White light, 375–440	Yes	WL (82), WL (10)	HAL (154), 5-ALA (16)	-	-	-	4
2002	Chan et al. [33]	Rats	OC (NuTu-19)	9	105	5-ALA	100	iv	3	430–470	N/A	93%	95%	100	83.3	0.3	3.83
2002	Gahlen et al. [34]	Rats	CRC (CC531)	55	463	5-ALA	5 mL 3%	ip	8	380–440	Yes	NA	+35%	-	100	1	6.27
2001	Canis et al. [35]	Rats	OC (BD IX rat ovarian adenocarcinoma)	31	-	5-ALA	100	ip	3	380–440	Yes	-	-	-	-	0.5	-
2001	Gahlen et al. [36]	Rats	CRC (CC531)	12	296	5-ALA	5 mL, 3% 100 mg/kg	ip iv	4	380–440	Yes	WL (142), WL (116)	IP (172), IV (124)	-	-	1	-
2000	Aalders et al. [37]	Rats	CRC (CC531)	36	-	5-ALA	5, 25, 100	iv	24	405–430	-	-	-	-	-	-	3
1999	Gahlen et al. [38]	Rats	CRC (CC531)	5	-	5-ALA	5 mL, 3%	ip	4	380–440	Yes	-	-	-	-	-	4.7
1999	Gahlen et al. [39]	Rats	CRC (CC531)	6	172	5-ALA	5 mL, 3%	ip	-	380–440	Yes	142	172	100	100	0.5	-
1998	Hornung et al. [40]	Rats	OC (NuTu-19)	20	-	5-ALA	100	iv	1, 3, 6, 9	UV	-	-	-	-	-	0.4	-
1997	Major et al. [41]	Rats	OC (NuTu-19)	41	-	5-ALA	25, 50, 100 100	ip iv	6	310–395	-	-	-	-	-	<0.5	70% TNR>1, 30% TNR=1

PDD = photodynamic diagnosis; PS = photosensitizer ; Dx = diagnosis; TNR = tumor-to-normal ratio; CRC = colorectal cancer; 5-ALA = 5-aminolevulinic acid; ip = intraperitoneal; GC = gastric cancer; OC = ovarian cancer; hGSA-NMP1 = human galactosyl serum albumin conjugated NMP1 (bacteriochlorin-based near-infrared dye); BPD-MA = benzoporphyrin derivative monoacid; He-ALA = hexylester aminolevulinate; WL = white light; iv = intravenous; HB = hepatoblastoma; HAL = hexaminolevulinate; UV = ultraviolet.

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[35]. The sensitivity and specificity for in situ tumor detection were derived from examining of hundreds of metastatic nodules (e.g., 555 [27], 171 [28], and 105 [33]) and were within the range 21%–100% and 53%–100%, respectively. The diagnostic accuracy has been validated in experiments using tumor cells expressing red [27] or green [16,26] fluorescent proteins. Selective localization of photosensitizer in tumor versus normal tissue was measured by fluorescence spectroscopy and expressed as the tumor-to-normal ratio (TNR), and the reported values varied from 1.17 to 6.27. Time series measurements indicated that the maximum fluorescence intensity differed in tissues in different anatomical regions (small bowel, peritoneum, and liver) [37,40]. This has clinical implications, since PC nodules in a patient may have different fluorescence readings during PDD depending on the anatomical site and time between ALA administration and fluorescence detection. This requires further investigation.

Clinical trials

5-ALA is the only photosensitizer used to date for PDD of PC arising from gastric, ovarian, and pancreatic cancers (**Table 2**). In most studies, 20 mg 5-ALA was administered orally 3–4 hours before PDD. Unlike in animal models, not all patients had metastatic cancer nodules; therefore, the sensitivity and specificity could not be determined. However, the accuracy of PDD has been compared with that of white light tumor visualization: the detection rate under white-light (range, 11.7%–100%) [16,42,43,45,49,50,54,55] increased by an average of 10% (range, 0–33%) [26,43,45,49,53-56] when 5-ALA PDD was also used. In addition, fluorescence imaging identified patients with metastatic nodules that were missed under white-light investigation [43,45,49,55,56]. The prognostic impact of these additionally detected nodules was not determined. A study of 113 patients with metastatic nodules revealed by PDD, and subsequently resected, had survival times similar to those in 51 patients with no metastatic nodules [43]. However, this important finding needs to be confirmed using larger sample sizes. Regarding the size of peritoneal nodules that can currently be detected by PDD, Menon et al. [57] found that nodules as small as 1 mm in diameter contained measurable levels of PpIX. Interestingly, another study revealed no detectable fluorescence, even in primary tumors, in patients who underwent neoadjuvant chemotherapy prior to PDD [16]. Although the regimen and mechanism were not described in the report, this finding should be investigated in patients receiving neoadjuvant chemotherapy.

