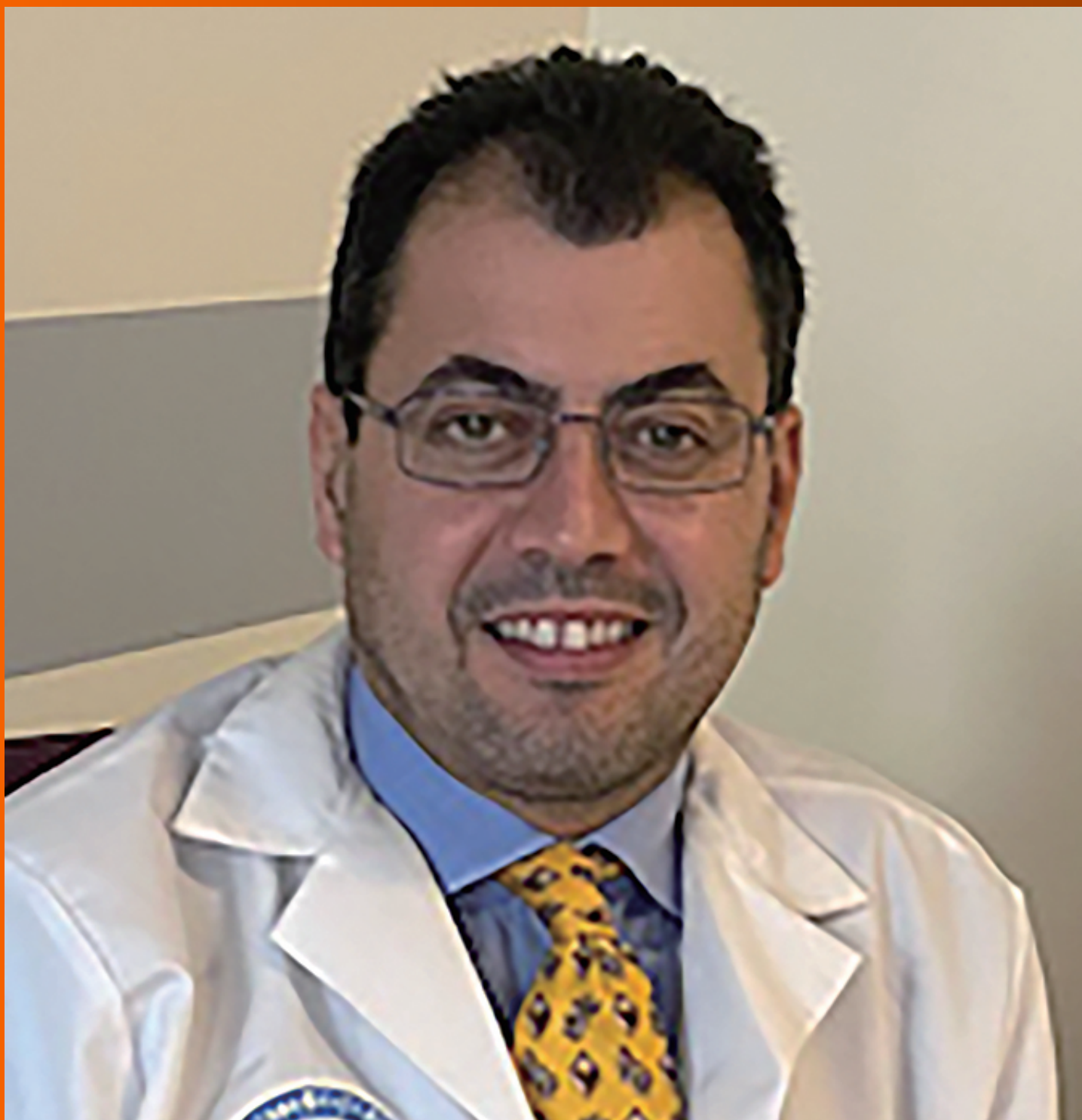


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Contents

Monthly Volume 13 Number 12 December 27, 2021

FRONTIER

- 1523 Photodynamic therapy: A next alternative treatment strategy for hepatocellular carcinoma?
Zhu F, Wang BR, Zhu ZF, Wang SQ, Chai CX, Shang D, Li M

