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Advancements in photodynamic therapy of esophageal cancer

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The poor prognosis of patients with esophageal cancer leads to the constant search for new ways of treatment of this disease. One of the methods used in high-grade dysplasia, superficial invasive carcinoma, and sometimes palliative care is photodynamic therapy (PDT). This method has come a long way from the first experimental studies to registration in the treatment of esophageal cancer and is constantly being improved and refined. This review describes esophageal cancer, current treatment methods, the introduction to PDT, the photosensitizers (PSs) used in esophageal carcinoma PDT, PDT in squamous cell carcinoma (SCC) of the esophagus, and PDT in invasive adenocarcinoma of the esophagus. For this review, research and review articles from PubMed and Web of Science databases were used. The keywords used were "photodynamic therapy in esophageal cancer" in the years 2000–2020. The total number of papers returned was 1,000. After the review was divided into topic blocks and the searched publications were analyzed, 117 articles were selected.

KEYWORDS

photodynamic therapy, esophageal cancer, Barrett's esophagus, high grade dysplasia, 5-ALA, porfimer sodium, temoporfin, talaporfin

Esophageal cancer

Esophageal cancer is diagnosed in advanced stages. Esophageal cancer needs improved detection and prediction methods prior to cancer treatment. Esophageal cancer originates in the epithelial cells that line the esophagus. The treatments for esophageal cancer depend on its etiology. Malignant neoplasms include squamous cell carcinoma and adenocarcinoma; 95% of all esophageal malignancies are squamous cell carcinomas or adenocarcinomas but other types of cancer, including other carcinomas,

melanomas, leiomyosarcomas, carcinoids, and lymphomas, have also been reported (1, 2). Esophageal cancer is the eighth most common form of cancer worldwide. The increased risk factors for developing esophageal cancer include smoking (3, 4), the consumption of high-percentage alcohol (5), obesity (6), long-term inflammation of the esophagus mucosa (7), achalasia (8), atrophic inflammation of the tongue and esophagus (9), Barrett's esophagus (10, 11), burns of the esophagus with chemicals (12), occupational exposure to vulcanization products (13), asbestos and metal dust (14), dietary factors (11), vitamin deficiencies (15) and trace elements, and frequent consumption of hot and pickled foods (16).

In patients with esophageal carcinoma *in situ* and lesions limited to the mucosa, local endoscopic resection may be used. Neoplastic lesions of a more advanced stage (beyond the mucosa) are indications for surgery. In some cases, preoperative chemoradiotherapy is used. In patients who are not eligible for surgery, radical chemoradiotherapy is recommended. The goal of palliative treatment in inoperable or disseminated esophageal cancer is to provide natural nutrition, slow disease progression, and improve quality of life. In order to restore the esophagus, prosthesis, laser treatment of the esophagus, or intra-esophageal brachytherapy can be used. The effectiveness of palliative chemotherapy is greater in patients with adenocarcinoma of the esophagus, but it is not associated with a significant increase in the overall survival time of patients. In some cases of advanced esophageal cancer, a nutritional gastrostomy or jejunostomy may be necessary. The reasons for its rapidly increasing incidence include the rising prevalence of gastroesophageal reflux and obesity combined with the decreasing prevalence of *Helicobacter pylori* infection (17).

For mucosal cancer, endoscopic mucosal resection and endoscopic submucosal dissection are standard, while for locally advanced cancer, esophagectomy remains the mainstay. The three most common techniques for thoracic esophagectomy are transhiatal approach, the Ivor–Lewis esophagectomy (right thoracotomy and laparotomy), and the McKeown technique (right thoracotomy followed by laparotomy and neck incision with cervical anastomosis). Surgery for carcinoma of the cervical esophagus requires an extensive procedure with laryngectomy in many cases. When the tumor is more advanced, neoadjuvant chemotherapy or neoadjuvant chemoradiotherapy is added. Neoadjuvant concurrent chemoradiotherapy (CCRT) is a strategy to decrease tumor size. However, CCRT may enhance toxicity levels and possibly cause a delay in surgery for patients who respond poorly to CCRT (18). The theoretical advantages of adding chemotherapy to the treatment of esophageal cancer are potential tumor down-staging prior to surgery, as well as targeting micrometastases and, thus, decreasing the risk of distant metastasis. Cisplatin- and 5-fluorouracil-based regimens are used worldwide. Chemoradiotherapy is the standard for unresectable esophageal cancer and could also be considered an option for resectable tumors. For patients who are medically or technically inoperable, concurrent chemoradiotherapy should be the standard of care. Although neoadjuvant chemoradiotherapy followed by surgery or salvage surgery after definitive chemoradiotherapy is a practical treatment, judicious patient selection is crucial. It is important to have a thorough understanding of these therapeutic modalities to assist in this endeavor. Despite advances in surgical techniques and optimization of chemoradiotherapy regimens, overall survival benefits have been incremental at best. Esophageal cancer requires a concerted multidisciplinary approach, perhaps more so than any other tumor type given the integral role played by the esophagus in maintaining calorific intake and the propensity for early spread through the lymphatics (19–21).