Complications associated with the diagnostic use of ALA-PpIX for fluorescence detection are rare. Since the PpIX concentration in skin peaks around 3–4 hours after ALA administration, and is undetectable by 24 hours [58], patients are advised to avoid direct sunlight and bright artificial lights for 1 day, and few complications have been reported. Self-limiting nausea and vomiting were the only morbidities reported following oral ALA administration at diagnostic doses (<30 mg/kg body weight); however, the possibility of adverse events should be considered during the procedure [46,54].

STATUS OF PDT IN PC

Preclinical studies

Ovarian cancer is the most common primary tumor that has been investigated in preclinical studies of PDT for PC, followed by gastric cancer (**Table 3**). A variety of photosensitizers and corresponding treatment wavelengths have been used in mouse and rat models. Thus, the treatment protocols have varied in terms of the photosensitizer-light time interval and light doses. Unlike human trials, repeat treatment schedules have been used often. Molpus et al.

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Table 2. PDD: clinical trials

Year	Author	Disease	No.	Surgery	PS	Dose (mg/kg)	Route	Time interval (h)	Wavelength (nm)	Detect additional patients?	Detect additional lesions?	Dx (%) using white light only	Dx (%) using white light+fluorescence	Sens.	Spec.	Complications
2018	Harada et al. [42]	PanC	34	SL	5-ALA	20	Oral	3	400	No	No	11.7	11.7	-	-	No
2017	Ushimaru et al. [43]	GC	113	SL	5-ALA	20	Oral	4	400	Yes	Yes	43.4	57.5	-	-	-
2017	Hillemanns et al. [44]	OC	20	SL	5-ALA	10	Oral	5	400	-	-	-	-	75	100	No
2016	Kishi et al. [45]	GC	38	SL	5-ALA	16.6	Oral	4	400	Yes	Yes	31.5	42.1	81.1	-	-
2016	Yonemura et al. [46]	Heterogenous	115	CRS+HIPEC	5-ALA	20	Oral	4	400	-	-	-	35.5	35.6	100	Nausea (1), vomiting (1)
2015	Yonemura et al. [47]	Heterogenous	138	CRS+HIPEC	5-ALA	20	Oral	2	400	-	-	-	45.6	46	100	-
2014	Namikawa et al. [48]	GC	21	SL	5-ALA	16.6	Oral	4	400	-	-	-	52.4	57.7	100	No
2014	Kishi et al. [49]	GC	52	SL	5-ALA	16.6	Oral	4	400	Yes	Yes	46.1	55.7	88.1	-	-
2014	Kondo et al. [26]	CRC	12	SL	5-ALA	20	Oral	3	400	-	Yes	-	66	-	100	No
2014	Liu et al. [50]	OC, PPC	20	CRS+HIPEC	5-ALA	20	Oral	2	440	No	-	100	100	95	100	No
2014	Canbay [51]	PPPSC	1	CRS+HIPEC	5-ALA	3.3	Oral	2	400	-	-	-	-	-	-	No
2012	Kishi et al. [16]	GC	13	SL	5-ALA	16.6	Oral	4	400	-	-	39	72	93	100	-
2012	Murayama et al. [52]	GC	13	SL	5-ALA	15	Oral	3	405	-	-	-	38.4	100	100	No
2006	Loning et al. [53]	OC, FTC	17	Second-look laparoscopy	5-ALA	30	ip	5	400	No	Yes	-	55	100	88	-
2005	Zopf et al. [54]	Heterogenous	30	SL	5-ALA	20	Oral	6	440	No	Yes	23.3	23.3	100	96	Sunburn (1), nausea (1), fever (1), bradycardia (1)
2004	Loning et al. [55]	OC	13	Second-look laparoscopy	5-ALA	30	ip	5	400	Yes	Yes	27.5	41.3	92	95	No
2000	Orth et al. [56]	PanC	12	SL	5-ALA	20	Oral	6	400	Yes	Yes	-	-	-	-	-

PDD = photodynamic diagnosis; PS = photosensitizer; Dx = diagnosis; PanC = pancreatic cancer; SL = staging laparoscopy; 5-ALA = 5-aminolevulinic acid; GC = gastric cancer; OC = ovarian cancer; CRC = colorectal cancer; PPC = primary peritoneal carcinoma; PPPSC = primary peritoneal papillary serous carcinoma; CRS+HIPEC = cytoreductive surgery hyperthermic intraperitoneal chemotherapy; FTC = fallopian tube cancer; ip = intraperitoneal.

