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Review

The LMIT: Light-mediated minimally-invasive theranostics in oncology

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Abstract

Minimally-invasive diagnosis and therapy have gradually become the trend and research hotspot of current medical applications. The integration of intraoperative diagnosis and treatment is a development important direction for real-time detection, minimally-invasive diagnosis and therapy to reduce mortality and improve the quality of life of patients, so called minimally-invasive theranostics (MIT). Light is an important theranostic tool for the treatment of cancerous tissues. Light-mediated minimally-invasive theranostics (LMIT) is a novel evolutionary technology that integrates diagnosis and therapeutics for the less invasive treatment of diseased tissues. Intelligent theranostics would promote precision surgery based on the optical characterization of cancerous tissues. Furthermore, MIT also requires the assistance of smart medical devices or robots. And, optical multimodality lay a solid foundation for intelligent MIT. In this review, we summarize the important state-of-the-arts of optical MIT or LMIT in oncology. Multimodal optical image-guided intelligent treatment is another focus. Intraoperative imaging and real-time analysis-guided optical treatment are also systemically discussed. Finally, the potential challenges and future perspectives of intelligent optical MIT are discussed.

Keywords: minimally-invasive diagnosis and therapy, intelligent theranostics, intraoperative imaging, optical diagnosis and therapy, image-guided surgery

1. Introduction

Cancer is a very difficult disease to cure and represents a group of diseases characterized by rapidly proliferating cells that can spread to other tissues in a process called metastasis. The complete resection of tumorous tissues by surgery or direct ablation is also challenging due to the difficulty in the identification of residual cancerous tissues. In recent decades, precision medicine has been the focus in the treatment of cancers [1]. Light has been widely used in modern biomedical and clinical applications [2,3]. Optical diagnosis, therapy are important methods for the treatment of cancerous tissue. Currently, with the rapid development of optical technology (OT), information technology (IT) and artifact intelligence (AI) [4], the intelligent integration of precision diagnosis and interventional therapeutics for

minimally-invasive surgery (MIS) plays an important role in the treatment of soft tissue carcinomas, i.e., minimally-invasive theranostics (MIT). Currently, some minimally-invasive devices based on optical technology, so-called optical MIT devices or light-mediated MIT (LMIT) devices, are routinely researched and developed in the clinical applications.

During malignant tumor eliminating (such as multiform glioblastoma, GBM), the conventional therapeutic is surgical resection based on skilled surgeons' experience during an open operation [2]. In the conventional treatment of tumors, surgical resection is also a primary and conventional means. Computer-assisted surgery [5,6] can provide a more convenient and intuitive view for the real-time resection of soft tissue sarcoma to increase the

resection accuracy, maximize normal tissue and improve the success rate of surgical resection. The quantitative identification of tumors can also precisely guide surgery or other treatment methods. To identify and segment tumorous tissue, some biomedical technologies have been proposed to acquire real-time intraoperative data and guide surgical operations. Light-mediated methods [7,8], magnetic resonance imaging (MRI) [9], X-ray [10], computer tomography (CT) [11], ultrasound [12] and ultrasound theranostics [13], five-aminolevulinic acid (5-ALA) fluorescence [14], Raman spectroscopy [15], mass spectrometry [16], laser speckle contrast imaging (LSCI) [17], multimodality imaging [18], and terahertz technology [19] have been used in clinical trials. Optical diagnosis is an effective tool for identifying diseased tissue and normal tissues to guide precise surgical resection. Hyperspectral imaging [20-22], photoacoustic imaging (PAI) [23-26] and optical coherence tomography (OCT) [27-30] have been investigated in identifying tumors and normal tissues or guiding the surgical resection of lesions.

Currently, surgery is the main treatment method for tumorous tissues [31]. Optical treatment as an effective treatment tool for tumorous tissues has gradually been investigated in clinical trials. MIT is a future direction in the treatment of diseased tissue. Laser ablation has been integrated into a theranostic system to diagnose and treat brain tumors [32,33]. Laser ablation is used as a rapid diagnostic tool to identify tumorous tissues and guide treatment of cancers. Clinical trials need direct views of the tumorous area for surgeons to guide surgical implementation. Currently, some methods, such as laser ablation, photodynamic therapy (PDT) and photothermal treatment (PPT) [2], are also useful for the treatment of diseased tissues. Similarly, before intelligent treatment, precision diagnosis, including pathology [34], provides precise and therapeutic guidance. However, these technologies still have some disadvantages, and some of them have low-resolution, low-intelligence and low-speed imaging such that they cannot achieve intraoperative real-time intelligent identification of tumorous tissues, junction zones and normal tissues. The integration of diagnosis and therapeutics, i.e., theranostics, is a novel development trend in clinical application. The technology meets the requirements of interventional operation and minimally-invasive treatment [35]. Combined with optical biomarkers, optical imaging and diagnosis could be enhanced and provide a biomedical detection method for contrast enhancement. However, suffering from intraoperative imaging, real-time and automatic diagnosis, and effective navigation, theranostics is still not realized

intelligently and effectively in current clinical trials. Medical optical technology, including optical diagnosis, and treatment technologies, provides effective and precise diagnosis and therapeutic information. Overall, light-mediated diagnosis and therapy may be a potential high-precision solution for the treatment of soft tissue carcinoma for future intelligent MIT.

In this paper, we summarize the recent advances in optical diagnosis, therapy, and intelligent MIT (**Figure** 1) and highlight the future perspectives of intelligent MIT. Intraoperative imaging-guided treatment provides great convenience in the treatment of cancerous tissues. Multimodal image-guided treatment mediated by optical technology is also reviewed and discussed. Intelligent light-medicated MIT could be effectively employed in clinical applications in the future.

2. Optical diagnosis and therapy

Intraoperative diagnosis is important for MIS. Optical- imaging biomarkers [36] provide sufficient information in clinical workflows for the noninvasive detection and characterization of disease states. The precision of the clinical diagnosis directly determines the treatment effect. Furthermore, MIS requires real-time information and imaging to support clinical decision-making. **Table 1** lists the main topics to be addressed in this review illustrating the key features and current and future research trends in the field of light-mediated diagnosis, treatment, and theranostics.

2.1 Optical diagnosis

Optical diagnosis tools, such as OCT, confocal microscopy and photoacoustic imaging, have been widely used in the research on intraoperative surgical diagnosis. Label-free imaging [34,37] is a very potentially outstanding diagnostic method. Hence, optical imaging is a very powerful intraoperative tool in guiding oncologic surgeons in radical resection to achieve optimal clinical results.

OCT has been widely used in the clinical diagnosis of disease theranostics [38-46], which usually focuses on ophthalmology, skin, and cardiovascular disease diagnosis [47]. Due to the good performance of high-speed and high-resolution imaging, OCT-mediated intraoperative imaging has great potential in clinical cancer treatment [48]. In terms of brain tumor diagnosis, OCT can provide real-time imaging and intelligent identification of cancers [27,29]. For the diagnosis of breast cancers, the possibility using deep neural networks (DNN) of margin assessment has been investigated [49], demonstrating performance significantly higher than other reported results and close to the level of a

human expert. Recently, optical coherence elastography (OCE) enabled the *in vivo* detection of residual breast cancer in the surgical cavity during breast-conserving surgery (BCS) [50]. In a first-in-human study, twenty-one BCS patients were scanned *in vivo* with an OCE probe by five surgeons. The results indicate that *in vivo* quantitative microelastology can identify residual cancer by directly imaging the surgical cavity. Furthermore, optical characterization [51,52] (**Figure 2A**) is a useful parameter in evaluating tissue features for identifying cancerous and normal tissues based on optical transmission model. *En-face* polarization-sensitive OCT (PS-OCT) can be applied to effectively characterize protruding, flat, and depressive type esophageal squamous cell carcinoma in both animal and human specimens [53]. In addition, the tumor margin could be drawn and determined on a broad *en face* view. The determined tumor margin could be in the proximity of 2 mm to the actual margin, which was proven directly using histology. Intelligent classification and segmentation methods, including deep learning [28,50,54-59] and other methods [60,61], could promote the detection and diagnosis of cancerous tissues.