Early cancer detection is the most important, and numerous imaging and diagnostic methods are utilized for this purpose, including computed tomography (CT) (22), magnetic resonance imaging (MRI) (23), positron emission tomography (PET) (24), and endoscopic procedures (25) and especially gastroscopy (26).

In this review, the authors searched through the available literature and analyzed the available photosensitizers, methods of carrying out the procedure, the effects of PDT treatment of esophageal cancer, and concepts for the future development of new therapy.

Figure 1 shows a diagram illustrating the procedure for analyzing the source articles.

Treatment methods

Surgery is an important component of treatment for esophageal cancer (27).

However, surgery alone presents poor overall survival rates; therefore, combined modality therapy has been introduced for the treatment of esophageal cancer (28). Randomized trials have proven that preoperative chemoradiation (CRT) and perioperative chemotherapy significantly improved survival in patients with respectable esophageal and gastroesophageal junction cancers (29–32).

If due to clinical indications a patient with locally advanced or metastatic cancer cannot be treated surgically, chemotherapy should be considered. Cisplatin has proven to be an efficient chemotherapeutic agent, with a single-agent response rate of approximately 20% or even higher (33). Other anti-cancer drugs including irinotecan (34, 35), docetaxel (36), paclitaxel (37, 38), etoposide (39), and more recently gemcitabine (40, 41) cisplatin plus paclitaxel or docetaxel, with or without 5-fluorouracil (5-FU) have also demonstrated activity in patients with locally advanced or metastatic disease (42–44). Palliative care patients and those with esophageal obstruction may also benefit from photodynamic therapy (PDT) (45). The chosen treatment method must be personalized to the individual needs of a particular patient (46).

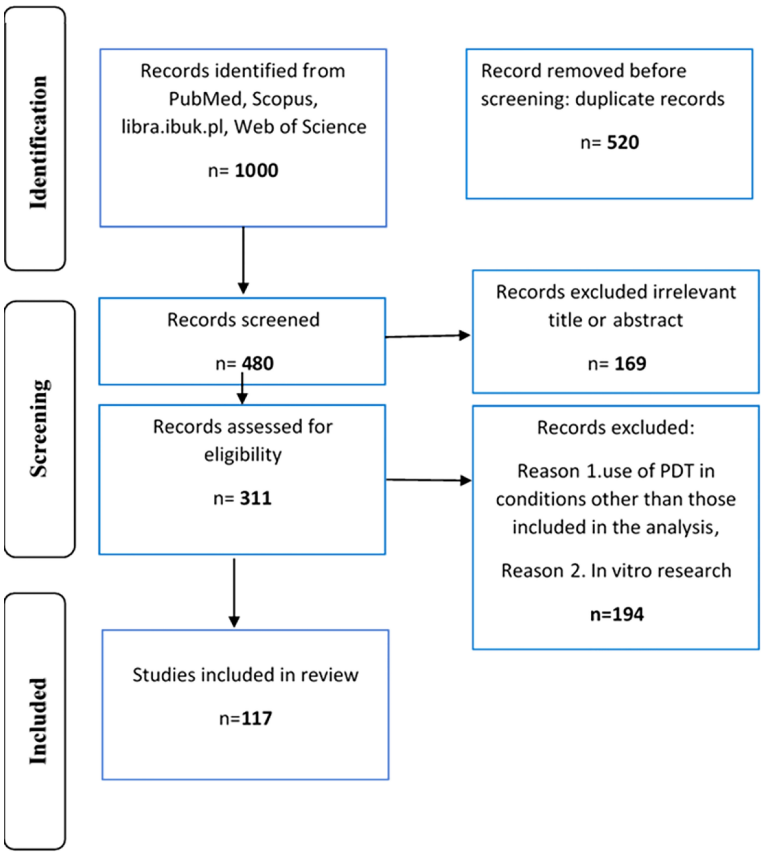

FIGURE 1
Diagram illustrating the procedure for analyzing the source articles.