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Table 3. PDT: preclinical studies

Year	Author	Host	Disease	No.	PS	Dose (mg/kg)	Route	Time interval (hr)	Wavelength (nm)	# repeats	Fluence (light dose, J/cm^2)	Primary endpoint
2017	Kato et al. [59]	Mice	PanC (AsPC1, BxPC3)	21	Mal3-Chlorin	1.25	ip	4	660	2	13.9	Tumor burden (day 21), cell death pathology (1 day)
2016	Harada et al. [60]	Mice	OC (SHIN3-luc-RFP)	20	GSA-IR700	0.025	ip	3	NIR	3	100	RLU (7 days)
2016	Ishida et al. [61]	Mice	GC (MKN-45-luc)	20	TRA-IR700	80 μg/mouse	ip	24	690	1	50	Survival (120), tumor burden (weight, 28 days)
2016	Yokoyama et al. [62]	Rats	OC (DISS)	20	5-ALA	250	ip	3	600	1	90	Survival (90 days)
2015	Li et al. [4]	Rats	OC (NuTu-19)	40	PBCA-NP-HB	10	ip	1	N/A	1	50	Survival (110 days)
2015	Sato et al. [63]	Mice	OC (SKOV-luc-D3, HER2$^+$)	64	TRA-IR700	100 μg/mouse	iv	24	NIR	1	100	RLU (14 days)
2014	Sato et al. [64]	Mice	GC (N87-GFP, Her2$^+$)	60	TRA-IR700	100 μg/mouse	iv	48	NIR	6	450	TV (24 day), survival(80D)
2014	Tsujimoto et al. [5]	Mice	GC (MKN-45-luc)	16	ICGm,s	100 μL	iv	48	808	1	500	Survival (70 days), tumor burden (number and weight of tumor, 21 days)
2013	Hino et al. [65]	Mice	GC (MKN-45 EGFP)	20	5-ALA	250	ip	5	410, 525, 635	1	4.5	Histologic response (48 hr)
2011	Mroz et al. [66]	Mice	CRC (CT26-Luc)	60	BB4	5	ip	24	White light, 540, 635	1	100	Survival (35 days), histology (24 hr)
2010	Estevez et al. [67]	Rats	OC (NuTu-19)	60	HAL	100	ip	4	532	Fract vs. Cont	45	Necrosis value (0–4) (1 day)
2010	Kishi et al. [68]	Mice	GC (MKN-45 EGFP)	30	Talaporfin	10	ip	4	664	1	10	Pathologic response (24 hr), toxicity (3 days)
2010	Piatrouskaya et al. [69]	Rats	Sarcoma (SaM-1)	18	Fotolon	2.5	iv	N/A	670	1	5	Necrosis area (pathology) (4 days)
2010	Raue et al. [70]	Mice	CRC (DHD/K12/TRb)	90	5-ALA	150	ip	6	630	1	N/A	Tumor burden (tumor weight, ePCI, day 21)
2009	Zhong et al. [28]	Mice	OC (NIH:OVCAR5)	7	BPD-MA	0.25	ip	1.5	690	1	25	Tumor burden (day 19)
2008	Ascencio et al. [71]	Rats	OC (NuTu-19)	36	HAL	100	ip	4	532	Fract vs. Cont	45	Necrosis value (0–4) (1 day)
2008	Ascencio et al. [72]	Rats	OC (NuTu-19)	52	HAL	100	ip	4	532	1	45	Necrosis value (0–4) (1 day)
2007	Ascencio et al. [73]	Rats	OC (NuTu-19)	54	5-ALA	60	ip	4	532, 630	1	150	Necrosis value (0–4) (1 day)
2007	Song et al. [74]	Rats	OC (NuTu-19)	26	HMME	10	ip	3	Red	1	50	Survival (60 days)
2005	del Carmen et al. [75]	Mice	OC (NIH:OVCAR5)	155	BPD	0.25	ip	1.5	690	1	20	Survival (180 days), tumor burden, weight (day 21)
2000	Molpus et al. [76]	Mice	OC (NIH:OVCAR5)	107	Ce6-OC125	1	ip	3	664	3	25J/mice	Survival (8 days), tumoricidal (72 hr), phototoxicity (N/A)
1998	Lilge et al. [77]	Mice	OC (NIH:OVCAR5)	40	BPD-MA	0.25	ip	1.25	690	3	45	Tumor burden (72 hr), irradiation dose
1996	Goff et al. [78]	Mice	OC (NIH:OVCAR3)	190	Ce6-OC125	0.5	ip	24	656	4	75	Survival (80 days), toxicity (1 hr)
1996	Molpus et al. [79]	Mice	OC (NIH:OVCAR5)	259	BPD-MA	2	ip	1.5	690	9	20	Survival (88 days), BPD-MA conc. in tissue, phototoxicity (72 hr), tumoricidal (72 hr)