Endoscopic OCT (EOCT) imaging [62] could promote the effective diagnosis of intraluminal tumors, such as gastric tumors and tracheal tumors. To emulate simultaneous clinical procedures and characterize healthy and diseased tissues, a 23 cm by 23 cm optical phantom was developed [66] to mimic the thickness and near-infrared optical properties of each anatomical layer of a human colon. The surface topography of colorectal polyps and visual appearance are acquired by endoscopic OCT compatible with white light endoscopy. Microelectromechanical systems- (MEMS-) based OCT probes have also been investigated [62,67] and can realize circumferential scanning of the intravital structure. The MEMS mirrors have a 0.5 mm × 0.5 mm mirror plate and a chip size of 1.5 mm × 1.3 mm. Full circumferential scans have been demonstrated based on different numbers of MEMS mirrors, typically two or six MEMS scanning units. Furthermore, a miniaturized OCT catheter was manufactured (outer diameter of 3.8 mm, lateral resolution of ~7 μm, and axial resolution of ~6 μm) [68]. A passive, single-fiber probe in the gastrointestinal (GI) tracts of unsedated human patients [69] has been demonstrated and can be used to guide device placement. This probe conducts device-tissue physical contact sensing and obtains two-dimensional (2D) OCT images via M- to B-mode conversion. A customized ResNet is utilized to classify these OCT catheter colorectal images for automatic image processing and real-time diagnosis. An area under the receiver operating characteristic (ROC) curve (AUC) of 0.975 was achieved in distinguishing between normal and cancerous colorectal tissue images.
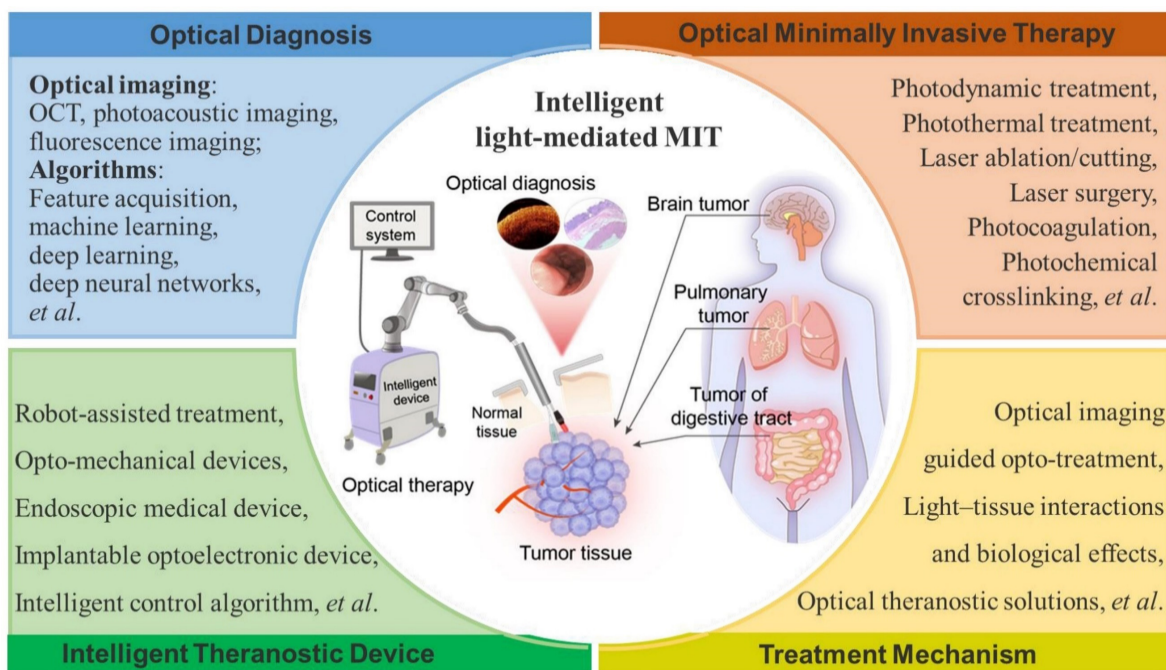

Figure 1. Light-mediated minimally-invasive theranostics (LMIT) or optical minimally-invasive theranostics (OMIT).

Table 1. Overview of topics and technical trends addressed in this review

Topic	Example terms/References	Key features	Trends/Future researches	Comprehensive comments
Optical diagnosis	Boppart SA *et al*, [40]	Optical coherence tomography (OCT), and intraoperative imaging	Intraoperative imaging, and endoscopic optical diagnosis; Multimodal optical imaging, and combining with intelligent algorithm to realize the automatic identification	First-time intraoperative imaging and guidance
	Fan Y *et al*, [62-64]	Endoscopic OCT		Endoscopic imaging for diagnosis
	Lin L *et al*, [71]	Photoacoustic tomography (PAT)		First-time whole-body PAT
	Jabbour M *et al*, [76]	Confocal microscopy		Classical pCLE in gastric cancer
	Patel KB *et al*, [80]	Other types of optical diagnosis		*In vivo* high-resolution pathological examination
Optical therapy	Jermakowicz WJ *et al*,[89]	Laser ablation	Exploring the treatment mechanism of optical treatment, and need to be guided by medical image and robot	Simulation and prediction of laser ablation for tumor treatment
	He G *et al*, [116]	Photodynamic therapy (PDT)		A transdermal theranostic microneedle patch
	Jivraj J *et al*, [90]	Laser cutting		Smart laser cutting: OCT monitors laser ablation procedure
	Meyer C *et al*, [95]	Other types of optical treatment		Some different methods based on thermal, photoacoustic, and thermomechanical effect of laser
Optical image- guided MIS	Wang C *et al*, [127]	Optical molecular imaging guided surgery	Computer- and robot-assisted navigation, and autonomous robot for surgery	Optical biomarkers for detecting tumors and guiding surgery, benefits from safety, high-spatial resolution, and high-speed capability
	Shademan A *et al*, [128]	Robot-assisted fluorescent surgery		First-time autonomous NIRF imaging guided robotic suturing
	Liu YY *et al*, [136]	ICG-guided surgery		A better signal-to-background ratio (SBR), suffering from unclear tumor boundary
	Liu YY *et al*,[138]	Multimodal optical image-guided minimally-invasive surgery		Cross-scaling imaging, suffering from difficulty in registration of multimodal images
OCT-guided laser ablation	Fan Y *et al*, [140]	OCT-guided laser ablation	Endoscopic theranostic catheter/platform, and real-time monitoring process of laser ablation	Common-scanning path integrated OCT and laser ablation
	Li Y *et al*, [144]	OCT-guided automated laser ablation		Autonomous OCT guided laser ablation
	Katta N *et al*, [142,143,147]	A fiber-laser platform		Common-path of OCT and ablation laser
	Yuan W *et al*, [150]	Theranostic needle		Rigid probe integrated OCT and laser ablation
Fluorescence imaging-guided laser ablation	Liao H *et al*, [32,33]	5-ALA fluorescence guided laser ablation	High-resolution and high-contrast imaging guided precise ablation; Endoscopic imaging with wide field of view (FOV) guided ablation	Preoperative MRI and intraoperative fluorescence guided autonomous robotic laser ablation at the first time
	Meyer T *et al*, [153]	CARS-guided fs-ablation		A new CARS-guided fs-ablation platform
	Wang H *et al*, [154]	Endomicroscopy imaging -guided ablation		Endoscopic imaging guided laser ablation (a surface-scanning device)
Multimodal imaging guidance of laser ablation	Murgu SD *et al*, [155]	White light bronchoscopy (WLB), endobronchial ultrasound (EBUS), and OCT guided YAG ablation	Integration of multimodal imaging and laser using a single-port theranostic platform for treatment of cancers; Preoperative navigation and intraoperative multimodal imaging fusion guided ablation for minimally-invasive theranostics of cancers	Multimodal imaging (WLB, US, and OCT) guidance for laser ablation (Clinical research, case study)
	Nguyen VP *et al*, [156]	PAM and OCT guided laser ablation		PAM and OCT guided laser ablation
	Basij M *et al*,[157]	Ultrasound and photoacoustic (PA)-guided laser ablation theranostic device		A platform and device integrated PAI guided laser ablation at the first time
	Yan Y *et al*, [159]	An integrated PAI and HIFU guided laser and ultrasound		PAI guided laser and HIFU (*in vivo*)
OCT-guided PDT/PTT	Hamdoon Z *et al*, [167]	OCT guided PDT	Endoscopic functional OCT guided PDT/PTT; Exploring the mechanism of PDT/PTT using functional OCT	Structural OCT image guided PDT
	Standish BA *et al*, [168]	Doppler OCT guided PDT		Functional OCT guided PDT: Doppler, Angiography, and elastic imaging for exploring the mechanism of PDT and PTT
	Sirotkina MA *et al*, [169]	OCTA guided PDT		
	Sirotkina MA *et al*, [171]	OCTA and OCE guided PDT		
Multimodal optical image-guided PDT/PTT	Liu L *et al*, [174]	NIRF/PA/CT multi-modality imaging guided PTT and PDT	Endoscopic functional optical imaging guided PDT/PTT; Exploring the mechanism of PDT/PTT using functional optical imaging	Based on tumor microenvironment-responsive nanocomposites
	Lee H *et al*, [8]	Endoscopic bioelectronics and theranostic nanoparticles		An excellent MIT framework, suffers from the safety of theranostic nanoparticles, and the lack of endoscopic control strategies for MIT
	Sim C *et al*, [177]	Photoacoustic imaging and near-infrared light-triggered theranostic platforms		Functional imaging to monitor theranostic effect, lack of effective theranostic method or devices
	Muhanna N *et al*, [180]	Multimodal image-guided surgical and photodynamic interventions		Multimodal image-guided surgical and photodynamic interventions, lack of theranostic methods

The real-time imaging feature of OCT enables doctors to observe and intervene in a timely manner, especially during ophthalmic surgeries and biological tissue sampling processes. OCT can be combined with other imaging techniques such as ultrasound or fluorescence imaging to provide more comprehensive

information and improve diagnostic accuracy. Compared with radiation imaging such as X-ray imaging, OCT does not produce radiation, making it safer. Furthermore, the imaging depth of OCT is limited and suitable for observation of shallow tissues. Endoscopic OCT can display the fine structures inside organs, which is helpful for the diagnosis of early diseases within organs, such as intestinal mucosal abnormalities and esophageal lesions. However, although EOCT is relatively mild, it still requires the insertion of an endoscope, which may cause complications such as discomfort, bleeding, or infection. In addition, the use of EOCT requires experienced doctors to ensure correct navigation and image acquisition. Currently, more and more research on image navigation technology in endoscopic surgery is expected to break away from this limitation.