Photodynamic therapy

PDT is a treatment when the tumor site is irradiated with light of an appropriate wavelength in the presence of a photosensitizer (PS) (Figure 1). The main mechanism of PDT is based on the generation of reactive oxygen species (ROS), which are lethal to cancer tissues by damaging them directly (necrosis) and inducing apoptosis (47). Additionally, it has an indirect effect by modifying tumor vascularization and stimulating the immune response of the patient (48). PDT acts selectively, only at the site where the light is provided, thus accounting for fewer adverse effects than systemic treatment. Figure 2 presents the mechanism of PDT and reactive species generation.

The side effects include phototoxicity due to PSs accumulating in healthy tissues, which is why patients should avoid sunlight during treatment. The downside is also its limited use. PDT is not an efficient treatment method for patients with lymph nodes or distant metastases (49).

The photosensitizers used in esophageal carcinoma photodynamic therapy

Photosensitizers (PSs) are molecules that build up in cancerous cells and less intensively in healthy cells. The effectiveness of PDT (Supplementary Figure 1) is based on PSs used; therefore, a large number of clinical studies are aimed at the synthesis and optimization of physicochemical photoactive (PT) compounds (50). There are several characteristics of an optimal PS: availability of pure chemical substance, long-wavelength absorbing (wavelengths from 600 to 800 nm), strong photocytotoxicity, selectivity in accumulation in target cells, not having phototoxic effects in normal tissues, the absorption bands of the photosensitizer different from absorption of endogenous dyes, e.g., melanin or hemoglobin, the smallest possible number of side effects, easy and rapid excretion from the body, ease of administration through various routes, low cost, and simple synthesis (51–54).

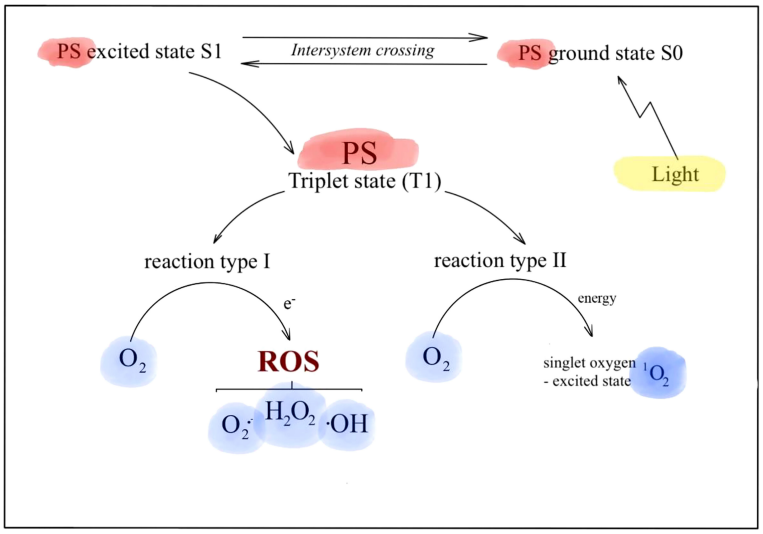

FIGURE 2
The mechanism of photodynamic therapy (PDT).

There are various ways of PS classifications, such as classification due to chemical structure: porphyrins, chlorins, bacteriochlorins, and phthalocyanines with their derivatives (54). The first-generation PSs are porphyrin/hematoporphyrin and their derivatives (hematoporphyrin derivatives (HpD)). The second-generation PSs have various structures including porphyrins, chlorophyll derivatives, and dyes. Third-generation PSs contain first- and second-generation PSs conjugated to various modifiers such as antibodies and nanoparticles (55, 56). Among all those molecules, the most common and clinically approved in esophageal diseases are porfimer sodium (Photofrin), mTHPC/temoporfin (Foscan), talaporfin sodium (Laserphyrin), and 5-aminolevulinic acid (Alabel) (57). Porfimer sodium, mTHPC, and 5-ALA are activated by similar red light energy (630, 652, and 635 nm, respectively) and produce a depth of mucosal necrosis varying from 6 to 7 mm for Photofrin, 5 to 10 mm for Foscan, and 2 mm for 5-ALA (58–63). Talaporfin sodium is expected to reach deeper layers including the muscularis propria because the excitation wavelength of the diode laser used is longer than in the excimer dye laser used in other PSs (Supplementary Figure 2). The general instrumental setup is presented in (Supplementary Figures 3, 5).