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Table 3. (Continued) PDT: preclinical studies

Year	Author	Host	Disease	No.	PS	Dose (mg/kg)	Route	Time interval (hr)	Wavelength (nm)	# repeats	Fluence (light dose, J/cm²)	Primary endpoint
1991	Perry et al. [80]	Mice	Sarcoma (MCA-207)	40	Photofrin2	10	ip	24	630	1	2	Photofrin level (day 7)
1986	Tochner et al. [81]	Mice	Teratoma	80	HPD	10	ip	2	514	4	N/A	Survival (50 days)
1985	Tochner et al. [82]	Mice	OC (OECC)	68	HPD	50	ip	2	514	2	N/A	Survival (90 days)

PDT = photodynamic therapy; PS = photosensitizer; PanC = pancreatic cancer; Mal3-Chlorin = 5,10,15,20-tetrakis-(4-[b-D-maltotriosylthio]-2,3,5,6-tetrafluorophenyl)-2,3-(methano-[N-methyl]iminomethano)-chlorin; ip = intraperitoneal; OC = ovarian cancer; GSA-IR700 = galactosyl serum albumin and PS agent IR-700; PBCA-NP-HB = poly butyl-cyanoacryate nanoparticles entrapped with hypocrellin B; NIR = near infrared; RLU = relative light unit; GC = gastric cancer; TRA-IR700 = trastuzumab and PS agent IR-700; 5-ALA = 5-aminolevulinic acid; iv = intravenous; TV = tumor volume; ICGm = indocyanine green loaded lactosome; CRC = colorectal cancer; BB4 = N-methylpyrrlidinium-fullerence; HAL = hexaminolevulinate; BPD-MA = benzoporphyrin derivative-monoacid; N/A = not applicable; HMME = hematoporphyrin monomethyl ether; Ce6-OC125 = chlorin e6 conjugated with murine anti-ovarian cancer monoclonal antibody; HPD = hematoporphyrin derivative.
*Fluence noted is either the highest dose group compared to the validated dose after the initial dose-finding study.

(benzoporphyrin derivative monoacid [BPD-MA], 690 nm activation) [79] and Kishi et al. (talaporfin, 664 nm) [68] reported details of phototoxicity, photosensitizer biodistribution, tumor response, and survival following treatment. Kishi et al. [68] used (laser) light doses of 2, 5, or 10 J/cm² at 2 or 4 hours after talaporfin injection in mice. Animals treated with 2 J/cm² at 2 hours drug-light interval died of intestinal perforation within 2 or 3 days, whereas there were no complications in the group treated with 2 J/cm² at 4 hours [79]. The efficacy of different treatment wavelengths has also been investigated. For example, Hino et al. [65] used 5-ALA and 4.5 J/cm² of violet (405 nm), green (532 nm), or red (635 nm) light delivered at laparotomy. Furthermore, Mroz et al. [66] used fullerene nanoparticles as the photosensitizer, with white (400–700 nm), green (540 nm), or red (635 nm) external-beam irradiation at a light dose of 100 J/cm². Overall, red light demonstrated an inferior therapeutic effect despite its common use in ALA-PpIX PDT for other indications, such as interstitial PDT for pancreatic [83] and brain tumors [84]. Several studies have used other photosensitizers activated by near-infrared light following external application [5,59-61,63,64]. This approach was effective, because the small body size of mice allowed the light to penetrate the abdominal wall into the peritoneal cavity; however, it would be ineffective in patients. Indeed, as discussed below, a major technical challenge in PDT for PC is how to deliver the treatment light so that all tissue surfaces within the complex anatomy of the peritoneal cavity receive an adequate light dose to optimize the efficacy and safety.

Clinical trials

Data from limited clinical trials of PDT in PC have been published (**Table 4**). In all cases, PDT was applied in a single session as an adjunct to cytoreductive or debulking surgery. Multiple factors need to be considered to optimize the efficacy versus safety profile of intraperitoneal PDT, including the choice of photosensitizer, the photosensitizer-light time interval, the irradiation wavelength, and the light dose and dose rate.