REVIEW

- 1536 Role of mesenteric component in Crohn's disease: A friend or foe?
Yin Y, Zhu ZX, Li Z, Chen YS, Zhu WM
- 1550 Neoadjuvant treatment strategies for hepatocellular carcinoma
Xu L, Chen L, Zhang W
- 1567 Mucinous adenocarcinoma: A unique clinicopathological subtype in colorectal cancer
Huang A, Yang Y, Shi JY, Li YK, Xu JX, Cheng Y, Gu J

MINIREVIEWS

- 1584 Endoscopic therapy of weight regain after bariatric surgery
Bulajic M, Vadalà di Prampero SF, Boškoski I, Costamagna G
- 1597 Patient-centered developments in colon- and rectal cancer with a multidisciplinary international team: From translational research to national guidelines
Link KH, Kornmann M, Staib L, Kreuser ED, Gaus W, Röttinger E, Suhr P, Maulbecker-Armstrong C, Danenberg P, Danenberg K, Schatz M, Sander S, Ji ZL, Li JT, Peng SY, Bittner R, Beger HG, Traub B
- 1615 Advances in liver transplantation for unresectable colon cancer liver metastasis
Cui X, Geng XP, Zhou DC, Yang MH, Hou H

ORIGINAL ARTICLE

Retrospective Study

- 1628 Pediatric T-tube in adult liver transplantation: Technical refinements of insertion and removal
Spoletini G, Bianco G, Franco A, Frongillo F, Nure E, Giovinozzo F, Galiandro F, Tringali A, Perri V, Costamagna G, Avolio AW, Agnes S
- 1638 Preoperative calculation of angles of vision and working area in laparoscopic surgery to treat a giant hiatal hernia
Lara FJP, Zubizarreta Jimenez R, Moya Donoso FJ, Hernández Gonzalez JM, Prieto-Puga Arjona T, del Rey Moreno A, Pitarch Martinez M
- 1651 Effect of aluminum phosphate gel on prevention of early rebleeding after ligation of esophageal variceal hemorrhage
Zhang ZL, Peng MS, Chen ZM, Long T, Wang LS, Xu ZL

- 1660** Postoperative complications after robotic resection of colorectal cancer: An analysis based on 5-year experience at a large-scale center

Huang ZX, Zhou Z, Shi HR, Li TY, Ye SP

- 1673** 'Short' pancreaticojejunostomy might be a valid option for treatment of chronic pancreatitis in many cases

Murruste M, Kirsimägi Ü, Kase K, Veršinina T, Talving P, Lepner U

- 1685** Risk factors for perioperative complications in laparoscopic surgeries of retrorectal cystic lesions

Wang PP, Lin C, Zhou JL, Xu KW, Qiu HZ, Wu B

- 1696** Liver resection *vs* radiofrequency ablation in single hepatocellular carcinoma of posterosuperior segments in elderly patients

Delvecchio A, Inchingolo R, Laforgia R, Ratti F, Gelli M, Anelli MF, Laurent A, Vitali G, Magistri P, Assirati G, Felli E, Wakabayashi T, Pessaux P, Piardi T, di Benedetto F, de'Angelis N, Briceño J, Rampoldi A, Adam R, Cherqui D, Aldrighetti LA, Memeo R

Observational Study

- 1708** Expression of adipokine ghrelin and ghrelin receptor in human colorectal adenoma and correlation with the grade of dysplasia

Stojasavljevic-Shapeski S, Virovic-Jukic L, Tomas D, Duvnjak M, Tomasic V, Hrabar D, Kralj D, Budimir I, Barsic N, Ljubcic N

SYSTEMATIC REVIEWS

- 1721** Right sided diverticulitis in western countries: A review

Epifani AG, Cassini D, Ciocchi R, Accardo C, Di Candido F, Ardu M, Baldazzi G

- 1736** Platelet rich plasma effectiveness in bowel anastomoses: A systematic review

Geropoulos G, Psarras K, Giannis D, Martzivanou EC, Papaioannou M, Kakos CD, Pavlidis ET, Symeonidis N, Koliakos G, Pavlidis TE

- 1754** Current and future role of three-dimensional modelling technology in rectal cancer surgery: A systematic review

Przedlacka A, Pellino G, Fletcher J, Bello F, Tekkis PP, Kontovounisios C

ABOUT COVER

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Photodynamic therapy: A next alternative treatment strategy for hepatocellular carcinoma?