Porfimer sodium

Porfimer sodium (Supplementary Figure 4), a first-generation PS, is the most widely used and investigated PS in esophageal PDT. After injection into a vein, the drug is removed from most tissues within 40–72 h. It remains significantly longer in tumors, skin, and organs of the reticuloendothelial system. It is excited with 630-nm light, which initiates a photodynamic reaction leading to the destruction of abnormal cells (64–66). Many clinical trials using porfimer sodium were carried out, and porfimer sodium is currently approved for use in PDT worldwide.

Lightdale et al. compared the PDT with porfimer sodium with thermal ablation therapy with Nd : YAG laser in the palliative treatment of esophageal cancer (67). The result of the therapy with PDT was the eradication of the segment of Barrett's esophagus (BE). This finding led to many clinical trials (randomized, follow-up, and retrospective) testing the effectiveness of porfimer sodium PDT in the treatment of dysplastic BE (68–72). The study findings resulted in the approval of porfimer sodium PDT for the treatment of high-grade dysplasia associated with Barrett's metaplasia (BE-HGD) and superficial esophageal adenocarcinoma (73–76). Current recommendations for porfimer sodium PDT (manufacturer/Food and Drug Administration (FDA)) for BE and esophageal cancer lesions are as follows: ablation of high-grade dysplasia in the BE in patients not undergoing surgery, cancer lesions smaller than half of the circumference of the lumen and 2 cm in diameter that are limited to the submucosal layer in depth and lesions (which are difficult to remove with endoscopic resection), and also the palliative treatment of patients with completely or partially obstructing esophageal cancer (Supplementary Figure 5). Other applications include the ablation of non-dysplastic Barrett's mucosa (77).

5-ALA

5-ALA (Supplementary Figure 6) is a second-generation PS. It is a pro-drug that stimulates the endogenous production of protoporphyrin IX, mostly within the gut mucosa (78, 79). There are some important benefits of using 5-ALA in gastrointestinal tract diseases (80–82). It preferentially accumulates in tumors as compared with normal cells. An important advantage of using 5-ALA PDT is the short time period of photosensitivity after the procedure, lasting only 24 to 48 h (83–85). It targets the superficial mucosal layer and therefore rarely induces the development of strictures (81).

In a study by Tan et al., 5-ALA-PDT presented insufficient tumor selectivity in the treatment of esophageal adenocarcinoma, and thus, only carcinoma *in situ* could be eradicated (86). However, it could relieve dysphagia in patients with strictures (87). Another disadvantage of 5-ALA PDT is a high recurrence rate in patients with early cancer (65). So far, the 5-ALA PDT procedure was applied mostly in Europe, Scandinavia, and the United States for the treatment of patients with BE-HGD (88).

Temoporfin (mTHPC)

mTHPC (Supplementary Figure 7) is a second-generation PS and is associated with photosensitivity lasting for 2 to 3 weeks after administration. In gastroenterology, mTHPC has been used intravenously at a dose of 0.15 mg/kg with 652-nm light activation (89). There were only a few clinical studies, mainly in Europe, evaluating the role of mTHPC in the treatment of BE-HGD and early esophageal cancer (90, 91). Gossner et al. used mTHPC as a complementary therapy in a small number of patients with BE-HGD who had failed previous treatment with 5-ALA PDT (92). In 2002, Javaid et al. treated patients with BE-HGD using mTHPC with an argon-pump dye laser light of 652 nm and a xenon arc lamp with equivalent results, demonstrating that efficient photosensitizers may not require high-power laser light sources for effective activation (93). Some studies report initial positive results in using mTHPC in BE-HGD and superficial esophageal cancer with green light (at 514 nm) (89–93), but none of the patients had successful disease eradication or reached a long-term remission (90).