Photosensitizer

Each photosensitizer has unique pharmacokinetic and optical absorption (activation) characteristics. Patients in clinical trials on the first-generation photosensitizer, Photofrin® (Pinnacle Biologics, Inc., Bannockburn, IL, USA) [20,22,24,85], were instructed to avoid direct sunlight for 6 weeks after PDT. Second-generation photosensitizers (e.g., meta-tetrakis[3-hydroxyphenyl]chlorin [mTHPC] and 5-ALA) are more convenient because they

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Table 4. PDT: clinical trials

Year	Author	Design/aim of study	Disease	No.	PS	Dose (mg/kg)	Route	PS-light time interval (hr)	Wavelength (nm)	Fluence (light dose, J/cm²)	Boost (light dose, J/cm²)	Survival	TNR	Photosensitivity period	Major complications
2006	Hahn et al. [20]*	Phase 2: efficacy and toxicity	Heterogenous	71	DHE	2.5	iv	48	532/630	2.5	15	Little benefit	2.1	60 days	Two deaths: myocardial infarction and sepsis (bleeding → reoperation → sepsis), 4 bowel fistulae or anastomotic leak, 2 wound infection, 2 delayed wound healing, 3 prolonged ileus or small bowel obstruction, 20 grade 1–2 photosensitivity, common "capillary leak syndrome"
1997	Wierrani et al. [21]†	Phase 1: efficacy and side effect	GYN tumors	8	mTHPC	0.15	iv	96	652	5	-	Good	4.5	24 hr	One cardiac insufficiency death, 1 ileus 28 months after PDT death, 3 cutaneous burn on the hands
1995	Harlow [22]	PDT effect	CRC	8	Photofrin	2	iv	48	488/514	50	-	Little benefit	-	1 mo	One burn to perineum and ureteral leak, 1 MI (not PDT related)
1994	Allardice [23]	Adjuvant intraoperative PDT effect	CRC (+other)	17	HPD	5	iv	48	510	50	-	-	-	NA	One heart attack, 3 anastomosis break down, 3 skin burn, 1 subphrenic abscess requiring drainage
1993	Delaney et al. [24]‡	Phase 1: maximum tolerated dose	OC (+other)	39	DHE	2.5	iv	48	514	3.75	15	Good	-	6 weeks	Three small bowel perforations, 2 pleural effusion, thoracentesis, 1 gastric perforation, 1 colo-cutaneous fistula
1986	Herrera-Ornelas et al. [85]	Pain relief	CRC	14	DHE	2	iv	96	630	3	-	Good	-	6 weeks	One first-degree sunburn at the time of 2 weeks after Tx, 1 second-degree burn on unprotected perineum

PDT = photodynamic therapy; PS = photosensitizer; TNR = tumor-to-normal ratio; DHE = dihematoporphyrin ethers; iv = intravenous; GYN = gynecological; mTHPC = meta-tetrakis(3-hydroxyphenyl) chlorin; CRC = colorectal cancer; HPD = hematoporphyrin derivative; OC = ovarian cancer; MI = myocardial infarction.
*Han et al. [20] published other reports [25,57,86-89] based on this clinical trial. †Wierrani et al. [21] published a further report [90] based on this clinical trial. ‡Delaney et al. [24] published other reports [91,92] based on this clinical trial.

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require the avoidance of direct sunlight or bright artificial light exposure for only 24 hours and are associated with lower systemic toxicity [21].

Photosensitizer-light time interval

The optimum time for PDT following photosensitizer administration depends primarily on the rates of uptake and clearance in tumor and normal host tissue. In addition, using a short drug-light interval ensures the photosensitizer is still in circulation, meaning that the primary anti-tumor effect is mediated by microvascular damage, primarily thrombosis; this strategy has been employed in the PDT of solid tumors [93]. However, since PC usually involves small and superficial targets following surgical debulking, and considering that oxygen diffusion can reach approximately 200 μm in tissue [94], using a longer interval to allow photosensitizer uptake by the tumor cells is preferred for direct photodynamic killing.

Treatment light wavelength

The optimum treatment wavelength for relatively superficial disease as in PC may differ from that for interstitial PDT of bulk tumors. For example, in the PDT of prostate cancer, in which a minimum light dose is required throughout a significant tissue volume [95], red or near-infrared light (up to 630–800 nm) is advantageous because of its deeper penetration, mainly due to reduced absorption of light by hemoglobin. Conversely, in PC, the risk of bowel perforation is less at shorter (e.g., blue or green) wavelengths. The light penetration depth in tissue generally increases with wavelength, and clinical trials have assumed that red and green light provide effective treatment depths of up to 5–10 mm and <3 mm, respectively [89,91,96]. Even with red light, the response of bulky tumors may be poor, as reported for rectal cancer [22]. An alternative is to perform cytoreductive debulking surgery followed by PDT with green light, with the option of adding a selective boost dose with red light in cases of gross tumor involvement [20,24]. If the photosensitizer has significant absorption at shorter wavelengths, as with porphyrin-based compounds, it may also be possible to reduce the total light energy dose while generating sufficient singlet oxygen for effective treatment, assuming that the full depth of the tumor can be adequately treated.