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Abstract

Liver cancer is one of the most common cancers in the world. Of all types of liver cancer, hepatocellular carcinoma (HCC) is known to be the most frequent primary liver malignancy and has seriously compromised the health status of the general population. Locoregional thermal ablation techniques such as radiofrequency and microwave ablation, have attracted attention in clinical practice as an alternative strategy for HCC treatment. However, their aggressive thermal effect may cause undesirable complications such as hepatic decompensation, hemorrhage, bile duct injury, extrahepatic organ injuries, and skin burn. In recent years, photodynamic therapy (PDT), a gentle locoregional treatment, has attracted attention in ablation therapy for patients with superficial or luminal tumors as an alternative treatment strategy. However, some inherent defects and extrinsic factors of PDT have limited its use in clinical practice for deep-seated HCC. In this contribution, the aim is to summarize the current status and challenges of PDT in HCC treatment and provide potential strategies to overcome these deficiencies in further clinical translational practice.

Key Words: Hepatocellular carcinoma; Photodynamic therapy; Photosensitizers;

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Core tip: The application of photodynamic therapy (PDT) in hepatocellular carcinoma (HCC) therapy is limited due to its low penetration depth of light irradiation, the reduced generation of reactive oxygen species by conventional photosensitizers in the aggregated state, and the nontargeted accumulation in cancer cells. Once these problems are resolved, PDT will be a promising alternative treatment strategy for HCC.

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INTRODUCTION

Liver cancer is one of the most common causes of cancer-related death worldwide[1]. Of all types of liver cancer, hepatocellular carcinoma (HCC) is known to be the most frequent liver malignancy[2,3]. The main risk factors for HCC are chronic hepatitis B virus or hepatitis C virus infection, alcohol consumption and the resulting cirrhosis, nonalcoholic fatty liver disease, nonalcoholic steatohepatitis, dietary intake of aflatoxin B1, etc[4,5]. The incidence and mortality of HCC are rapidly rising in the USA and several European regions and slightly declining in traditionally high-risk regions such as East Asia and Africa[4]. Population-based studies have revealed that the incidence rate continues to approximate the death rate, indicating that most patients who develop HCC die of it[6]. HCC has seriously compromised the health status of the general population. In general, there are several treatment options for the management of HCC, but each treatment has its limitations and side effects[7]. In recent years, photodynamic therapy (PDT) has been a palliative treatment option that could improve quality of life and median survival with minimal invasion for cancer patients [8] and some studies have investigated its applications in ablation therapy for HCC. The aim of this frontier article was to summarize the current status and challenges of PDT for HCC as an alternative locoregional ablation and to propose potential strategies to overcome the deficiencies in clinical translational practice.

THERAPY

In general, several treatment options have emerged for the management of HCC. These options include surgical treatment with curative intents such as hepatic resection[9] or liver transplantation[10], systemic therapy (e.g., sorafenib, lenvatinib, regorafenib and apatinib)[11,12], immunotherapy (e.g., atezolizumab plus bevacizumab, nivolumab, pembrolizumab, ramucirumab, and camrelizumab)[13-16], external beam radiotherapy and catheter based embolic therapies (e.g., chemoembolization and radioembolization)[17-20]. In addition, locoregional therapies include ablative techniques inducing tumor necrosis by injection of chemicals (e.g., ethanol and acetic acid), and temperature modification (ablation by radiofrequency, microwave, laser or cryoablation)[21-25]. Recently, locoregional thermal ablation techniques, radiofrequency and microwave ablation, have attracted interest in clinical practice as alternative strategies for HCC treatment[26-28]. According to the guidelines of the China Liver Cancer Staging, locoregional ablation is recommended for HCC patients in stages Ia, Ib and IIa as an alternative treatment[29]. The obvious benefits of radiofrequency ablation are its minimally invasive nature, lower rate of complications, and decreased cost of treatment. The efficiency of microwave ablation allows for an increased volume of necrosis, better vessel coagulation, and decreased ablation times [7]. However, the aggressive thermal effect of locoregional ablations may cause

undesirable complications, such as hepatic decompensation, hemorrhage, bile duct injury, extrahepatic organ injuries, and skin burn[30]. Therefore, the development of a novel locoregional ablation technique is an imperative task for alternative treatment strategies for HCC therapy.