PAI was developed to provide effective and functional information regarding breast tissue [70,71] and brain tissue [72,73]. A single-breath-hold photoacoustic computed tomography (SBH-PACT) system [70] (**Figure 2B**) was investigated and revealed detailed angiographic structures in human breasts. SBH-PACT features a deep penetration depth (4 cm *in vivo*) with high spatial and temporal resolutions (255 μm in-plane resolution and a 10 Hz 2D frame rate). Recently, real-time three-dimensional (3D) contour scanning of tissue via ultraviolet photoacoustic microscopy in the reflection mode was used to intraoperatively evaluate undecalcified and decalcified thick bone specimens [73]. This method may allow for the rapid diagnosis of bone-tissue pathologies and aid the intraoperative determination of tumor margins. Furthermore, miniature microfibers with a large evanescent field encapsulated in polydimethylsiloxane (PDMS) [74,75] provide an excellent platform for the interaction between optical signals and ultrasound waves, exhibiting a high sensitivity of 3.5 mV/kPa, which is approximately 10 times higher than that of single-mode fiber sensors. The highly sensitive microfiber ultrasound sensor provides a competitive alternative for various applications, such as industrial nondestructive testing, biomedical ultrasound, and photoacoustic imaging.
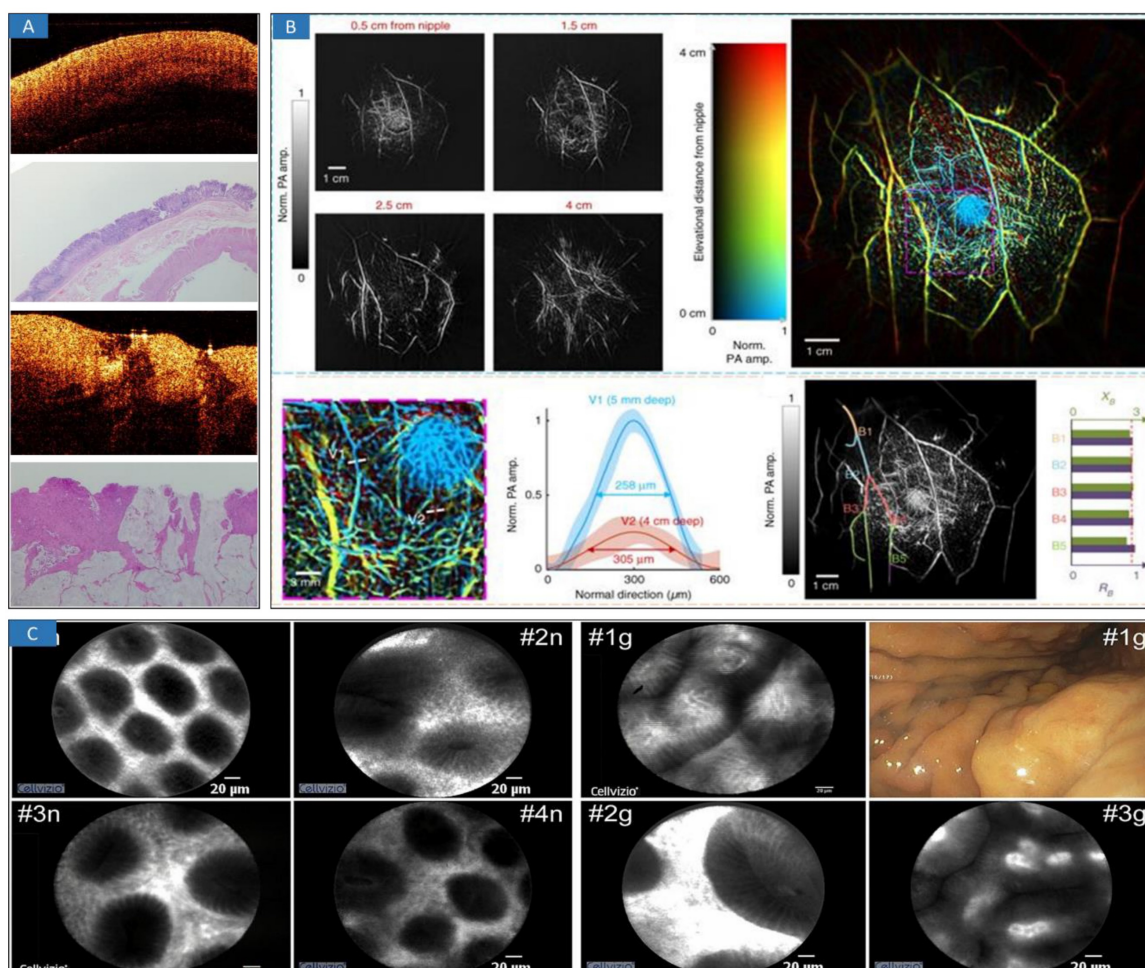

Figure 2. Optical minimally-invasive diagnosis. **A** OCT images and histology of normal tissue and cancerous tissue. Adapted with permission from [52], copyright 2019 IOP Publishing. **B** SBH-PACT of healthy breasts. Vasculature in the right breast of a 27-year-old healthy female volunteer. Adapted with permission from [71], copyright 2018 Springer Nature. **C** CLE images of a normal gastric mucosa ("n") and mild gastritis ("g"). Adapted with permission from [76], copyright 2021 Springer Nature.

Confocal microscopy has been used in the diagnosis of gastric cancers [76] (**Figure 2**C), such as confocal laser endoscopy (CLE). This high-resolution, noninvasive imaging technology provides the ability to microscopically evaluate cellular and subcellular features in tissue *in vivo* by optical sectioning [77]. Because many cancers originate in epithelial tissues accessible by endoscopes, confocal endomicroscopy [78,79] has been explored to detect regions of possible neoplasia at an earlier stage by imaging morphological features *in vivo* that are significant in histopathologic evaluation and screening.

Other types of optical diagnosis are emerging over times with the innovation of optical technology, such as light-sheet microscopy [80], Mueller matrix imaging [81], and near-infrared fluorescence (NIRF) [82]. Multimodal optical images are a hot topic in current research [83,84]. A tri-modality imaging system [85,86] that integrates US, OCT, and NIRF for pancreaticobiliary duct imaging has been proposed. Similarly, an integrated PAT, OCT, and OCTA system has been developed to extract the human cutaneous microvasculature. This multimodal system has been demonstrated as a valuable tool for comprehensive noninvasive human skin vasculature and morphology imaging *in vivo*. Similarly, a dual modality imaging system that integrates PAT and OCT has also been developed and is like OCT and autofluorescence imaging [87]. These systems have great clinical potential in mechanistic studies of real-time light-mediated treatment, early diagnosis, and prognosis evaluation of malignant pancreaticobiliary carcinomas. Endoscopic optical diagnosis could be a potential effective solution for noninvasive cancer diagnosis in MIT, such as endoscopic multimodal imaging systems [88]. Hence, optical diagnosis could be more widely used in the clinical realm in the future.

Recently, the rise of deep learning has greatly increased the applicability of optical imaging diagnosis and improved its diagnostic accuracy. Deep learning models can be used to automatically segment different tissue layers in optical images and identify disease markers; optical images can also be classified to help doctors diagnose diseases. It can also help doctors monitor the progress of patients' diseases. Finally, deep learning technology can improve the quality of optical images, reduce noise, and improve the interpretability of images. However, the labeling cost of optical images is high, and the dataset is relatively limited. The model performs well on specific datasets, but its generalization to other datasets or clinical practice may be unstable. In addition, the successful integration of deep learning technology into clinical diagnosis requires appropriate norms.

2.2 Optical therapy

Optical therapy includes photothermal, photomechanical, and photochemistry treatments. There are three important methods as follows: laser ablation, PDT, and PTT. Currently, laser ablation and PDT are mainstream clinical applications. Laser ablation is widely used in current clinical applications [89]. Through photothermal refection and vaporization, biological tissues can be effectively removed and ablated. Other optical therapies, such as laser cutting and laser osteotomy [90], are promising for future clinical applications.