Light dose and rate

Tissues, including tumors, generally display a threshold behavior to PDT; that is, a minimum photosensitizer-light dose product needs to be reached to induce necrosis (or other endpoint) [97]. For a given tissue concentration of photosensitizer, the effective treatment depth is logarithmically proportional to the applied light dose (J/cm^2); thus, to double the treatment depth, an approximately four-fold increase in light is required. This is a purely biophysical effect. However, a light dose that is high enough to induce significant tumor necrosis may also generate damage-associated molecular patterns (DAMPs), initiating an inflammatory response that triggers immune upregulation, which contributes to the overall tumor response [98]. At lower doses, PDT-induced apoptosis may still occur, but rarely stimulate an immune response, while at very low doses there may be increased tumor cell growth [99]. Conversely, delivering too high a light dose risks causing damage to normal tissue within the light field, unless there is a high tumor-to-normal tissue photosensitizer concentration. In general, the rate of light delivery in clinical PDT is selected to avoid significant tissue heating, typically being below approximately 200 mW/cm^2 for well-perfused tissues. This has been reported for all clinical trials in PC to date [20,85]. Dose rates as low as 10 mW/cm^2 demonstrated efficacy in a preclinical study [81], since this avoids the tissue oxygen being photochemically depleted faster than it can be replenished by blood perfusion, at least in relatively hypoxic (e.g., tumor) tissue.

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CONSIDERATIONS FOR THE CLINICAL APPLICATION OF PDT IN PC

In this section, we will consider the factors that contribute to the efficacy and safety of PDT for PC in clinical practice. As summarized above, intraperitoneal PDT has demonstrated favorable outcomes in terms of tumor responses [24,85,90]. However, because the patient cohorts have been heterogeneous within and between studies, and have included patients with various primary tumors (colorectal, ovarian, and sarcoma), the clinical benefits of PDT remain unclear. Interestingly, one study performed a recurrence-pattern analysis to assess the treatment response [87], which suggested the value of PDT for local control, based on recurrence being rarely observed at sites treated by a PDT boost dose.

Regarding safety, the high rates of adverse events, primarily perforation of the stomach, small intestine, and colon, as well as capillary leak syndrome, currently limit the clinical application of PDT. Some studies have also reported ureteral injury, but it is unclear whether this was related directly to the PDT [22,91]. One report described bilateral ureteral leaks that required bilateral nephrostomies for urinary diversion [22]. Capillary leak syndrome is the most serious toxicity reported, manifesting as tachycardia and hypotension requiring massive fluid resuscitation and prolonged mechanical ventilation, with a high incidence of pulmonary complications and significant whole-body edema [20,25,89]. The effects occurred during the first 4–5 days post-PDT, peaking at 1–3 days. Patients typically received a net positive fluid balance of 20 L in the first 24 hours [20]. A retrospective analysis of a phase II trial [25] found that this syndrome was significantly associated with surgical duration and nodule number. However, the analysis did not include the light irradiation dose. Thus, we assume that more extensive light irradiation follows more extensive surgery. The degree of systemic inflammatory response following cytoreductive surgery with PDT is more severe than in other major gastrointestinal surgeries, such as hepatectomy, pancreaticoduodenectomy, and esophagectomy. Thus, one can infer indirectly that trauma associated with intra-peritoneal PDT significantly contributes to capillary-leak syndrome.

Using conventional PDT treatment protocols comprising single doses of photosensitizer and light, the greatest challenge for improving the clinical efficacy is to increase the tumor specificity of the photosensitizer, such that greater tumor control can be achieved using higher light doses while limiting off-target toxicity. A technical challenge for light delivery is ensuring that a minimum (threshold) light dose is delivered throughout the peritoneal cavity. Here, we will consider other novel approaches that may alter the equation for optimizing the photosensitizer and light parameters.

