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Review

The capability and potential of new forms of personalized colon cancer treatment: Immunotherapy and Photodynamic Therapy

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ABSTRACT

Introduction: PDT can interfere with cytokine-mediated responses that play an important role in the processes of cancer progression, tumor angiogenesis and metastasis. Therefore, based on the identification of these cancer biomarkers, the therapy of combining various forms of treatment, including immunotherapy and PDT, may be a justified strategy for colorectal cancer treatment that focuses on individualized comprehensive therapy.
Method: We reviewed the major approaches on the use of immunotherapy in colorectal cancer, with the special regard to photodynamic therapy, its immunological effect and new oncological treatment directions, connected with adjuvant immunotherapy including use of nanoparticles. Databases such as PubMed, ScienceDirect and Springer were utilized to search the literature for relevant articles.
Purpose: To review studies of the immunotherapy in colon cancer and immune response to PDT.
Conclusion: Based on the identification of immunological cancer biomarkers, the therapy of combining various forms of treatment, including immunotherapy and PDT, may be a justified strategy for colorectal cancer treatment that focuses on individualized comprehensive therapy.

1. Photodynamic therapy

Classical radical and palliative treatments have been joined by new therapies that are used currently as complementary therapies, but it is possible that in the future they will become treatments of choice. One of them is photodynamic therapy (PDT), which is non-invasive method of treatment for premalignant and neoplastic lesions, based on low- and medium-energy monochromatic light combined with a photosensitizer. This method, in combination with preceding photodynamic diagnosis (PDD), distinguishes the cancer-altered area against the background of healthy tissue, with the possibility of determining the boundary between them. The antineoplastic effect of photodynamic therapy is based on the effect it exerts on the host immune and inflammatory responses, as well as on the direct cytotoxic mechanism and the indirect mechanisms of occlusion of lymphatic and blood vessels and of the induction the complex immune response that potentiates antitumor immunity and could destroy also residual cancer cells (Fig. 1).

The underlying mechanisms responsible for these effects are poorly understood but are likely to involve mediation by cytokines and induction of a T cell response crucial for systemic tumor eradication. The biggest problem in cancer treatment is the recurrence of cancer associated with the presence of residual cancer cells [1–6], which leads to the progression of tumor growth and metastasis by the secretion of progression factors (Fig. 2).

The experimental and clinical studies demonstrate the importance of combined therapy as well as the expected benefits of PDT using immunoregulatory mechanisms. Photodynamic therapy can interfere with the cytokine-mediated response chain, including IL-6 that plays an

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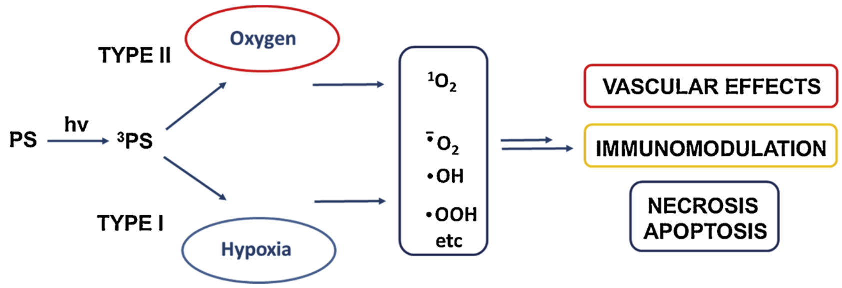

Fig. 1. A simplified diagram depicting photodynamic therapy mechanisms of action.