Talaporfin sodium

Talaporfin sodium (Supplementary Figure 8), a second-generation PS utilized in Japan (Laserphyrin for injection; Meiji Seika Pharma, Tokyo, Japan), has fast skin clearance and is associated with photosensitivity lasting for only 2 weeks (94, 95). Talaporfin sodium can reach deeper layers in the muscularis propria (39). The talaporfin sodium used for the PDT procedure consists of i.v. administration of 40 mg/m^2 dose of the PSs followed by laser illumination at a 664-nm wavelength 4–6 h after administration (45). The first clinical trials with talaporfin sodium assessed the tissue damage of a normal esophagus caused by photo-activation in a living canine model (78). After that, phase I and II clinical trials were planned and carried out by Yano et al. to assess the usefulness of using talaporfin sodium PDT for salvage treatment in esophageal cancer for local failures after CRT (96, 97). In 2019 and 2020, Minamide et al. and Ishida et al. respectively further confirmed that talaporfin sodium PDT is effective in patients who did not benefit from chemoradiotherapy or radiotherapy for esophageal cancer (98, 99).

2-[1-Hexyloxyethyl]-2-devinyl pyropheophorbide-a

Nava et al. studied 2-[1-hexyloxyethyl]-2-devinyl pyropheophorbide-a (HPPH)-PDT (Supplementary Figure 9) for precancerous lesions in BE. Patients treated with HPPH showed less photosensitivity than those treated with porfimer sodium. HPPH doses ranged from 3 to 6 mg/m^2, and lesions were irritated with one endoscopic exposure to 150, 175, or 200 J/cm of light with a wavelength of 665 nm. At a 1-year follow-up, 72% of patients had complete remission (no dysplasia or cancer present). Side effects included mild-to-moderate chest pain requiring symptomatic treatment in most patients and grade 3 and 4 adverse events in 16.6% of patients including esophageal strictures. The authors concluded that further clinical studies are required to establish the usefulness of HPPH-PDT in esophageal carcinoma (100).

Photodynamic therapy in squamous cell carcinoma of the esophagus

PDT was used in patients with early-stage esophageal squamous cell carcinoma (SCC) with curative intent. Seven patients with SCC or HGD were included in the experiment, and none of them had lymph node metastases. The team injected porfimer sodium intravenously (2 mg/kg) and exposed the tumor site to a laser with a wavelength of 630 nm. In some of the cases, a second irradiation of the lesion was performed. All treated lesions were eradicated. Follow-up (range 4–51 months) did not show a recurrence in any of the patients. There were no adverse effects after the procedure (50).

Yano et al. described 13 patients with initial treatment failure: nine patients with remaining tumors after CRT and four patients with tumor recurrence. Inclusion criteria included no metastases in lymph nodes, T1 or T2 stage, and contraindications to surgical treatment. Eight patients (62%) had complete remission after treatment, and at a 12-month

follow-up, nine were still alive and six were still disease-free. The overall survival rate after salvage PDT after 1 year was 68.4%. During the PDT treatments, six patients experienced significant complications: esophagotracheal fistula (1), stenosis (3), skin phototoxicity (1), and radiation-induced pleural effusion (1). The authors expressed hope that PDT could be used as a treatment with curative intent (97).

Takana et al. assessed 52 patients with esophagus cancer who underwent PDT from 1999 to 2007 in a retrospective study. Fourteen patients had a different type of therapy prior to PDT, and 31 patients received PDT only. Photosensitizer was administrated 48 h prior to light irradiation (excimer laser, 75 J/cm^2). Complete remission was obtained in 33 patients (87%): 25 patients after the first PDT and 8 patients after more than one course of PDT. Four patients had recurrence after 12 months: two of them were successfully treated with another PDT course, and two developed lung or lymph node metastases. Common complications were chest pain and fever >38°C, all managed with non-steroidal anti-inflammatory drugs. Cutaneous phototoxicity was observed in 6 patients (16%) (101).