PDT

PDT is a palliative treatment option that can improve quality of life and median survival with minimal invasion for patients, and has caused extensive concern for tumor therapy in recent years since *Paramecium* spp. killing was described through the interaction between acridine and infrared radiation by Oscar Raab in 1900[31]. Due to its low economic cost, few side effects, less invasiveness than surgery, short treatment time, precise targeting, and repeated treatment at the same site, PDT has been extended to the treatment of a variety of tumors, such as brain tumors[32], head and neck tumors[33,34], skin tumors[35], breast cancer[36], esophageal cancer[37], gastrointestinal tumors[38], lung cancer[39], extrahepatic cholangiocarcinoma[40-43], and bladder cancer[44].

PDT kills cancer cells by reactive oxygen species (ROS) generated from light-activated photosensitizers (PSs), resulting in the destruction of tumor cells and blood vessels and the stimulation of the host immune system[45-47]. Specifically, after activation by light irradiation, PSs accumulating in malignant tissues are electronically excited and transfer an electron to molecular oxygen or other electron acceptors to yield superoxide anions and radicals (*i.e.*, type I reaction, in a hypoxic microenvironment) or transfer their electronic energy to ground-state molecular oxygen to yield singlet oxygen (*i.e.*, type II reaction in a hyperoxic microenvironment)[48], which leads to antitumor effects and stimulates immune effects[49]. Moreover, activating the innate immune system increases the priming of tumor-specific T lymphocytes that can recognize and destroy distant tumor cells and lead to the development of immune memory that can combat the recurrence of cancer at a later point in time[50].

Among the three essential elements, PSs play a crucial role in ensuring the successful implementation of PDT. However, several inherent limitations of conventional PSs, such as high demand for oxygen in the microenvironment, inefficient generation of ROS and no organelle targeting, limit therapeutic outcomes in PDT[51]. In other words, several extrinsic factors impact the effectiveness of PDT. For instance, conventional PSs hardly have active accumulation in tumor lesions and tumor cell uptake[52], resulting in inefficient anticancer effects and phototoxicity of other normal tissues.

PDT FOR HCC

Although the clinical practice of PDT for deep-seated solid tumors has been limited by the penetration of laser irradiation and the defects of PSs, many studies have shown that PDT has better potential to improve HCC treatment than other traditional therapies owing to its noninvasiveness and localized therapeutic effect in the presence of specialized laser irradiation[8]. For example, experimental studies have shown that PDT can effectively kill hepatoma cells and shrink tumor tissues[53-55], and clinical investigations have also revealed that PDT can prolong the survival rate in patients with inoperable cancers to significantly improve their quality of life[56,57]. Specifically, this work summarizes the previous literature on PDT for HCC in Tables 1 and 2, to provide some insight for future research on PDT for HCC.

As described in Table 1, indocyanine green (ICG) is a clinical infrared imaging agent approved by the US Food and Drug Administration[70,71] and has been applied in optical imaging in liver surgery[72-74], fluorescence angiography[75], cancer theranostics[72], surgical navigation[76], vascular grafts[77] and so on. In addition, a large number of studies have shown that ICG is widely used as a PS in PDT, and is able to rapidly generate singlet oxygen upon exposure to a near-infrared (NIR) laser and thus destroy cancerous cells[78,79]. Hence, ICG has been considered a promising theranostic agent. In addition, HCC cells notably take up ICG molecules with high efficiency but it cannot be easily excreted to bile ducts owing to the abnormal structures of bile capillaries[80]; thus, the retained ICG in HCC can kill cancer cells *via* PDT. For example, Kim *et al*[58] tested the cytotoxicity of ICG after NIR light irradiation in cancerous cell lines (Huh-7 and Hep3B) *in vitro* and investigated the tumoricidal ability after treatment with intravenous injection of ICG (5–20 mg/kg²)

Table 1 Summary of photosensitizers molecules in photodynamic therapy for hepatocellular carcinoma in recent years

PSs	Animal model	Ref.
ICG	Patient-derived orthotopic xenograft mice	Hong <i>et al</i> [58]
ICG	Huh-7 tumor-bearing nude mice	Shirata <i>et al</i> [49]
<i>m</i> -THPC (Foscan®)	Rat model with Walker-256 hepatoma cells	Wang <i>et al</i> [59]
Endogenous PpIX from 5-ALA	Diethylnitrosamine-induced HCC in Fisher-344 rats	Otake <i>et al</i> [60]
HpD	2-Acetylaminofluorene-induced HCC in Fisher-344 rats	Kita <i>et al</i> [61]

PSs: Photosensitizers; ICG: Indocyanine green; *m*-THPC: Meta-tetra (hydroxyphenyl) chlorin/temoporfin; PpIX: Protoporphyrin IX; 5-ALA: 5-aminolaevulinic acid; HpD: Hematoporphyrin derivatives; HCC: Hepatocellular carcinoma.