Laser ablation is a solution involving the surgical removal or direct radiation of a tumor using laser technology to effectively eliminate tumorous tissue. By applying direct radiation with a high-power focused laser, tumorous tissue can be rapidly changed into vaporization and carbonization, thus eliminating the tumorous tissues. In the clinic, laser therapy is mainly applied for the treatment of tumors in the skin [91] and head and neck [92] and in neurology departments [93], but lasers are also suitable for the treatment of liver [94], lung [95], stomach [96], kidney [97], intestine [98] and other internal tumors [99]. For the treatment of pancreatic adenocarcinoma, laser ablation under the guidance of endoscopic ultrasonography (EUS) [100] has been introduced, and the results demonstrate that, complete tumor ablation (CTA) was achieved in 94% of the patients in the US-laser ablation group and 100% of the patients in the EUS-laser ablation group (p=0.261). To demonstrate the feasibility of laser ablation, an EUS-guided PC ablation technique with enhanced safety was developed [101] (**Figure 3**). *Ex vivo* tests showed that both the ablation thickness and volume increased linearly with the applied power without carbonization and fiber degradation.

The treatment mechanism of laser ablation is very important for exploring the laser-biological tissue effect and thermal propagation during laser treatment. A laser hot needle has been proposed for tissue tract ablation [102,103] that is powered by a 4500-nm-diode laser incorporated with a closed loop control system that comprises a uniform fiber Bragg grating (FBG) temperature sensor and a computer. The laser power based on the real-time feedback input from the FBG temperature sensor [104] is regulated by a proportional–integral–derivative (PID) control system to control the needle temperature. To improve the strength and quality of laser tissue welding, the influence of temperature on the welding strength of biological tissue during the welding process was explored to establish a model of the relationship

between welding temperature and tensile strength [105]. In addition, OCT and infrared thermal imagers are applied to monitor the morphology and temperature during laser ablation [106]. The results demonstrated that there was a good linear relationship between the radiation duration and temperature variation. Furthermore, the numerical simulations [107,108] match the experimental results in terms of temperature development and thermal damage. Measuring the interaction effect between light (or lasers) and biological tissue is very difficult during the laser ablation of diseased tissues. Numerical simulation and blackbody measurement may be useful methods for obtaining the relevant parameters in the process of laser ablation interaction [109-111]. Hence, real-time monitoring and numerical simulation would be important methods for studying the mechanism and precision treatment of laser ablation for cancer treatments. Furthermore, real-time temperature monitoring is also important during LA. Infrared monitoring is a useful method to sensing the temperature of biological tissues' surface. MRI and FBG are treated as depth-related temperature monitoring methods. With automatic temperature regulation algorithms and estimation of thermal parameters, these methods would be a good solution of laser treatment for cancer therapy.

PDT started approximately in 1960 by Lipson [112], who adopted a photosensitizer and a relevant red-colored laser to destroy tumor cells in terms of single oxygen. PDT is being tested in the clinic for use in oncology [113] to treat head and neck, brain, lung, pancreas, intraperitoneal cavity, breast, prostate, and skin cancers. How does PDT work, and how can it be used to treat cancer [114]? This seems to be a difficult question and be still a substantial challenge in clinical cancer treatment due to the low-level targeting and specificity of photosensitizers. Recently, a synthetic biology approach [115] was proposed to construct a transdermal theranostic microneedle patch integrated with 5-ALA and catalase coloaded tumor acidity-responsive copper-doped calcium phosphate nanoparticles by maximizing the enrichment of intratumoral protoporphyrin IX. A new form of PDT has been demonstrated [116] (**Figure 4**) in which nonlinear optical interactions of laser radiation with a biological medium *in situ* produce light that falls within the absorption band of the photosensitizer. Photosensitizers combined with functional microrobots [117] are being explored in medical fields. PPT is a treatment method that injects materials with high photothermal conversion efficiency into the human body [118], uses targeted recognition technology to gather near tumorous tissue, and converts light energy into heat energy under the radiation of external light sources (generally near-infrared light) to kill cancer cells. PTT usually results in localized thermal damage to normal tissues [119]. Exogenous photothermal contrast agents [120] are not required for PTT but can enhance the efficiency and efficacy of treatment. To further improve the survival rate of cancer patients and reduce possible side effects in other parts of the body, it is still necessary to explore PTAs (**Figure 3**) with high selectivity and precise treatment [121,122].
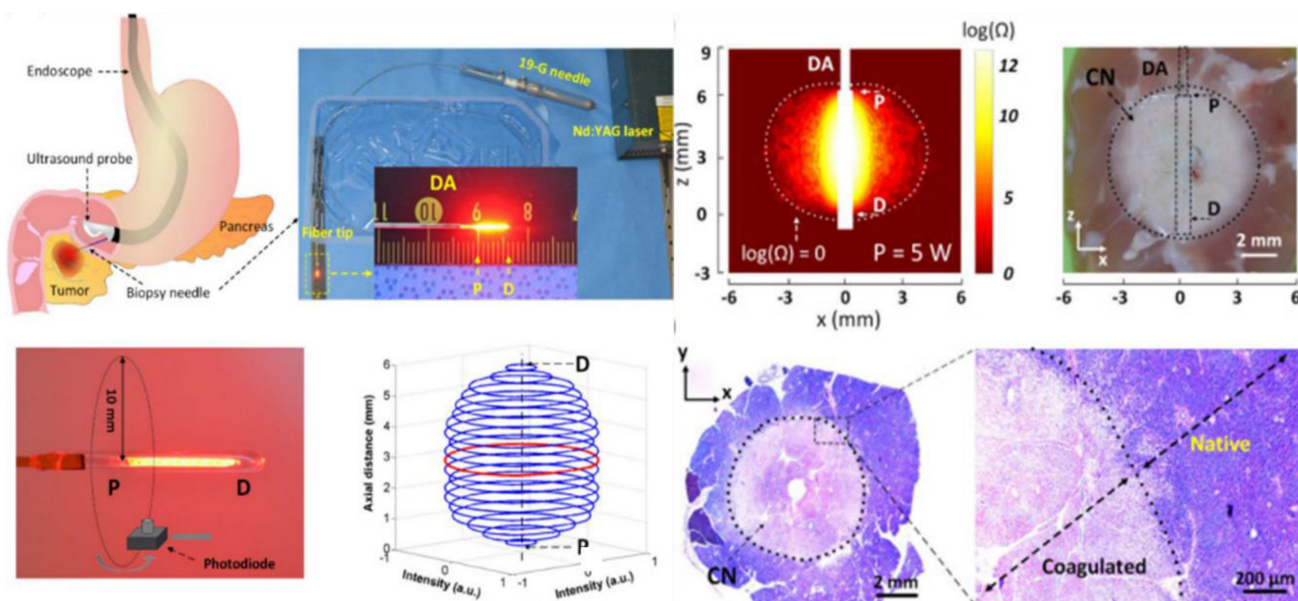

Figure 3. Laser ablation for cancer treatment. Circumferential interstitial laser ablation (CILA) of pancreatic tissue; illustration of endoscopic ultrasound (EUS)-guided CILA of pancreatic adenocarcinoma with a diffusing applicator through a small biopsy needle (19-G), uniform HeNe light distribution along a diffusing applicator, and 3D normalized spatial emission profile measured by photodiode. Adapted with permission from [101], copyright 2021 Optica Publishing Group.
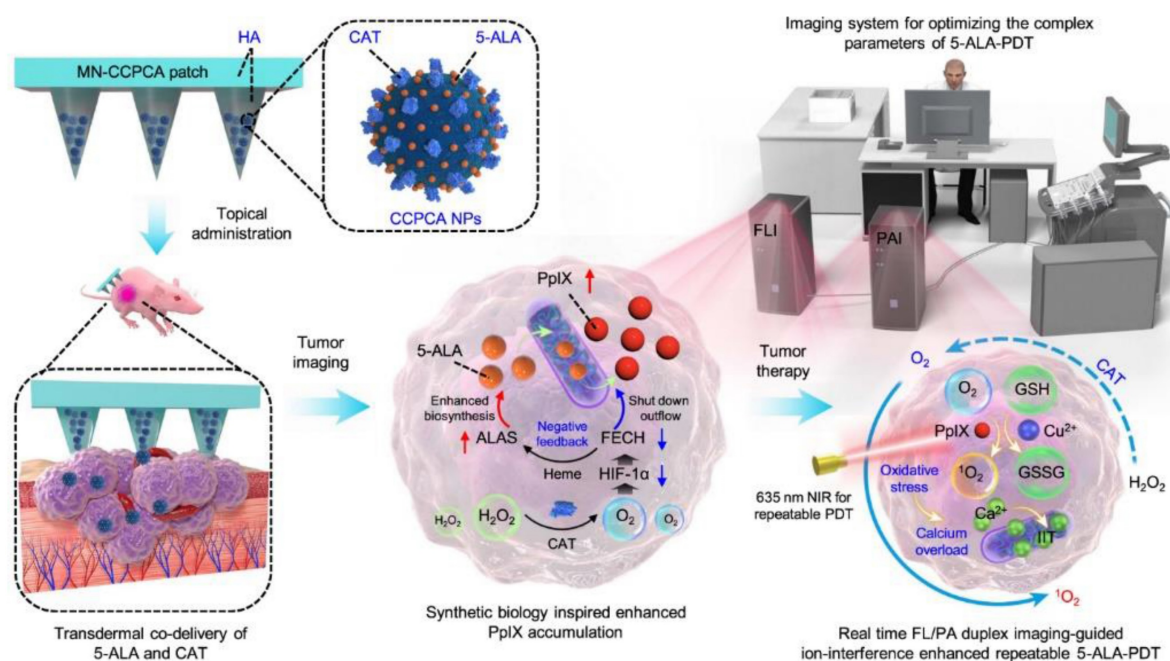
Figure 4. PDT and PPT for the treatment of cancers. *In vivo* real-time companion theranostics by a MN-CCPCA patch. The MN-CCPCA patch platform offers a strategy to monitor *in vivo* real-time PpIX and sO$_2$ levels and optimize treatment parameters through duplex FL and PA imaging, ultimately improving the therapeutic efficacy and biosafety of 5-ALA-PDT. Adapted with permission from [116], copyright 2022 Springer Nature.