In another study, Yano et al. treated 25 patients who previously underwent CRT with PDT using talaporfin sodium. This was meant to be a salvage therapy for patients with esophageal cancer recurrence (14 patients) or residual lesions (11 patients). Complete remission was observed in 76% (19/25) of patients. The median follow-up was 48 months. At that time, only 11 patients from the complete remission group were disease-free. The commonly reported adverse effects of PDT were chest pain (61%), pharyngeal pain (17%), dysphagia (39%), fever (48%), and photosensitivity (32%). There was one treatment-related death: the patient developed severe gastrointestinal hemorrhage (102).

In 2012, Yano et al. achieved a complete response after PDT of esophageal SCC in five of nine patients (55.6%). In this study, they found optimal laser irradiation fluence rate for PDT using talaporfin sodium and diode laser (100 J/cm^2) and achieved no dermatological adverse effects (103).

Lindenmann et al. presented a retrospective study about an individualized approach to palliative procedures in esophageal cancer that included PDT. They evaluated 248 patients excluded from surgery. PDT with hematoporphyrin was performed in 171 cases (first treatment in 118 cases). The median survival rate was 50.9 months if PDT was the initial treatment and 17.3 months if other methods were used first. The mean survival time for all patients was 34 months. The side effects of PDT included esophageal tumor perforation within 5 days from PDT (8.8%) and tumor necrosis-associated hemorrhage (7.6%). PDT as an initial endoluminal treatment improved and prolonged the survival rate of patients without massive invasion of the mediastinum, trachea, bronchial tree, or great vessels (104).

In 2017, Yano et al. presented results of PDT in patients with local failure of CRT (21 patients) or radiotherapy (5 patients) in esophageal SCC carcinoma. There were 26 patients with 28 lesions qualified for the study. Lesions were confirmed as T1b (21) and T2 (7). Twenty-three patients with 25 lesions (88.5%) had local complete remission (L-CR). In lesions staged as T1, L-CR was 100%; in lesions staged as T2, it was 57.1%. There was no skin phototoxicity observed; 53.8% of patients suffered from esophageal pain and 30.8% from fever. The median follow-up of 8.4 months showed no death from esophageal progression, but two of three patients without L-CR developed progression, and one patient from the L-CR group suffered from recurrence after 14 months. Three patients developed lymph nodes or distal metastases (105).

Photodynamic therapy in Barrett's esophagus

Barrett's esophagus is a premalignant disease that predisposes to the development of esophageal adenocarcinoma.

PDT is one of the longest-used ablation techniques in the treatment of BE. The first studies concentrated on the use of porfimer sodium in Barrett's disease and early esophageal cancer (106). The results of these clinical trials led to the approval of PDT in the United States, Europe, and Japan, which allowed for the expansion of research. There have been many subsequent reports proving the high effectiveness of photodynamic therapy.

In the clinical trial of Overholt et al., patients with BE and HGD were divided into two groups: one using porfimer sodium PDT with concomitant proton pump inhibitor (PPI) therapy and one with PPI therapy alone. The 5-year follow-up showed that porfimer sodium PDT was significantly more effective than omeprazole, with the elimination of HGD in 77% and 39% ($p < 0.0001$). The second endpoint assessed was the progression to adenocarcinoma, which was 15% for the first group and 29% for omeprazole ($p = 0.027$), with a significantly longer progression time for the first group ($p = 0.004$) (73).

Equally favorable effects were achieved in a study that assessed the effects of PDT using 5-ALA in BE with HGD (group A) and in superficial esophageal cancer (group B). Of the patients, 97% in group A and 100% in group B achieved complete remission with a mean follow-up of 37 months. Local recurrence was observed in one patient in group A and 10 patients in group B. The estimated 5-year survival was 97% in group A and 80% in group B (107).

In a study comparing the effects of PDT with 5-ALA and Photofrin in patients with BE and HGD, complete dysplasia regression (CR-HGD) was achieved in 47% and 40% of cases, respectively. Esophageal stricture and photosensitivity were statistically more common in patients treated with porfimer sodium PDT (33% *vs.* 9% and 43% *vs.* 6%, $p = 0.05$). The study showed a better risk profile and better outcomes with BE lengths ≤ 6 cm using 5-ALA PDT. With the longer BE segment, no

statistically significant difference was observed with the use of both methods (108).

There were only a few clinical studies, mainly in Europe, evaluating the role of mTHPC in BE. Gossner et al. used mTHPC PDT as salvage therapy in a small number of patients with BE-HGD who had failed previous treatment with 5-ALA PDT (109). Other studies included the treatment of both BE with high-grade and low-grade dysplasia (102, 103). The trials demonstrated that mTHPC-PDT is useful in BE PDT, but further studies are needed to establish its exact effectiveness.