Route of photosensitizer administration

The pharmacokinetics and biodistribution of photosensitizers depend on the route of administration, as well as on their intrinsic properties. Perry et al. [80] evaluated the efficiency and toxicity of Photofrin2 following intraperitoneal (ip) injection versus intravenous (iv) administration in a mouse model [80]. The results suggested that ip injection is a safer and more effective route than iv administration. Kishi et al. [68] reported similar preclinical findings with talaporfin, leading to a switch from iv to ip administration. In clinical trials, Loning et al. [53,55] delivered 5-ALA ip without complications. Considering that ip photosensitizers can be absorbed on the surface of the peritoneal organ, which is analogous to topical treatments for skin tumors, direct uptake into tumor nodules may improve the tumor-to-normal tissue profile if the photosensitizer is distributed throughout

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the peritoneal cavity. Depending on the formulation, a fraction of the total photosensitizer dose will enter the circulation and be delivered through the systemic route. Optimizing the formulation and dispersal of photosensitizers for ip administration to achieve the highest tumor uptake and TNR should be elaborated in future studies.

Irradiation schedule

During the early development of X-ray therapy, large single doses of radiation were found to be less effective and caused greater damage to normal tissue than multiple small doses (fractionation), which is now standard clinical practice. PDT has generally been delivered in a single session, partly because it is necessary to reach a minimum threshold dose. This approach has been successful in a variety of tumors and stages [12,13,95] and has the added advantages of patient/clinician convenience and of avoiding the need for multiple photosensitizer administrations. However, there are exceptions to this. For example, Kato et al. [59] used two irradiation sessions, on days 0 and 7, to kill disseminated pancreatic cancer cells following ip administration of Mal3-Chlorin (maltotriose-conjugated chlorin) in a mouse model. Harada et al. [60] delivered light irradiation daily for up to 3 days using a near-infrared photosensitizer (GSA-IR700) in an ovarian cancer mouse model. Furthermore, Sato et al. [64] delivered 50 J/cm^2 on day 1 and 100 J/cm^2 on day 2, and repeated these conditions every week for up to 3 weeks with the photosensitizer TRA-IR700 in a gastric cancer mouse model. Using BPD-MA, Molpus et al. [79] delivered 20 J light irradiation in three to five treatments at 3–7-day intervals in a murine tumor model. The rationale for this approach was to exert the maximum therapeutic effect and reduce complications. Other preclinical studies have demonstrated that fractionized PDT using a relatively low light dose performed better than conventional single high-dose PDT [67,71].

A more radical approach, termed metronomic PDT (mPDT), has been proposed by Wilson and colleagues [11,84,100,101], in which both the photosensitizer and light are delivered continuously or in many small fractions at very low rates over an extended period. This is analogous to metronomic chemotherapy using low doses over an extended duration [102], although the mechanisms of action differ. Thus, in an intracranial glioma model, ALA was administered without toxicity in drinking water at a low rate of 100 mg/kg per day over several days. An optical fiber implanted in the tumor delivered light at 23 μW/cm^2 over 5 days, for a total energy dose of 10 J/cm^2, which was comparable to the total dose used in conventional "acute" single-fraction PDT [84]. Importantly, tumor cells underwent apoptosis with no evidence of necrosis. Additionally, there was no evidence of either necrotic or apoptotic damage to the adjacent normal brain, and post-PDT edema was reduced. This concept has been used clinically, at least in multiple-fraction rather than full continuous metronomic mode, for treating chest wall recurrences in patients with breast cancer [103,104]. We suggest that this strategy could be used for intraperitoneal PDT of PC, with treatment extending over several days, which would also allow treatment to be terminated if side effects are observed. The limitations of mPDT include the potential for increased tumor growth if the tumor is very aggressive [99] and the risk that apoptotic cell death may not trigger an immune response that contributes to the anti-tumor efficacy of PDT [98,105]. The main technical challenge will be how to safely deliver light at a low-dose rate throughout the peritoneal cavity. We are currently addressing this; at least in principle, one could envisage metronomic treatment being delivered even in an ambulatory setting following intraoperative source implantation.

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Uneven bowel contours

The small bowel, large bowel, and omentum are packed tightly into the peritoneal cavity; therefore, irradiating the entire peritoneal surface with a uniform dose is technically challenging during PDT light delivery. Historically, light-scattering media [106] have been used to distribute light more uniformly in order to improve treatment efficacy. A National Cancer Institute report described protocols for irradiating and monitoring light energy in the peritoneal space [24,91]. Thus, diluted (0.2%) Intralipid™ (Sigma-Aldrich, St. Louis, MO, USA), a liquid fat-protein suspension used for intraparental feeding, served as the light-scattering medium to distribute light into deep-seated bowel surfaces. A diffusing "wand" connected to a laser source was used for light delivery, protecting the tissues from thermal or mechanical injury due to direct contact [91]. In a subsequent study, 1.5% dextrose peritoneal dialysis solution was used instead of Intralipid, which caused hypocalcemia and hypomagnesemia. In turn, this was then changed to Ringer's solution with 1.7 mEq/L additional magnesium [24]. The visceral peritoneal surfaces (diaphragm, omentum, retroperitoneal gutters, pelvis, and abdominal wall) were illuminated by manually moving the wand, which comprised an optical fiber placed within a cuffed endotracheal tube, capped and filled with 0.1% lipid emulsion, with 0.02% emulsion used to inflate the cuff.