Table 2 Summary of photosensitizers-loaded nanoparticles-mediated drug delivery systems in photodynamic therapy for hepatocellular carcinoma evaluated in recent years

PSs	Delivery vehicle	Ligand	Matching receptor	Drug agent	Animal model	Ref.
Pu-18- <i>N</i> -butylimide-NMGA	Gold NPs	/	/	/	Huh-7 tumor-bearing nude mice	Kwon <i>et al</i> [62]
ZnPc	BSA-assembled NPs	/	/	Sorafenib	SMMC-7721 tumor-bearing nude mice	Yu <i>et al</i> [51]
ICG	Nanoliposomes	/	/	Sorafenib	Hep3B tumor-bearing nude mice	He <i>et al</i> [63]
Porphyrin	MOF	Folic acid	Folate receptor	/	Doxycycline-induced HCC in <i>kras</i> ^{G12V} zebrafish	Chen <i>et al</i> [64]
Ce6	SPIONs	Cancer cell membrane	/	/	SMMC-7721 tumor-bearing nude mice	Li <i>et al</i> [65]
Porphyrin	PEGylated Zr-MOF	Galactose	ASGPR	DOX	Huh-7 tumor-bearing nude mice	Hu <i>et al</i> [66]
Mitoxantrone	PEGylated UCNP micelles	Anti-EpCAM antibody	EpCAM	/	BEL-7404 tumor-bearing nude mice	Han <i>et al</i> [46]
Ce6	DNA hybrids	TLS11a aptamer	/	DOX	HepG2 tumor-bearing nude mice	Zhang <i>et al</i> [67]
Ce6	Gold NPs	TLS11a aptamer	/	AQ4N	HepG2 tumor-bearing nude mice	Zhang <i>et al</i> [68]
IR780	Phospholipid/Pluronic F68 NPs	Pullulan	ASGPR	Paclitaxel	MHCC-97H tumor-bearing nude mice	Wang <i>et al</i> [69]

PSs: Photosensitizers; Pu-18-*N*-butylimide-NMGA: Purpurin-18-*N*-butylimide-*N*-methyl-*D*-glucamine; NPs: Nanoparticles; ZnPc: Zinc phthalocyanine; BSA: Bovine serum albumin; ICG: Indocyanine green; MOF: Metal-organic frameworks; Ce6: Chlorin e6; SPIONs: Superparamagnetic iron oxide nanoparticles; ASGPR: Asialoglycoprotein receptor; DOX: Doxorubicin; AQ4N: Banoxantrone.

and daily NIR exposure (0.5–1.75 W/cm²) in a patient-derived orthotopic xenograft (PDoX) mouse model *in vivo*. The results demonstrated that complete remission of deep-seated PDoX hepatoma could be achieved through NIR-irradiated ICG, indicating that ICG-based PDT is promising for the noninvasive destruction of deep-seated HCC. Meanwhile, a series of fluorogens, such as chlorin e6[81], porphyrin[64], and 5-aminolaevulinic acid[82] were investigated as new PSs for anti-HCC therapy.

However, traditional PSs have low selectivity for accumulation in neoplastic tissues with an affinity for healthy tissues, which results in phototoxicity during treatment[83, 84]. Therefore, a long period of light protection is required for patients after PDT. Additionally, PSs are easily degraded and excreted in blood circulation and have a tendency to aggregate in aqueous milieu, resulting in low bioavailability and the loss of photodynamic activity[85]. Recently, nanocarrier systems have shown potential to overcome the defects mentioned above[86–88]. In tumorous tissues, the absence of vasculature supportive tissues intimates the formation of leaky vessels and pores (100