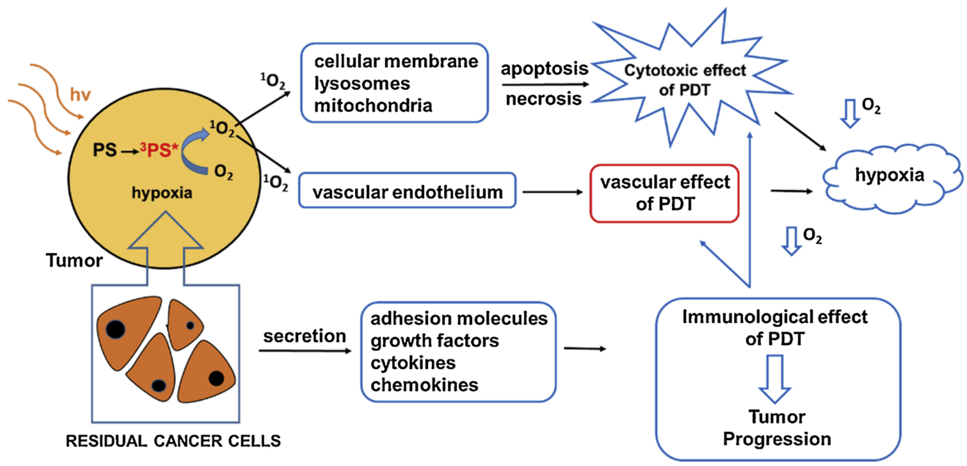

Fig. 2. A scheme of immunological effects induced by the photodynamic processes.

important role in the processes of cancer progression, tumor angiogenesis and metastasis. Therefore, based on the identification of these cancer biomarkers, the therapy of combining various forms of treatment, including immunotherapy and PDT, may be a justified strategy for colorectal cancer treatment, focusing on individualized comprehensive therapy.

The new oncological strategy of immunotherapy activates the immune system, enhancing its natural role and is studied as one of the most promising treatments not only for the inhibition of recurrence but also for the treatment of recurrent and metastasized cancer.

2. Overview of immunotherapy in colorectal cancer

The key factors determining the progression of colorectal cancer are inflammation and anti-cancer immunity [7]. Increased activity of Interleukin 4 (IL-4) in the early stages of colorectal cancer, hyperplastic polyps, adenomas, and its low concentration in the adenocarcinoma was demonstrated [8]. The IL-4 and IL-13 alpha receptor was tested in an experiment in a mouse colorectal cancer model associated with inflammation induced by AOM and DSS expression. The component of this receptor for both interleukins caused a decrease in the number of tumor [9]. Interleukin, which is involved in the development, invasion and metastasis of colorectal cancer, is IL-6 [10,11]. Studies show a higher concentration in patients with colorectal cancer than in a healthy population [12], while it is a bad prognostic [13,14]. IL-8 and VEGF are involved in tumor angiogenesis, which favors cancer recurrence, and IL-8 expression is higher [15,16]. In addition, they affect growth, metastasis, chemical resistance and tumor angiogenesis [17,18]. It has been shown that IL-8 contributes to an increase of $\alpha v\beta 3$ integrin concentration, which is a key proangiogenic factor, and, secreted by mesenchymal stem cells promotes angiogenesis and growth of colorectal cancer. In all stages of colon cancer, increased expression of both genes is observed [19]. IL-8 possesses the CXRC2 receptor, with which they may play an important therapeutic role, may have antitumor activity but also sensitize the tumor to chemotherapy [20]. Thanks to these disadvantageous properties, IL-8 may become a new therapeutic target for the treatment of colorectal cancer in the future. For poor prognosis and shorter survival, the receptor is expressed for Interleukin 9 by phosphorylation of STAT5 [21,22]. Patients with colorectal cancer show a lower concentration of IL-9 in serum and intestinal tissues and this correlates to the progression of colon cancer [23]. Decreased survival of patients is associated with an increase in serum IL-10 in patients with progression of colorectal cancer [24,25]. The newly-described cytokine belonging to the IL-6 subgroup is IL-11, both it and its receptors are overexpressed in colon cancer and its tumor activity is stronger than IL-6 [26]. Another new interleukin that belongs to the IL-1 family is IL-33. The experiment showed that its overexpression in intestinal adenomas and adenocarcinomas, stimulates carcinogenesis and increases its concentration in cancer patients [27–29]. Despite the treatment being used, new methods are always sought that will improve patients' survival and reduce side effects. One of the methods that has a promising effect is immunotherapy, which involves the use of drugs to help your immune system better recognize and destroy cancer cells [30]. There are satisfactory reports of the use of immunomodulatory monoclonal antibodies (Abs) ipilimumab, nivolumab and pembrolizumab, which may be a breakthrough in anticancer therapy for the treatment of colorectal cancer [31]. The first clinical trial with chemoimmunotherapy was conducted in 2008 in patients with colorectal cancer. The patients were followed by chemotherapy followed by granulocyte colony stimulating factor and IL-2, prolonging progression and survival. The results of the study suggest that chemoimmunotherapy may be used as a new first line treatment regimen in patients with advanced colorectal cancer [32]. In 2017, the US FDA approved the use of nivolumab in patients with colorectal cancer [33]. Another suggestion for the treatment of colorectal cancer is autologous vaccines, which use cells removed from the patient's tumor. In this way, the vaccine will contain tumor-associated antigens individually for the patient [34], although to date they have been of limited effectiveness.