Currently, some flexible and controllable endoscopes can be used to assist laser ablation [123], PDT, and PDD [124] in achieving efficient tumor removal. The integration of lasers with robotic control represents the next frontier in laser microsurgery. The device is 6 millimeters in diameter and 16 millimeters in length and can focus and steer a fiber-delivered laser beam at high speed (1.2-kilohertz bandwidth) over a large range (over ±10 degrees in both axes) with excellent static repeatability (200 micrometers) [123]. A new flexible laser endoscope that integrates PDD and PDT and provides a controllable laser radiation field for the surgeon. Experimental results proved that the resolution of both diagnosis and treatment images was five times higher than that of standard laparoscopy [124]. With the assistant of flexible device, optical therapy would will play a bigger role for the treatment of cancers.

3. Optical imaging-guided minimally-invasive therapy

3.1 Optical image-guided MIS

Optical image-guided MIS is a promising technique for adequately detecting tumor margins by tumor-specific targeting and effectiveness, potentially resulting in the complete resection of tumor tissue with improved survival and quality of life [125]. Optical molecular imaging [126] for tumor detection severely depends on the imaging probes, which have been developed to target these biomarkers to improve the tumor contrast over the background tissue [127].

Robot-assisted tissue surgery provides supervised autonomous operation [128]. Due to limitation in the probe's safety and effectiveness, such surgery has a small number of clinical applications. Furthermore, the identification of the photons from the fluorescent contrast agent is complicated by autofluorescence, optical tissue properties, and accurate fluorescent targeting agents and imaging systems. Recently, some high-contrast fluorescent contrasts have been proposed. Aggregation-induced emission luminogens (AIEs) represent a promising probe for enhancing the imaging contrast of soft tissue tumors [129]. However, these contrasts have only been explored in animal experiments and are currently difficult to apply in clinical practice. Multimodal optical image-guided minimally-invasive therapy [130,131] is an important development direction in the future. By the fusion of multimodal optical images, more abundant biological-tissue information and a greater surgical field of view (FOV) can be obtained effectively.

Computer- and robot-assisted navigation are important development directions for optical image-guided MIS [132,133]. A supervised autonomous three-dimensional (3D) path planning, filtering, and control strategy for smart tissue autonomous robot (STAR) was developed to enable precise and consistent incisions in complex 3D soft tissues [134]. The proposed strategy reduces the surface incision error and depth incision error by 40.03% and 51.5%, respectively, compared to a teleoperation strategy via the Da Vinci system. A concept of automated augmented reality (AR) registration, while the organs

undergo deformation during surgical manipulation, is presented based on finite element modeling (FEM) coupled with optical imaging of fluorescent surface fiducials [135]. The mean measured distance between the estimated tumor by biomechanical propagation and the scanned tumor (ground truth) was 0.84 ± 0.42 mm. Indocyanine green (ICG) for fluorescence image-guided minimally-invasive treatment of cholangiocarcinoma and hepatocarcinoma has been demonstrated to increase safety [136-137]. Preliminary clinical results demonstrated this technique of NIR cholecystocholangiography by intragallbladder ICG injection during laparoscopic cholecystectomy [136]. It can be considered in difficult cases to increase the safety of laparoscopic cholecystectomy. The feasibility of fluorescence liver segmentation by superselective intrahepatic arterial injection of ICG has been evaluated [137]. ICG plays an important role in MIS or MIT. Intrahepatic arterial ICG injection rapidly highlights hepatic target segment borders with a better signal-to-background ratio (SBR) than portal vein injection. Therefore, ICG is an effective tool to enhance the tumorous tissues, while, the tumor boundary is still unclear. This question is a challenge in clinical applications, more targeted contrast and automatic identification algorithms would be developed for enhancing the SBR and clear boundary of diseased tissues to future improved clinical applications.

3.2 OCT-guided laser ablation

In 1999, OCT-guided laser ablation for minimally-invasive treatment was proposed for the first time [139]. Real-time OCT imaging is used to guide placement and observe the dynamics of surgical laser ablation in a variety of tissue types. OCT-guided laser ablation of brain tumors was proposed in our previous research [140] (**Figure 5A**). OCT, as a fast and high-resolution imaging method, is used to monitor and sense laser surgery and ablation [141]. Usually, OCT imaging is only used as a mean of monitoring but not as an effective method of intelligent intraoperative diagnosis and guided real-time treatment. Recently, Nitesh Katta et al proposed the integration of OCT and laser ablation for the minimally-invasive treatment of cancers, and animal experiments were conducted in which phantom blood vessels [142] and animal brain tumors [143] were treated. The combination of high-resolution, fast OCT coaligned with a nanosecond pulsed thulium (Tm) laser [142] offers advantages over conventional surgical laser systems. A tissue removal rate of 5.5 mm^3/sec was achieved experimentally in comparison to the model prediction of approximately 6 mm^3/sec. The theranostic system

[140,143] (**Figure 5B**) combines OCT guidance with surgical lasers for high-precision tumor ablation (Er: YAG) and microcirculation coagulation (thulium (Tm) fiber laser). Our previous research revealed that intelligent theranostics is an important development direction through intelligent robot assistance and precise surgical-path planning [144,145], and the surgical robot can reach the planned position with high precision, which is approximately 1.16 mm. Experiments show that the proposed system is capable of clearing lesions efficiently and precisely. Intelligent OCT-guided laser ablation provides feedback information reflecting the intraoperative situation in real time [146]. But, this method is adjustable open surgery, and for minimally invasive surgery, it needs to be reconsidered.