In the next study, the efficacy of porfimer sodium PDT and radiofrequency ablation (RFA) was compared. The percentage of complete histopathological remissions of BE was 54.5% for PDT and 88.7% for RFA. There was one case of perforation in the PDT group, with no similar complications in the RFA group. However, the limitation of this study was the lack of randomization and the higher stage of the disease in patients treated with PDT (110).

Photodynamic therapy in invasive adenocarcinoma of the esophagus

In Japan, PDT for esophageal carcinoma was approved for patients with superficial cancer or in case of local failure after CRT. Tan et al. described a study of 12 patients, aged 55–88, with esophageal adenocarcinoma arising from Barrett's metaplasia. 5-ALA was chosen as the PS due to limited side effects and preferential accumulation in the mucosa and mucosal tumor. 5-ALA was given orally in the dose of 60 and 75 mg/kg body weight and irritated using laser light (630 nm) delivered *via* a cylindrical diffuser 4–6 h after the first dose of PSs. After PDT, the mucosa was examined, and histology showed fibrinoid necrosis. One patient with carcinoma *in situin-situ* had the tumor eradicated after one treatment with no recurrence at 28 months. Another patient with a small T1 tumor required four PDT treatments and had no evidence of recurrence after 36 months. The tumor size in the other, more advanced cases was not significantly reduced (86).

A study by Kashtan et al. had similar results. 5-ALA PDT did not prove to be efficient in the treatment of esophageal adenocarcinoma, due to low selectivity for tumor mucosa and eradication achieved only in preinvasive carcinomas (87).

Another PS used in PDT of esophageal adenocarcinoma was porfimer sodium (Photofrin). It has proven long-term efficacy and durability in the treatment of BE, HGD, and superficial esophageal adenocarcinoma. However, its continued use is hindered by serious side effects including prolonged cutaneous photosensitivity (4–6 weeks) and increased stricture risk (111).

In the United States, the FDA accepted PDT as a palliative treatment for patients with symptomatic obstructive esophageal cancer (SCC and adenocarcinoma) after studies comparing PDT with thermal YAG laser for patients with neoplastic esophageal obstruction were published. A previously mentioned study by Lightdale et al. is about a multicenter randomized trial that included 218 patients with advanced esophageal cancer from 24 centers. There was no significant difference in the dysphagia score, but tumor response 1 month after treatment was better in patients who underwent PDT (32% for PDT *vs.* 20% for Nd : YAG). The esophageal perforation rate was higher in the YAG laser group (PDT, 1%, *vs.* Nd : YAG, 7%), but PDT patients experienced severe skin photosensitivity (67).

Litle et al. examined 215 patients with symptomatic or recurrent esophageal cancer. In this group, adenocarcinoma was the dominant histological type (83%). Of patients who underwent PDT, 85% reported fewer swallowing disorders (94). However, the European Society of Gastrointestinal Endoscopy (ESGE) recommends metal stents as the method of choice in the treatment of dysphagia in patients with esophageal obstruction in the course of cancer (112).

The application of PDT in esophageal adenocarcinoma on a wider scale requires a better understanding of dosimetry and tissue properties and is currently limited only to superficial changes.

Development opportunities

Lack of oxygen in the treated tissues means no ROS and no cytotoxic effect of PDT. In 2020, to face this problem, Roque et al. introduced two osmium-based polypyridyl photosensitizers (mainly 1-4T and 2-4T complexes) that are active in hypoxia. These complexes were relatively non-toxic in the absence of a light source. Phototherapeutic indices (PIs; the ratio of dark-to-light cytotoxicity) under irradiation with red and visible light (fluence of 100 J/cm^2 and irradiance of approximately 20 mW/cm^2) were maintained even in hypoxia (1% O_2), which emulates an environment present in deep tissues and solid tumors. Both compounds were studied for *in vivo* treatment. This led to the determination of a maximum tolerated dose value, which turned out to be greater than or equal to 200 mg/kg in an intraperitoneal injection. The lead complexes demonstrated low toxicity *in vitro* with high tolerance in mice and are being prepared for *in vivo* validation (113). Another way to increase the efficiency of PDT is through nanocarriers. Carriers help to deliver the drug selectively to cancer cells and to multiply its concentration in the tumors while sparing healthy tissues. Nanotherapeutics as delivery tools for drugs have the potential to improve PDT therapeutic impact and are currently being developed and tested mostly in pre-clinical trials (114). The potential role of PDT in functionalized nanomedicine is often highlighted (115, 116). Fluoroscopy-guided PDT by using nanoparticle albumin-bound paclitaxel for esophageal cancer after chemoradiotherapy is known and well-described (117).