Another study combined IL-2 based and IFN-β based gene therapies to study anticancer effects. Studies in mice have shown that injection of IL-2 and IFN- β inhibits tumor growth and induces apoptosis *in vivo* [35]. Cytokine therapies which are currently being used in cancer treatment include IL-2 which has FDA approval for use in melanoma and renal cell carcinoma (RCC) and also IFN-α which is being studied in the treatment of multiple hematological malignancies as well as cervical cancer, carcinoid syndrome, medullary thyroid cancer, basal cell and squamous cell carcinoma. There have been limited studies involving cytokine therapies in CRC [36]. A phase I study of PEGylated recombinant IL-10 (AM0010) administered daily subcutaneously for 4 months to 33 patients with advanced solid tumors (including four CRC patients) showed that this had a manageable safety profile and resulted in a sustained systemic Th1 immune stimulation [37].

3. Photodynamic therapy with particular emphasis on its immunological effect and resulting from this the need of immunotherapy use in colorectal cancer

The problem of the efficacy of PDT against deep tumors is a consequence of low light penetration. Therefore, new directions have been explored in combining PDT with other treatment modalities with the hope of improving its effectiveness [38]. Additionally, due to solid tumor hypoxia, the therapeutic efficacy of PDT is also largely limited. On the other hand, PDT has additional functions associated with immunological effects. Photodynamic therapy not only directly kills cancer cells, but also could promote antitumor immune responses by different cellular pathways, including producing tumor-associated antigens [39]. Because of the shortcomings of PDT associated with limited light penetration depth, there are new research divisions connected with the combination of nanoparticles and organic photosensitizers [40].

The immunomodulatory effect is mainly seen during the use of PDT at cellular sublethal doses, which stimulate the immune system to wider antitumor responses through the activation of NK cells, neutrophils, tumor infiltration by leukocytes, the presentation of tumor antigens to T cells and appearance of heat shock proteins. Tumor cells prejudiced by PDT release factors modulating their proliferation and migration, e.g. macrophage migration inhibitory factor (MIF), which is reflected to be a determinant of colorectal carcinogenesis process. In our previous study, an increase of MIF secretion by colon cancer cells SW480 and SW620 after ALA-induced photodynamic effect was observed, simultaneously implying the need of immunotherapy against MIF and combination with ALA-PDT to improve its outcome in colon cancer treatment [41]. Wawrzyniec et al.,

in experiments on the colon cancer cell lines SW480 and SW620, revealed the negative effect of ALA PDT, manifesting in the stimulation of the secretion of granulocyte and macrophage colony stimulating factor (GM-CSF) [1]. GM-CSF induces tumor associated macrophages (TAMs) transformation from the M2 to M1 form, which plays a crucial role in macrophage antitumor activity. On the other hand, GM-CSF also stimulates cancer cells to growth and progress. For this reason, the authors emphasized that in order to exclude this undesirable effect of GM-CSF, PDT might be used in combination with GM-CSF antibody or other agent against this cytokine.

Interleukin 8 (IL-8) is a chemokine implicated in tumor development, maintenance, metastasis, and recurrence [18]. It participates in the inflammatory response by triggering leukocyte chemotaxis. It also acts on endothelial cells through the receptors that activate migration, invasion and proliferation of cells- a process that leads to angiogenesis [6]. The IL-8 receptors are CXCR1 (IL-8RA) and CXCR2 (IL-8RB) from the G-protein coupled receptor family (GPCR). They mediate neutrophil infiltration to the tumor microenvironment, which promotes metastasis [42]. When secreted by tumor cells, IL-8 further promotes tumor growth, invasion, angiogenesis and treatment resistance [43–45]

It is produced by most tumors and several studies have shown that cancers with high metastatic potential secrete relatively more IL-8 (e.g. melanoma and pancreatic cancer). Due to the association of IL-8 secretion levels with malignancy, metastatic potential and recurrence of gastrointestinal (GI) tract tumors it is often used as a prognostic factor in GI tract cancer treatment [16,17,46]. The increased secretion of IL-8 induced by ALA-PDT that we observed *in vitro* may explain tumor progression in clinical trials, where the effect of ALA-PDT was incomplete or the dose was sub-lethal. It is possible that IL-8 is also responsible for the resistance of colon cancer cells to PDT treatment by a mechanism similar to that involved in chemotherapy resistance. As such, determining IL-8 concentration is important in clinical practice and helps clinicians to choose appropriate treatment strategies including PDT with adjuvant immunotherapy for patients with colorectal cancer characterized by high IL-8 levels.