A fiber-laser platform integrated with OCT imaging has also been developed for precision brain surgery [147]. Two-fiber lasers were combined into a single biocompatible silica fiber to conduct brain surgery resection under the bench-top OCT system's imaging microscope. Thermal injury was measured to be less than 100 µm, while the removal rate was close to 5 mm^3/s with an average Tm fiber-laser power of 15 Watts. Furthermore, OCT guided endoscopic laser surgery [148] is a hot topic for future clinical cancer treatments. Endoscopic theranostic catheter of the OCT and ablation has been proposed [149]. The catheter consists of a fiber bundle including 41 multimode fibers with an outer diameter of 0.9 mm. A rigid theranostic probe was also developed by combining OCT and laser ablation [150] (**Figure 5C**). This theranostic needle's performance was demonstrated by *in vivo* ultrahigh-resolution (1.7 µm axial and 5.7 µm transverse), high-speed (20 frames per second) volumetric imaging of mouse brain microstructures and optical attenuation coefficients. Its translational potential was further demonstrated by *in vivo* cancer visualization and efficient tissue ablation in a deep mouse brain. This research implemented the hard theranostic endoscope with the OCT guided laser ablation rather than flexible or switchable-hardness endoscope as mentioned earlier, so it has some invasion during cancer treatment. As the development of material, mechanical, and information sciences, flexible endoscope with theranostic function using light-mediated diagnosis and therapy can be developed to provide minimally invasive invention and treatment by choosing approximate light energy. For example, switchable rigid-flexible robot endoscope would be integrated with fibers and MEMS mirrors to reflect the light of OCT-based diagnostic and ablation-based therapeutic to tissues using the common optical path method.
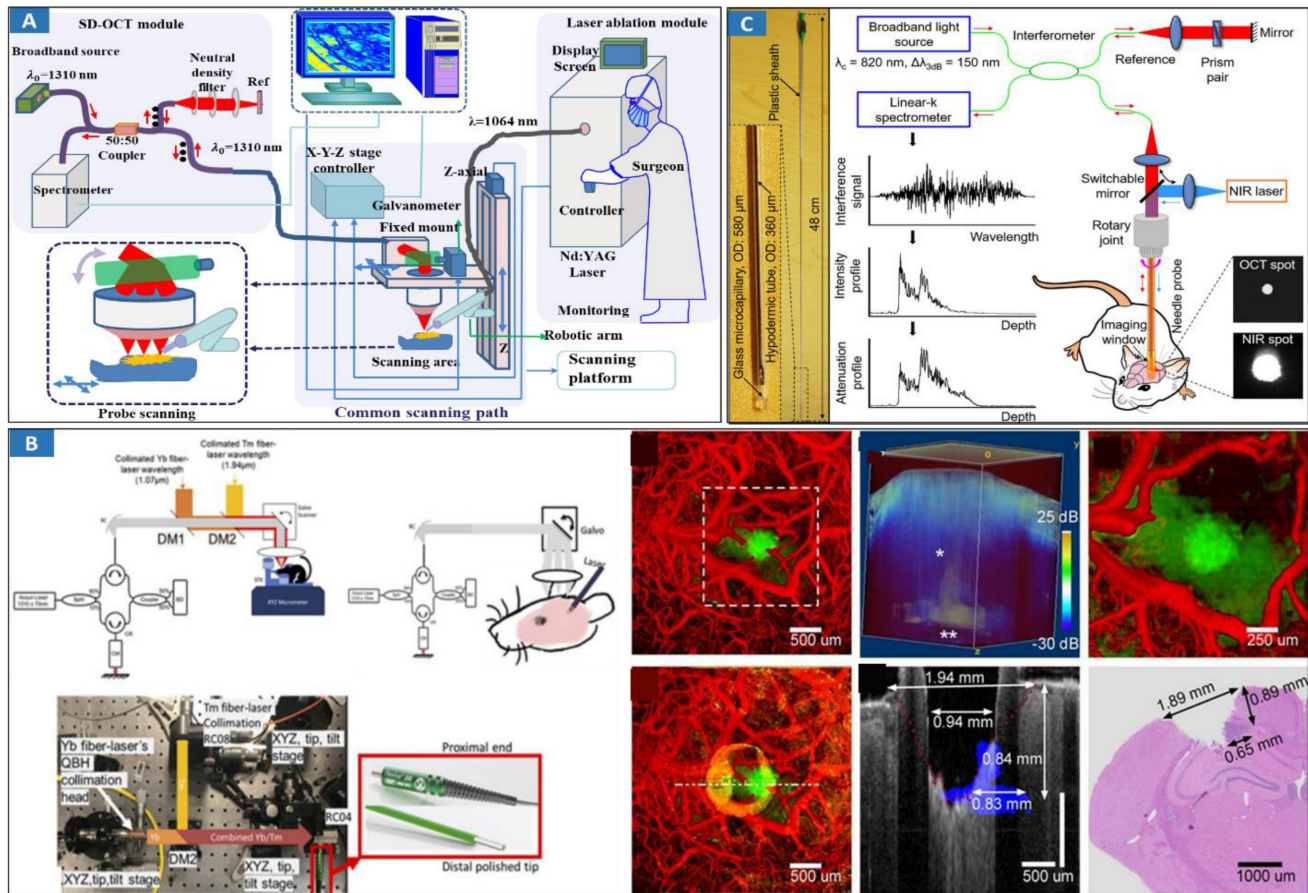
Figure 5. Optical MIT based on OCT-guided laser ablation for cancer treatment. **A** Principal schematic of the integrated SD-OCT and laser ablation system. The system includes an SD-OCT unit, laser ablation module, and endoscopic scanning platform module. Adapted with permission from [140], copyright 2018 Elsevier. **B** Benchtop OCT-guided laser surgery system with coaligned Tm/Er beams. Tm/Er and OCT beams are fiber delivered via reflective collimators (RC) and combined with di-chroic mirrors (DM). Histology of a 5 µm thick transverse section located 550 µm from the cortical surface, and B-scan of tumor regions (blue). Adapted with permission from [143], copyright 2018 Ivyspring International Publisher. **C** Theranostic microneedle system with ultrahigh-resolution OCT imaging and laser ablation. Photograph of the microneedle with a hypodermic tube of a 360-m OD and a 0.48-m rigid length. Adapted with permission from [150], copyright 2020 AAAS publications.

3.3 Fluorescence imaging-guided laser ablation

Fluorescence imaging-guided laser ablation provides a highly efficient treatment for cancers. 5-ALA fluorescence imaging has been incorporated into a robotic laser ablation neurosurgery system [32,33]. The accuracy of the fluorescent measurement of the tumor was improved using a high-precision spectral analysis. Fluorescence assists in the detection of malignant brain tumors intraoperatively and improves their removal rate. A contactless tumor removal system that utilizes endogenous fluorescence feedback to inform the laser ablation system to execute the autonomous removal of phantom tumor tissue was created [151] (**Figure 6A**). This completely noncontact surgical system can resect the tumor boundary of a tissue phantom with an average root mean square error (RMSE) of approximately 1.55 mm and an average max error of approximately 2.15 mm. A fluorescence-guided laser ablation system for the removal of residual cancer has been proposed [152] (**Figure 6B**). This pulsed Nd:YAG laser ablation system, when used in conjunction with a molecular

imaging system, can identify and ablate cancer *in vivo*. Laser ablation was guided by fluorescence imaging to target tumor tissues while avoiding normal structures.

CARS imaging has been combined with fs-laser ablation as a new approach for image-guided precision surgery [153] (**Figure 6C**). CARS-guided fs-ablation has been applied to ablate brain, liver, skin, muscular and vascular tissues with µm-level precision using sub 100 fs pulses at the µJ level. Superior imaging performance, contrast and detection of tissue margins is demonstrated by coherent Raman microscopy in comparison to laser reflectance imaging. A novel robotic device for intraoperative large-area endomicroscopy imaging and image-guided ablation has been proposed [154]. The device also includes a laser ablation fiber to precisely ablate target tissue under the image guidance without the need for additional assistance. As mentioned earlier, tumor boundary could be not clear so that laser ablation cannot effectively treat the tumor. Enlarged ablation area is needed to totally eliminate

tumorous tissues. Hence, classical assistant device should be developed.

3.4 Multimodal imaging guidance of laser ablation

Multimodal imaging can provide great information to guide laser ablation in the treatment of cancers. An integration of white light bronchoscopy (WLB), endobronchial ultrasound (EBUS), and OCT might identify *in vivo* airway wall changes before and those resulting from Nd:YAG laser ablation and dilation of tracheal stenosis [155]. High-resolution multimodal PAT and OCT were developed to improve the efficiency of visualizing newly developed retinal neovascularization (RNV) and monitor the dynamic changes in retinal vein occlusion (RVO) [156]. A novel photoacoustic (PA)-guided laser ablation theranostic device [157] was developed based on a traditional phased-array endoscope. The proposed technology exhibits the effective capabilities of lesion formation, tissue distinguishing, and temperature monitoring. An integrated photoacoustic imaging and high intensity focused ultrasound (HIFU) system [158] using a 5-ns tunable OPO laser system and a 5 MHz HIFU transducer was used to perform a photoacoustic analysis to identify the optical contrast and perform combined laser and ultrasound ablation [159]. US-guided laser ablation systems [100] have been developed for pancreatic tissue. US is a useful theranostic tool, which also can focus on US imaging guided HIFU treatment, and provide real-time imaging and diagnostic information, however, US suffers the limitation of resolution and contrast, is difficult to image the approximate cellular-size tissues.

MRI-guided laser ablation is an exciting new minimally-invasive technology for the treatment of cancers. MRI-guided laser interstitial thermal therapy (MRgLITT) is a procedure for destroying tissue using heat effects. This approach can be used in the treatment of epilepsy [160] and hepatocellular carcinoma [161]. The integration of MRI and bioluminescence imaging (BLI) can be used to guide laser ablation and provide quantitative information reflecting the laser ablation effect of carcinoma. Recently, we demonstrated that BLI and two-photon microscopy (TPM)-guided laser ablation of GBM decreased the tumor burden [162]. The BLI quantitatively and qualitatively evaluated treatment using laser ablation with the appropriate laser parameters and laser-tissue parameters. The accuracy of the laser ablation reached a submillimeter level, and the resection ratio reached more than 99% under the guidance of BLI. In future, it is possible to be combined with some intelligent or smart robotic technologies toward high-precision treatment for tumors ablation. Furthermore, multimodal imaging can provide plentiful and abundant information to guide laser ablation. Such information includes cross-sizing structural, and functional features for representing the tissues and can be used to guide the precision treatment of diseased tissues.

4. Optical image-guided PPT and PDT

PPT/PDT is a useful and efficient solution for the treatment of soft tissue carcinomas. Combined with OCT/OCTA and other optical imaging modalities, the treatment effect and response of PDT/PTT could be clearly presented through the visualization of multimodal images.