The delivered light intensity (fluence rate, mW/cm^2) was continuously monitored during irradiation by a photodiode sutured to the tissue surface in the right upper quadrant, left upper quadrant, and pelvis, with an additional, untethered diode placed in the target region. The wand was moved manually to achieve the highest uniformity in light delivery by equalizing the cumulative light dose received by the photodetectors. Depending in the organ, the target light dose was 5–10 J/cm^2, and was calculated (according to the power of light delivered by the wand), based on the surface of each region as a percentage of the total peritoneal surface, and assuming that the body surface area was the same as the peritoneal surface area [107]. Measuring the delivered light dose in this complex setting is challenging [108], and the use of an anatomical phantom to simulate, and thereby optimize, intraoperative PDT has been proposed [109]. There is significant room for improvement in the process of light-delivery and monitoring. For example, there could be more extensive use of multiple distributed light sources for the simultaneous illumination of different intraperitoneal surfaces, and by continuous imaging and multiple point measurements of the light distribution, with automatic feedback control to dynamically adjust the power from each light source. This type of on-line monitoring and control system has been used for other complex anatomical sites, such as whole-prostate PDT [110], guided by pre-treatment planning based on volumetric CT or MRI.

Surgical procedure

Several minor surgical issues could result in large differences in the efficacy of PDT. First, since blood on a tissue surface strongly absorbs the activating light (to a greater or lesser extent, depending on the wavelength), complete hemostasis should be ensured [23]. Likewise, when the peritoneal cavity is filled with a light-scattering fluid, it is important to avoid blood contamination, since the increased path length of the light amplifies the effect of hemoglobin absorption, such that continuous or frequent fluid exchange during light irradiation may be required. Second, bowel edema, ascitic fluid collection, and subsequent ileus are common after PDT of PC. One clinical trial reported a high incidence of perforations at the anastomosis sites [24], although there was no histological evidence of injury except at the enterotomy. Thus, the PDT-induced edema was thought to cause traction on the staple line or focal ischemia and subsequent perforation. Transient thrombocytopenia is also

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commonly observed in PC patients receiving PDT [24,89]. Although this was self-limiting, it could increase surgical morbidity.

CONCLUSIONS

Photodynamic diagnosis, that is, fluorescence imaging or point spectroscopy of the photosensitizer, could be used as an adjunct to improve the detection of otherwise unidentified peritoneal metastasis during diagnostic laparoscopy. Except for some self-limiting skin photosensitivity, the photosensitizer is associated with minimal side effects, given that low (sub-therapeutic) doses and light exposures are used. Since diagnosis of peritoneal metastasis is critical for clinical decision making, PDD is likely to become standard clinical practice. The main issue is which fluorescent agent to use (which may or may not be photodynamically active), while issues around the additional costs for the equipment and the photosensitizer, as well as the increased procedural time, are also important practical factors.

Regarding photodynamic treatment, the limited thickness of intraperitoneal nodules, especially after surgical debulking, makes PDT a suitable modality, given that the limited light penetration protects underlying organs from injury. The effective treatment depth depends on the photosensitizer, its concentration in the target tumor, the tumor-to-normal tissue selectivity, as well as the treatment wavelength, tissue optical properties at this wavelength, and tissue oxygenation. To date, clinical trials of PDT in PC have demonstrated moderate anti-tumor efficacy, but high complication rates. Therefore, the various treatment parameters, particularly the photosensitizer selectivity and light delivery, require further development and optimization to translate this modality into routine clinical practice with safe and reliable outcomes. Given i) the diverse range of photosensitizers available (including, in the future, active tumor targeting), ii) the increasing sophistication of PDT treatment planning, delivery, and monitoring technologies that have been demonstrated in the PDT of other cancers, iii) the use of novel photobiological strategies such as mPDT, and iv) the full exploitation of the immune effects of PDT, clinical translation and adoption are likely to be feasible in the foreseeable future. Current research in our laboratory on mPDT and specialized light delivery systems will hopefully advance this field.

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