nm to 2 μ m in diameter). Meanwhile, the poor lymphatic system offers a great opportunity to treat cancer, and this phenomenon is known as the enhanced permeability and retention (EPR) effect[89,90]. Nanoparticles (NPs) can essentially deliver PSs to tumor lesions, which contribute to their passive tumor-targeting abilities (*via* the EPR effect)[91-93]. For example, He's group[94] reported a new type of NP, copper-cysteamine (Cu-Cy), as a novel PS for anti-HCC treatment. Cu-Cy NPs not only significantly reduced the activity of HepG2 cells at a low dose after a short time of ultraviolet radiation *in vitro*, but also inhibited tumor growth *in vivo*. To further enhance the anti-HCC effects, Xu and his colleagues[63] designed NIR fluorescence imaging-guided nanoliposomes co-encapsulated with ICG and sorafenib. As expected, this nanocarrier could overcome the drawbacks of free ICG solution, such as instability in aqueous solution, rapid clearance in blood circulation, and lack of targeting, which leads it to achieve the PDT effect with negative targeting. Moreover, sorafenib also decreased the expression of vascular endothelial growth factor (VEGF) that was upregulated by PDT, which is a critical signaling factor for tumor recurrence. As such, this nanocarrier could inhibit HCC with synergistic therapeutic effects in a Hep3B tumor-bearing xenograft nude mouse model *in vivo*.

The free NPs used by PDT are subjected to inactive uptake and lack cancer cell-targeting abilities; hence, they cannot be internalized into cancer cells *via* active targeting with high efficiency[95,96]. Due to this limitation of free NPs, the paradigm of HCC treatment by PDT is now markedly shifting from NPs conjugating PSs to the tumor-specific targeting approach, which could lead to significantly improved PDT efficacy due to enhanced cellular uptake and minimize the toxic effects of associated therapeutic molecules[97,98]. Active targeting strategies using, for instance, specific ligands such as vitamins, antibodies or peptides, aptamers, could be a solution to overcome this limitation and achieve tumor-specific targeting properties[93]. The ligands can specifically bind with matching receptors on the hepatoma cell membrane and trigger receptor-mediated endocytosis[99]. For example, Li *et al*[64] designed and synthesized nanoscale gadolinium-porphyrin metal-organic frameworks as a skeleton for folic acid (FA) conjugation (FA-NPMOFs) to enhance the delivery of porphyrin into HCC cells. FA-NPMOFs exhibited a strong affinity for HCC cells with positive folate receptors and were delivered to tumor tissues in a targeted manner. Then, the porphyrin that accumulated in the tumor tissues could possess dual-function of fluorescence imaging and PDT in HCC tumor-bearing zebrafish model. After exposure to light at a specific wavelength, the singlet oxygen generated from porphyrin exerts a prominent anti-HCC effect rather than damaging the normal tissues contributing to the active targeting between FA of FA-NPMOFs and FR on HCC cells.

Another common problem of traditional PSs, such as the most widely used porphyrin derivatives and ICG, lies in their high hydrophobia and rigid planar structures as shown in Figure 1. Such a problem can collectively cause them to form aggregates in aqueous media through π - π stacking, resulting in an aggregation-caused quenching effect. This performance induces quenched fluorescence and a significant decrease in ROS generation that diminishes the imaging quality and PDT efficacy[100, 101]. Conversely, aggregation-induced emission (AIE) molecules with a twisted configuration that suppresses strong intermolecular interactions represent a new class of PSs for image-guided PDT[102-104]. These PSs with AIE characteristics (denoted as AIE PSs) present weak emission in the molecular state but exhibit strong fluorescence emission and efficient photosensitization ability in the aggregated state[105-107]. Thus, formulating targeted AIE PS dots for image-guided PDT is expected to be a new treatment for tumors[40,105,106,108,109]. In previous work[40], our group designed and fabricated integrin $\alpha_v\beta_3$ -targeted organic nanodots for image-guided PDT based on a red emissive AIE PS. The tetraphenylene derivative with typical AIE characteristic (TPETS)-encapsulated nanodots was prepared by nanoprecipitation method and further conjugated with thiolated cRGD through a click reaction to yield the targeted TPETS nanodots (T-TPETS nanodots), which could facilitate cellular uptake through active targeting by specific binding between cRGD and integrin $\alpha_v\beta_3$ and enhance ROS generation based on AIE PSs as the core of nanodots in the aggregate state. The data showed that the obtained nanodots showed bright red fluorescence and highly effective $^1\text{O}_2$ generation in the aggregated state. The T-TPETS nanodots could accumulate in tumor tissue through the EPR effect and further expedite internalization by HCC cells *via* receptor-mediated endocytosis. Based on these multiple features, both *in vitro* and *in vivo* experiments demonstrated that the nanodots exhibited excellent HCC-targeted imaging performance, which promoted image-guided PDT for tumor ablation in a HepG2-bearing nude mouse model. After light irradiation, the nanodots inhibited the growth of tumor foci and significantly extended survival. Moreover, further analysis revealed that nanodot-mediated PDT could induce time-