4.1 OCT-guided PDT/PTT

Due to the high resolution and rapid imaging speed, monitoring changes with OCT in blood flow
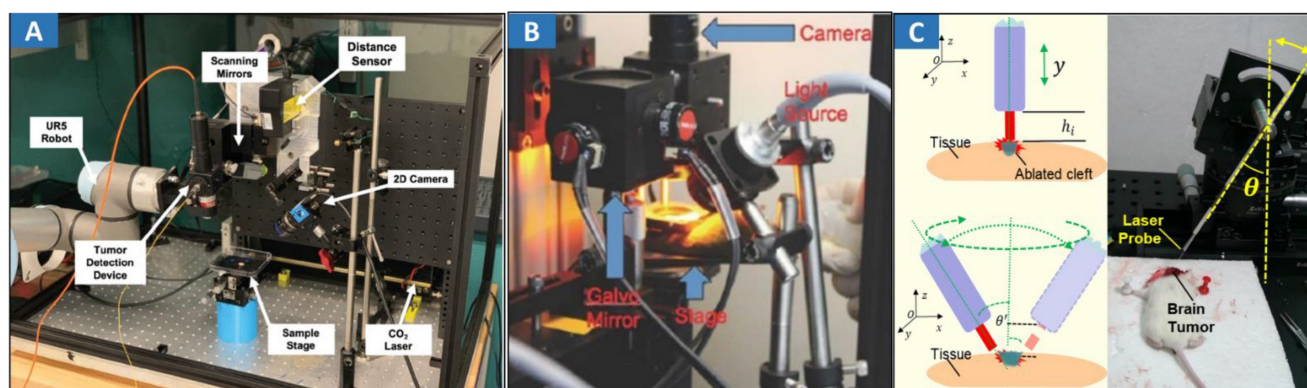

Figure 6. Optical MIT based on optical image-guided laser ablation for cancer treatment. **A** Experimental setup showing the TumorID positioned with the FOV of the TumorCNC by the UR5 robot. Adapted with permission from [151], copyright 2021 IEEE. **B** Paired imaging/laser ablation prototype and system characterization. The optical layout of the integrated image detection and laser ablation system is shown. A 1064 nm laser source is directed through a diffuser toward a series of motorized galvo-mirrors. A fiber bundle is connected to a xenon light source and attached to the system to illuminate the specimen. Adapted with permission from [152], copyright 2016 Ivyspring International Publisher. **C** Different heights between the fiber tip and tissue surface within the perpendicular incidence and different incidence angles of the fiber probe. Adapted with permission from [162], copyright 2018 Ivyspring International Publisher.

dynamics and vessel structure following pharmacological intervention and PDT have been demonstrated [163-166]. The technical feasibility of OCT has been demonstrated to map real tumor margins and monitor skin changes that occur post-PDT [167]. The technical feasibility of catheter-based intraluminal Doppler OCT (D-OCT) [168] for monitoring the microvascular response during endoluminal PDT was assessed in an animal model of Barrett's esophagus (BE). Distinct microstructural differences between normal squamous esophagus, BE, and the transition zone were clearly observed on DOCT images. Similar submucosal microcirculatory effects (47%-73% vascular shutdown) were observed during PDT of the normal esophagus and surgically induced BE. The controls displayed no significant microvascular changes. PDT monitoring with optical coherence angiography (OCTA) [169] has been proposed (**Figure 7A**), and M-mode-like OCTA (MML-OCTA) was able to sensitively detect PDT-induced microvascular alterations. OCTA for pretreatment assessment and treatment monitoring following PDT in patients has also been researched [170]. Pretreatment OCTA enabled differentiation between prevalent subtypes of BCC (nodular and superficial) and nodular-with-necrotic-core BCC subtypes with a diagnostic accuracy of 78%, which can facilitate more accurate biopsy, reduce the sampling error, and improve therapy regimen selection. Posttreatment OCTA images at 24 hours were 98% predictive of the eventual outcome. To assess the early tumor reaction and predict its long-term response, the combination of OCTA and compressional OCE enables complementary functional/microstructural tumor characterization [171]. Despite the different mechanisms of antiangiogenic action of antiangiogenic chemotherapy (ChT) and PDT, in both cases, OCA demonstrated high sensitivity to blood perfusion cessation. The novel method of OCE-based morphological segmentation revealed very similar histological structure alterations. To guide and assess PDT treatment, a handheld OCT probe was designed for real-time imaging of the PWS patient [172]. The system also has a spatial resolution of 8 µm (lateral) × 7 µm (axial), an imaging rate of four frames per second, and a 102 dB sensitivity. Functional monitoring of PDT for cancer treatment could provide useful information during and after PDT. OCT can use the characteristics of the tissues' Doppler effect, elastic properties, and angiography to detect the structural and vascular features of biological tissues treated by PDT method, then, monitor the changes during PDT.

4.2 Multimodal optical image-guided PDT/PTT

Multimodal optical image-guided PDT/PTT for cancer treatments has been widely researched [119,173-176]. ICG-guided photothermal ablation using a one-step method has been proposed for the preparation of holo-Tf-indocyanine green (holo-Tf-ICG) nanoassemblies for fluorescence and photoacoustic (PA) dual-modal imaging and PTT of glioma. Under near-infrared laser radiation, the holo-Tf-ICG nanoassemblies accumulated in tumor regions can efficiently convert laser energy into hyperthermia for tumor ablation. The novel theranostic nanoplatform holds great promise for precision diagnosis and the treatment of glioma. An endoscope with integrated transparent bioelectronics and theranostic nanoparticles has been developed for colon cancer treatment (**Figure 7B**) [8], and the nanoparticles are photoactivated within a highly localized space near tumors or benign growths. These advanced electronics and nanoparticles collectively enable optical fluorescence-based mapping, electrical impedance and pH sensing, contact/temperature monitoring, radiofrequency ablation and localized photo/chemotherapy as the basis of a closed-loop solution for colon cancer treatment. This work presents excellent MIT framework, which integrates the effective endoscopic imaging and therapy. However, it suffers from some demerits, such as the safety of theranostic nanoparticles, and the lack of endoscopic control strategies for MIT.

Photoacoustic imaging [177] and near-infrared light-triggered [178] theranostic platforms have great potential in applications, such as cancer-targeted fluorescent imaging and simultaneous ROS-activated chemo- and PDT in the near future. A multifunctional theranostic contrast agent [179] is presented for ultrasound/near infrared fluorescence imaging-based tumor diagnosis and ultrasound-triggered combined photothermal and gene therapy. The developed theranostic AuMB complexes could not only provide excellent US and NIRF imaging to detect tumors but also serve as an efficient US-triggered carrier for gene delivery and photothermal ablation of tumors in xenografted nude mice. Multimodal image-guided surgical and photodynamic interventions [180] have been proposed, demonstrating that multimodal porphyrin lipoprotein-mimicking nanoparticles (PLPs) intrinsically capable of PET, fluorescence imaging, and PDT show great potential to enhance the accuracy of HNC staging and potentially head and neck cancer (HNC) management. PDT is an effective adjuvant therapy for image-guided surgery in prostate cancer [181], demonstrating that the prostate-specific membrane antigen (PSMA)-targeted PDT agent PSMA-1-Pc413 selectively highlights

PSMA-expressing tumors, allowing IGS and more complete tumor resection compared with white light surgery. However, due to the safety and effectiveness of nanomaterials, nanomedicine [182] is difficult to apply in clinical diagnosis and treatment. Currently, photosensitizers approved clinically have important applications in tumor treatment. Multimodal optical imaging, such as OCT, confocal endoscopy, PAT, and narrowband spectral imaging (NBI) [183], combines photosensitizers to display the whole and wide FOV and present real-time dynamic information during PDT.