Photodynamic therapy instruments

An important part of the PDT research of esophageal cancer is the examination of the photosensitizer/fiber optic device flowing oxygen to optimize photosensitizer delivery to the tissues. PDT literature presents that singlet oxygen diffusion in cells is shorter than the diameter of a typical intracellular organelle. The formation of singlet oxygen at a specific biological site is extremely important to understand the properties of tumor destruction by directed and concentrated singlet oxygen. Reactive products formed by interaction with singlet oxygen give rise to the desired toxic effect. Since singlet oxygen diffusion over a distance is unlikely, we hypothesize that specific/controlled accumulation of a sensitizer in a tumor may result from cleavage from a fiber probe (118).

Visible light will be available from the fiber itself. The benefits expected from the new fiber device are improved selectivity of the photosensitizer in diseased cells and tissues, high-precision control of the production of singlet oxygen on the micro scale to lethally damage diseased tissues, and a point-source fiber-based $^1O_2$ method that is expected to kill tumor cells inaccessible by surgical methods.

It was also reported that the cationic PS-impregnated porous Vycor glass served as a new singlet oxygen generator and more importantly serves as a heterogeneous PS solid-phase PS scaffold for use in water systems without PSs being released into the water. The described heterogeneous system was then connected to a hollow optical fiber for supplying light and oxygen for wastewater treatment and as the first PDT approximation device (119) (Supplementary Figure 10).

The use of PDT aims to improve the methods of cytotoxic drug delivery, especially in terms of improving therapy and searching for improved methods of monitoring and visualizing their delivery. Currently, there are several PDT treatments approved for use in clinical medicine and several clinical trials. Photofrin® was the first PS approved for use in PDT in the treatment of bladder cancer, esophageal cancer, non-small cell lung cancer, esophageal cancer, and cervical cancer. Chlorin e6 (talaporfin sodium, approved for lung cancer in Japan) and Photochlor (in clinical trials in esophageal cancer, basal cell carcinoma, lung cancer, and Barrett's esophagus) are two PSs that I am researching to increase the depth of treatment in PDT therapy. From current data, it appears that Tookad® is a promising PS to find in prostate cancer clinical trials in the United States. There are also PSs approved for age-related macular degeneration (Visudine) and corneal degeneration (Levulan® and Metvixia). The primary limitation of this promising methodology is the depth of action at which visible light can penetrate the tissues, which ranges from a few millimeters (blue–green light) to just over 1 cm (red light). For example, Tookad®, which has found application in colon cancer clinical trials, absorbs red light at 761 nm and has been reported to induce tissue necrosis to a depth of 1.3 cm. Research has also been performed to develop a PS that dips near-infrared rays that can penetrate tissues to a depth of more than 2 cm. A fiber optic-based singlet oxygen generator for targeted singlet oxygen delivery is proposed for use in photodynamic therapy and drug delivery. The heterogeneous photodynamic therapy device that uses the optical excitation of sensitizer molecules released from porous ends on hollow photonic band-gap optical fibers through which O_2 flows is still a challenge in clinical studies (120–122).

Author contributions

Conceptualization, DB-A, MO, MA, JS, GC, AK-K, and DA; methodology, DB-A, MO, MA, JS, GC, AK-K, and DA; software, DB-A, MO, MA, JS, GC, AK-K, and DA; validation, DB-A, MO, MA, JS, GC, AK-K, and DA; formal analysis, DB-A, MO, MA, JS, GC, AK-K, and DA; investigation, DB-A, MO, MA, JS, GC, AK-K, and DA; resources, DB-A, MO, MA, JS, GC, AK-K, and DA; data curation, writing—original draft preparation, DB-A, MO, MA, JS, GC, AK-K, and DA. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2022.1024576/full#supplementary-material

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