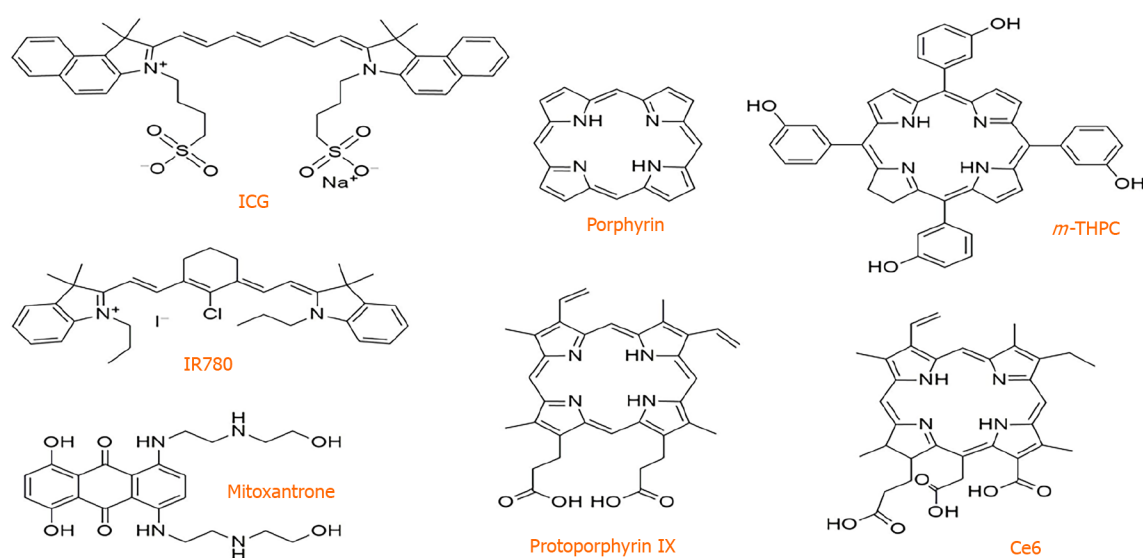


Figure 1 Chemical structures of common traditional photosensitizers for hepatocellular carcinoma in previous literatures.

and concentration-dependent cell death. Specifically, the high PDT intensity resulted in direct cell necrosis, while the mitochondria-apoptosis pathway was triggered under low PDT intensity. These results suggest that the targeted NPs loaded with AIE PSs are promising image-guided PDT agents in HCC treatment.

LIMITATIONS AND PERSPECTIVE

In recent years, numerous clinical trials have been registered of PDT for many types of tumors, but there are scarcely any trials on HCC. Therefore, some critical problems need to be conquered before further clinical practice of PDT for HCC can be realized (Figure 2). First, one major drawback of the currently available PDT is its low tissue penetration depth of light irradiation caused by the short-wavelength absorption of most PSs, which limits their clinical application[46]. The use of a self-illuminating system as a light source provides an intriguing solution to the light penetration issues of conventional PDT[110]. Some self-illuminating systems, including chemiluminescence[111] and bioluminescence[112], are promising candidates as internal light sources for PDT. These self-illuminators are small in size (ranging from the atomic/molecular to the nanometer scale) and thus can be delivered to any pathological tissue[113]. In addition, X-PDT exploits a nanoscale scintillator to down-convert external X-ray photons to visible light photons, and then the latter in turn activates nearby PSs to trigger PDT. Therefore, X-rays afford superior tissue penetration and can overcome this limitation of PDT[114,115]. Recently, Liu and her colleagues[116] developed a novel X-PDT system, taking advantage of an AIE PS with bright fluorescence and highly efficient $^1\text{O}_2$ generation in the aggregated state. Based on the high penetration of X-ray irradiation, this system could use ionizing irradiation to trigger localized PDT, indicating that effective $\cdot\text{OH}$ and SO generation was induced *via* radiosensitization-mediated energy transfer from X-rays to the AIE PS and then realized marked killing of cancer cells. This pioneering exploration revealed the great potential of AIE PSs in novel X-PDT systems to overcome the drawback of light irradiation penetration.