Secretion of these cytokines is likely linked to the malignant character and metastatic potential of the cancer cells. It was also demonstrated that PDT can enhance antitumor immune responses by release of biomarkers and danger signals, supporting combination protocols of PDT with immunotherapy. In our previous study, it was revealed that sublethal ALA-PDT has a negatively impact on tumor growth and metastasis by stimulation of IL-8 release from colon cancer [5]. This adverse effect of ALA-PDT implicates the necessity of the use of adjuvant therapies such as immunotherapy.

Currently, the combination of PDT with immunotherapeutic methods such as checkpoint block is a perfect aim of interest to realize antireccurance and antimetastatic therapy.

Because of immunoadjuvant limitations such as large sizes, low cellular uptake capacity and biocompatibility, and poor therapeutic efficacy Ding et al. performed a research study with monodispersed large-pore mesoporous-silica-coated β-NaYF4:20%Yb,2%Er UCNPs and found that UCMSs–MC540–OVA under 980 nm NIR irradiation provided the best synergistic immunopotentiation action verified by the strongest Th1 and Th2 immune responses and the highest frequency of CD4 +, CD8 +, and effector-memory T cells *in vivo* [47]. By loading of TF as antigens on UCMSs–MC540, the nanovaccines UCMSs–MC540–TF strongly inhibited tumor growth and prolonged lifetimes of CT26-tumor-bearing BALB/c mice compared with either PDT or immunological therapy alone.

Yang et al. designed enzyme-encapsulated photosensitizer-loaded hollow silica nanoparticles with rationally designed surface engineering as smart nanoreactors with a pH responsive surface coating, and revealed that in this form, PDT can target mitochondria and that this cellular organelle is the most sensitive to ROS [48]. The combination of nanoparticle-based PDT with check-point-blockade therapy could kill nonirradiated tumors 1–2 cm away, and this therapy is also promising for metastases.

Bao et al. used a combination of IRD-αCD276/Fab PDT with anti-PD-L1 therapy *in vivo* in 4T1 tumor-bearing mice divided into five different groups [49]. Mice were injected with PBS, and tumors were irradiated for 2 h postinjection of IRD-αCD276/Fab or IRD-IgG/Fab using a 690 nm laser (at 70 J/cm^2). At the end of this dual therapy, mice were euthanized and examined for lung metastases. The experiment revealed, that tumor PD-L1 levels were markedly increased after PDT using IRD-αCD276/Fab, as evidenced by noninvasive PD-L1-targeted small-animal PET imaging. In combination with an anti-PD-1/PD-L1 blockade, IRD-αCD276/Fab PDT markedly suppressed the growth of tumors and prevented their metastasis to the lung by recruiting the tumor infiltration of CD8 + T cells. Bao's data confirmed that CD276-targeted PDT for local immune modulation, and its combination with PD-L1/PD-1 axis inhibition is a promising strategy for eliminating primary tumors as well as disseminated metastases, by engendering antitumor reactions.

The results of experiments conducted by Smith et al. demonstrates that cell targeting using Photofrin® conjugated to monoclonal antibodies can result in significant reduction of tumor size in a LoVo xenograft tumor model *in vivo*. Photodynamic therapy was performed after intravenous injection of immunoconjugates, or neat Photofrin®

into mice bearing two tumors; one was irradiated, while the second was dark (control). Photofrin® was injected at a standard dose for PDT in mice. Then, two relevant (anti-CD104-porphyrin 1 and anti-CD104-porphyrin-2) conjugates and two irrelevant (anti-CD146-porphyrin 1 and anti-CD146-porphyrin-2) conjugates (controls) were investigated, and compared with Photofrin®. The immunoconjugates induced apoptosis *in vitro* (verified with experiment with annexin V/propidium iodide and caspase assays) on the level of the mitochondrial membrane [50]. Relevant conjugates stimulated an increase of fluorodeoxyglucose FDG uptake 24 h after PDT, an effect not observed for Photofrin® alone.

3.1. VEGF suppression

Vascular endothelial growth factor (VEGF), a potent endothelial cell cytokine that increases angiogenesis, is known to be produced by tumors including colorectal cancer [51]. Vascular endothelial growth factor can be produced by tumors as an inflammatory response to hypoxia and oxidative stress by the HIF-1α pathway during photodynamic action and studies have attempted to minimize VEGF production following PDT treatment [52]. Peng et al. have reported differences in treated tumor volume after a combination of PDT and administration of the monoclonal antibody bevacizumab which blocks VEGF binding in a mouse model of colon cancer. In this study, Foscan® PDT followed by bevacizumab administration resulted in a smaller tumor volume in the mouse model than that obtained when the treatment order was reversed (mean tumor volume: control (no treatment) 1143 ± 116 mm^3, PDT followed by bevacizumab 239 ± 128 mm^3, and bevacizumab followed by PDT 464 ± 198 mm^3) [53]. Bevacizumab administration in patients with metastatic colorectal cancer has also been reported to have a statistically significant positive effect on survival [54].

3.2. Osteopontin and heat shock protein 70

It has been suggested that production of the bone matrix protein osteopontin (OPN) by tumors is a strategy that serves to protect the tumor against attack by suppressing macrophage nitric oxide (NO) production [55]. Production of OPN as a result of photodynamic action is of particular concern as an immune response to PDT and is considered to have an unfavorable effect on treatment outcome. A study by Wozniak et al. reported increases in production of both OPN and the heat shock protein HSP70 in 5-aminolevulinic acid mediated *in vitro* PDT in Human tongue squamous carcinoma (SCC-4) and colorectal cancer cells (SW480) [56]. Production of HSP70 in response to photodynamic stress has also been implicated as a strategy for tumor self-protection as it can affect apoptosis [57].

3.3. Tumor-associated macrophages

Tumor-associated macrophages (TAMs) infiltrate tumor tissue and aid in circumvention of adaptive immunity facilitating tumor growth, angiogenesis and metastases; they are derived from tumor cytokines that impart a polarized M2 phenotype [58]. Mannose receptors present on TAMs have been targeted using PDT in attempts to destroy these cells without harm to normal functioning repair M2 macrophages as TAMs has been correlated to poor prognosis in human cancer [59]. Hayashi et al. investigated the *in vitro* toxicity of mannose-conjugated chlorin (M-chlorin) photosensitizer and apoptosis in human colon cancer HT29 M1 with M2-polarized THP-1 in comparison with chlorin and glucose-conjugated chlorin (G-chlorin). *In vitro* PDT using M-chlorin was found to be more effective in inducing apoptosis in TAMs than chlorin or G-chlorin. In addition, the authors report an IC_{50} for HT29 colon cancer cells of 3.46, 0.20, and 0.15 for chlorin, G-chlorin and M-chlorin respectively and suggest that this trend is partly due to an increase in effective targeting of TAMs [59].

3.4. PDT induced interlukin-6 expression

Photodynamic action within tumors is known to increase serum levels of the cytokine interlukin-6 (IL-6). Serum levels of IL-6 have been correlated with a poor prognosis in colorectal cancer survival in a recent meta-analysis performed by Xu et al. [60]. Recently, studies have suggested that IL-6 induces dendritic cell dysfunction leading to activation of cancer antigen-specific T helper cells imparting immunosuppression in cancer patients and that inhibiting IL-6/STAT3 signaling could potentially improve immunotherapies for colorectal cancer [61]. Brackett et al. has reported that PDT using pyrogen free 2-[1-hexyloxyethyl]-2-devinyl pyropheophorbide-a (HPPH) in murine colon cancer cells (Colo26) was more efficient in the absence of IL-6 implicating that the presence of IL-6 leads to increased tumor resistance to PDT [62].