Second, another critical limiting factor of conventional cancer PDT is the lack of specificity of PSs. Moreover, most PSs accumulate in normal and cancer tissues indiscriminately. This performance leads to both significantly important side effects and decreased therapeutic efficacy[117,118]. Due to these obstacles, many studies have focused on the development of strategies to deliver effective therapeutic concentrations of PSs and anti-cancer agents specifically to the tumor, thereby increasing their therapeutic efficacy while reducing toxicity[99,118]. Therefore, targeted delivery of phototherapeutics, such as NP-mediated targeted drug delivery systems, is promising to minimize drug toxicity to healthy tissues through both target-specific drug delivery and by precisely controlling phototherapy-initiating external light sources[99,119,120].

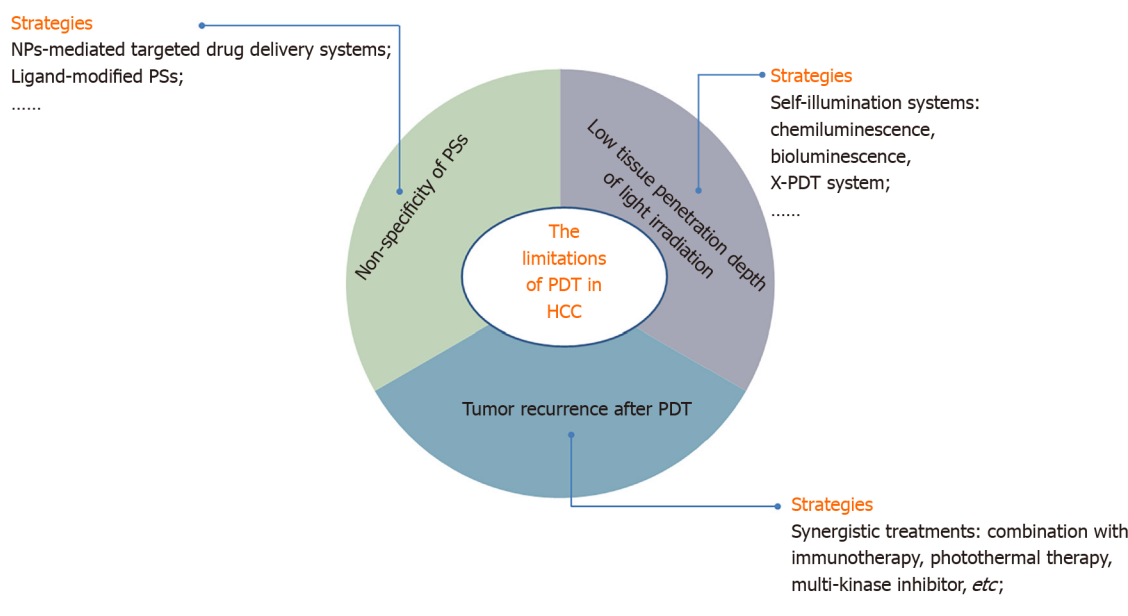


Figure 2 The limitations of photodynamic therapy in clinical practice for hepatocellular carcinoma and potential strategies to overcome the obstacles in further research.

Finally, the hypoxic microenvironment induced by PDT could secondarily accelerate the upregulation of angiogenic factors, such as hypoxia-inducible factor 1 and VEGF, and if the tumor cells are not killed completely under low light intensity, revascularization in tumor foci can be promoted, triggering the activation of signaling pathways for tumor recurrence[121,122]. Therefore, multiple combination regimens in the treatment of HCC, including immunotherapy, PDT/photothermal therapy, multikinase inhibitors and anti-VEGF agents, have attracted focus in recent years [123]. Combination therapies will hopefully increase objective responses and overall survival, contributing to the synergistic treatment of PDT and other anti-HCC therapies[124]. The multitude of available complementary and additive treatment modalities should encourage clinicians to implement a multidisciplinary treatment approach to improve the outcome in HCC patients[125].

CONCLUSION

The application of PDT in HCC has been limited due to its low tissue penetration depth of light irradiation, reduced generation of ROS, nontargeted accumulation in cancer cells, and tumor recurrence after PDT. There are several potential strategies to overcome these limitations, such as creating self-illuminating systems, NP-mediated targeted drug delivery systems, and synergistic treatments. Once these problems are resolved, PDT will be a promising alternative treatment strategy for HCC.

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