3.5. Autophagy and PDT

Autophagy, which can be induced by PDT in cancer cells, is the sequestering and compartmentalization of damaged cellular components that functions in cytoprotection and component recycling promoting cell survival and alternatively, in facilitating cell death [63]. Since the steps in autophagy leading to cell death occur in sequence, it is considered to be programed “type II cell death” [66]. The protective and type II programed apoptotic aspects of autophagy elicited by PDT has recently been reviewed by Garg et al. [64]. Rodriguez et al. has reported on enhanced efficiency of the photosensitizer silicon phthalocyanine (Pc4) functionalized with hydroxyl-bearing axial ligands that preferentially targeted lysosomes in *in vitro* PDT in MCF-7c3 breast cancer cells over that of unfunctionalized Pc4 which preferentially targets mitochondria [65]. In continuing studies on lysosomal targeting and autophagy inducing PDT, Kessel et al. performed a very thorough study in mouse hepatoma 1c1c7 cells deficient in autophagy-related protein 7 (ATG7) and autophagy-related protein 5 (ATG5) and wild type. In this study, *in vitro* PDT was performed in 1c1c7 cells using two lysosome targeting photosensitizers N-aspartyl chlorin e6 (NPe6, Talaporfin sodium) and the palladium bacteriopheophorbide WST11 [66]. It was found that the phototoxicity of both photosensitizers was enhanced in the absence of autophagy-related proteins implicating that autophagic protective role and it was suggested that the absence of ATG7 facilitates lysosome photodamage independent of its function in autophagy [66]. In a subsequent study by Kessel et al., evidence was provided that sequential use of lysosomal and mitochrondrial targeting photosensitizers can be advantageous in successful elicitation of cancer cell apoptosis [67]. Ouyang et al. have reported a related PDT study in human colon cancer cells (HCT116) using the photosensitizer protoporphyrin IX (PpIX) in combination with chloroquine (CQ), an inhibitor of autophagy. It was found that the addition of chloroquine with PpIX significantly increased apoptosis in the treated HCT116 cells when compared to PDT using PpIX alone [68]. This increase in apoptosis was also attributed to inhibition of autophagy [68].

3.6. Nanoparticles for immunogenic PDT

In an attempt to enhance the immune response to cancer cells in PDT, Lan et al. has recently reported on the development of iron-oxo clusters conjugated with porphyrins (Fe-TBP) that can locally generate oxygen from cellular hydrogen peroxide via the Fenton reaction which on the one hand serves the purpose of circumventing hypoxia, and, upon irradiation, yields higher concentrations of $^1O_2$. It was found that PDT in murine colorectal cancer cells using the Fe-TBP nanoparticle construct improved efficacy of an anti-programmed death-ligand 1 (PD-L1) treatment and additionally demonstrated abscopal effects [69]. The study also reported that tumors regressed over 90% and Fe-TBP induced T cell infiltration in the tumor model [69]. Li et al. has reported on the construction of porphyrin embedded cerasomes conjugated to the antiepidermal growth factor (anti-EGFR) monoclonal antibody cetuximab which is further conjugated to IRDye800CW and DOTA(Tetraxetan)-Gd for MR imaging [70]. Photodynamic therapy using the cerasome anti-EGFR nanoconstruct in conjunction with PD-L1 immunotherapy was found to more effective in *in vitro* mouse model colorectal cancer treatment than cerasome nanoparticles that lacked cetuximab [70].

4. Conclusion

The understanding of the relation between tumor environment and immune system is a crucial for the successful oncological treatment nowadays. This research direction resulted in the development of novel personalized therapy, as an immunotherapy or photodynamic therapy, especially in patients with advanced malignancies, include colon cancer. Furthermore, early phase clinical trial data, demonstrated favorable results and have led to FDA support of pembrolizumab for MSI-H colorectal tumors, and development of new immune agents, involving vaccine therapy, Indoleamine 2, 3-dioxygenase 1 (IDO1), and IDO2 inhibitors, and combinatorial agents.

On the other hand, it was shown that not lone immunotherapy, but also light therapy- PDT treatment can also destroy not only primary tumor, but also stimulates the immune response to destroy also metastases. Other new studies have established that PDT is an effective adjuvant treatment to surgery and that enhancements the likelihood of following operation cancer control. Maybe the new successful direction of the treatment of advanced colon cancer is the combination of PDT with the other forms e.g. an immunotherapy, which requires a next basic and clinical research.

Conflicts of interest

The authors declare there are no conflicts of interest.

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