5. Outlooks and challenges

In this paper, we outlined emerging optical MIT platform based on optical image-guided optical treatments for MIS of cancers. Comprehensively, we summarized the research of MIS, laser ablation, PDT, and PTT in LMIT in detail and provided some objective evaluations in relevant positions. LMIT toward intelligent medical devices could provide a solution for clinical applications. Optical imaging has a high resolution, is fast and noninvasive, has other important imaging characteristics and has important clinical application value. Furthermore, label-free optical imaging is safe and effective in clinical practice. It can present the anatomical structure of biological tissue and other high-resolution images (μm level) [27,28,38-48] without a contrast agent (label-free) and can provide functional images of biological tissue. Optical imaging can provide the elastic coefficient (OCE) [184] of biological tissues, blood flow in blood vessels (OCTA, and DOCT) and other functional information, which has very important clinical significance in the recognition of soft tissue diseases. Inventors of OCT is recently awarded the 2023 Lasker-DeBakey Clinical Medical Research Award [185]. This honor has encouraged more researchers to apply OCT to a wider range (including non-invasive, high-speed, and label-free imaging) of biomedical applications, and to develop some novel light-based medical devices to clinical cancer treatment. Optical therapy, such as laser ablation, has great advantages in minimally-invasive targeted therapy of tumor tissues due to its characteristics of minimal invasiveness, radiation free and good targeting. However, the photobiological effects in the process of PTT need to be further clarified, especially the biological effects, photothermal propagation model, photochemical effects, etc., which could provide theoretical support for the mechanism of optical treatment.
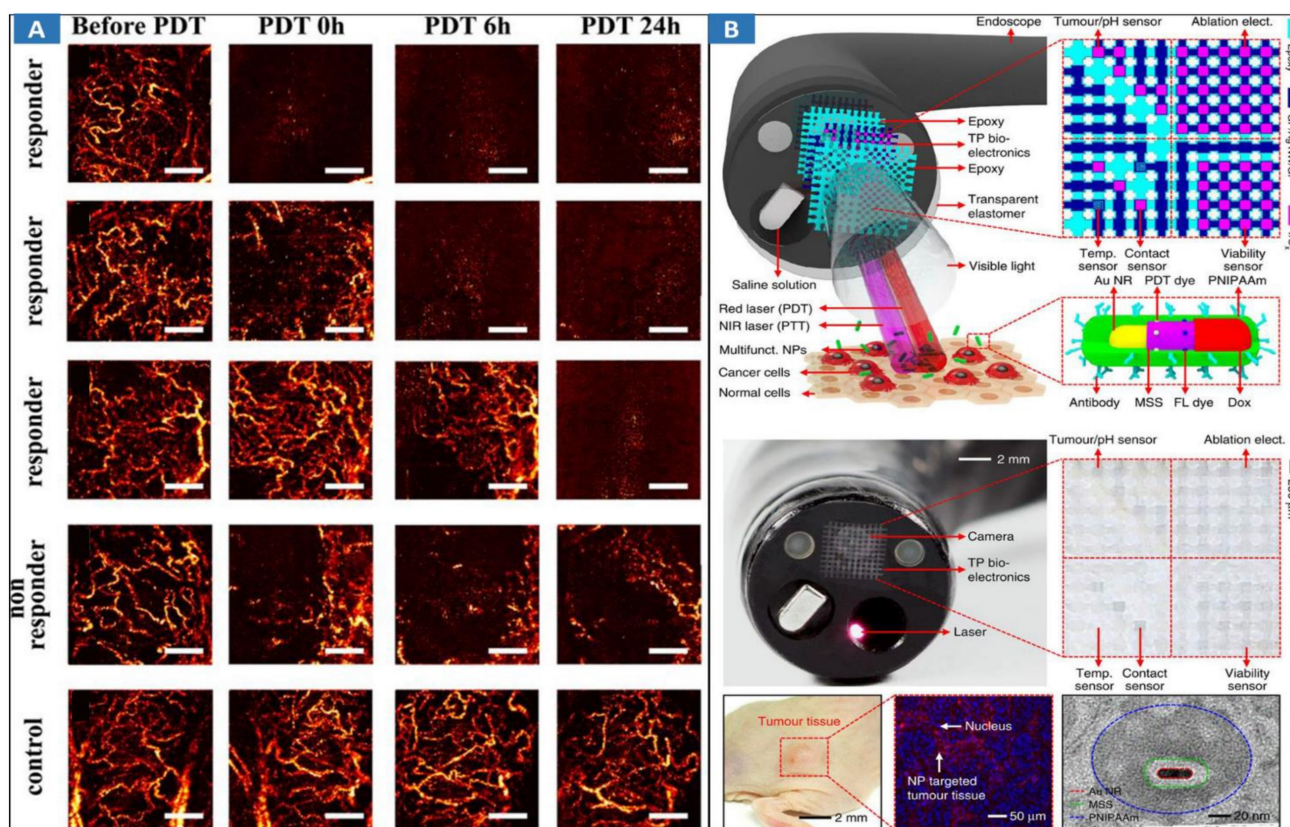

Figure 7. Optical MIT based on multimodal optical image-guided PPT/PDT for cancer treatment. **A** MML-OCA images of microvascular alteration dynamics prior to, immediately following, 6 hrs post, and a day after PDT (100 J/cm², 100 mW/cm²). Adapted with permission from [169], copyright 2017 Springer Nature. **B** Multifunctional endoscope system. Schematic illustrations of the design strategy and mode of use of the multifunctional endoscope system based on transparent bioelectronic devices and theranostic nanoparticles. Images of the system corresponding to the illustrations. Adapted with permission from [8], copyright 2015 Springer Nature.

Optical theranostics [144,145,162] include digitalized precision diagnosis, treatment, and their integration with automatic and intelligent diagnosis and treatment of diseased tissues under or without surgical assistance, which can be guided by laser ablation for cancer treatment. In terms of imaging and intelligent diagnosis, due to the limitation of the optical imaging depth (several-millimeter levels), enhancing the imaging depth is an important direction of future development, including popular optical transparency technology, which enables optical imaging diagnosis and treatment technologies to extend several millimeters in the longitudinal direction [186]. Intelligent algorithms for medical optical images can draw tumor boundaries and provide tumor grading information in the process of tumor imaging and diagnosis. With the continuous development of artificial intelligence and deep learning algorithms [50,58,59], fusion and registration based on optical images and other traditional medical images have already had extensive clinical application foundations in image-aided diagnosis, and could play a better and more extensive role in MIT for cancer treatment in the future.

Furthermore, multimodal optical images [187] provide effective and comprehensive intraoperative information regarding biological tissues, including cross-scale structural and functional information. OCT and photoacoustic imaging can complement each other in imaging depth and resolution. In the process of PDT and laser ablation, the presentation of structural and functional information provides an effective quantitative evaluation method for the clarity of intraoperative treatment. Cross-scale optical imaging could provide imaging effects on different scales for tissue precision diagnosis. Fluorescence imaging can present organ-size images; photoacoustic imaging can present submillimeter images; OCT can provide micrometer-level images of cancerous tissues; and microscopic optical imaging, such as confocal microscopy, can provide submicrometer-level images. The imaging depth and imaging resolution are contradictory. The integration of cross-scale imaging modalities can solve this problem [188].

In terms of light-mediated treatment, the mechanism of laser ablation based on NIR and visible light should be further explored. By combining numerical simulations [101,107,108,191], the thermal effect and propagation of laser radiation can be treated as an access to analyze the treatment effect on soft tissue carcinomas. The therapeutic mechanism could be established effectively to promote the further development of the theory of LMIT. In addition, the development of novel optical materials could lay a solid foundation for optical imaging and targeted

optical therapy. These materials enhance the imaging effect, including the imaging contrast, and strengthen the foreground of cancerous tissue's optical images. Furthermore, these materials could enhance the targeted feature for accumulation in cancerous tissues to intensify the treatment. However, the biological safety of these novel materials is a major challenge for novel materials. Prior to clinical application, it is urgent to carry out effectiveness verification research to determine the effectiveness and biological safety of novel materials and further prove their biological safety in humans in clinical trials.

The application of laser ablation in tumor therapy has some significant advantages. Firstly, laser ablation is a non-invasive treatment method, which can avoid the incision and trauma of traditional surgery, and reduce the pain and recovery time of patients. Second, laser ablation has less damage to surrounding normal tissues and relatively protects the integrity of healthy tissues. It can accurately locate and target tumor tissue *in vivo*, enabling precise treatment. However, laser ablation also has some limitations and risks in tumor treatment. First, the method has certain limitations on the size, shape, and location of the tumor, and it is not suitable for tumors that are large or located at specific locations. Secondly, laser ablation may not achieve the effect of comprehensive tumor removal, and there is a risk of recurrence. In addition, laser ablation may also cause some complications, such as thermal injury, scarring, or paresthesias. In view of these limitations and risks, doctors need to comprehensively consider the specific situation of the patient and the characteristics of the tumor to determine the most suitable treatment plan. In some cases, laser ablation may be used in combination with other treatments, such as surgical resection, radiation therapy, or chemotherapy, to improve outcomes. Overall, laser ablation, as a promising technique of tumor treatment, has certain application prospects and advantages. However, treatment options should be individualized for each patient and require full discussion and evaluation with a physician to ensure optimal therapeutic efficacy and safety. Precise treatment [153,162] and intraoperative monitoring [157] using laser are currently the main research directions and have great potential for future development.

Different types of tissue have different penetration capabilities of laser. Tissues, such as skin, fat, and blood vessels, penetrate laser better than bone and joint tissue. Depth is also a key factor, as laser energy tapers off in tissue, and deep tissue penetration may be limited. Laser wavelength plays an important role in its ability to penetrate tissue [189]. Different wavelengths of laser are absorbed to

different degrees by different types of tissue. Infrared laser wavelengths, for example, are outside the visible range and penetrate certain tissues better [190]. In addition, hemoglobin and melanin have high absorption capacity for laser at specific wavelengths, which may have an impact on certain therapeutic and diagnostic methods. Light scattering is an important phenomenon during the propagation of laser in tissue. Scattering causes spreading and attenuation of laser energy, limiting its penetration depth in tissue. The degree of light scattering is affected by the structural and optical properties of the tissue, such as the density and reflectivity of the tissue. Penetration in tissue is also limited by safety considerations. Higher energy lasers may cause excessive heating and risk of thermal damage to tissue. Therefore, in laser therapy, careful control of laser parameters is required to ensure a balance of safety and efficacy.

The ANSI Z136.1 standard plays an important role in laser safety management, providing guidance and requirements for the use and operation of laser equipment. However, users and operators should comprehensively consider relevant laws, regulations, and actual conditions when applying this standard to ensure the safe use of laser equipment and protect personnel and the environment from potential hazards of laser radiation. Furthermore, under the guidance of laser safety standard, medical laser and medical optical imaging can be safely researched and developed.

The automatic treatment of robotic-assisted surgery can remove the surgeon's hands, which promises enhanced efficacy and safety and improved access to optimized surgical techniques. *In vivo* supervised autonomous soft tissue surgery in an open surgical setting was enabled by a plenoptic three-dimensional and NIRF imaging system and an autonomous suturing algorithm [191]. Autonomous surgical robots have the potential to improve the efficacy, consistency, functional outcome, and accessibility of surgical techniques [192]. Through the automatic assistance of robot, optical imaging-guided microsurgery can be smoothly implemented after reinforcement learning [193]. Currently, intelligent MIT equipment [194] can provide an effective solution in laparoscopic surgery for intestinal anastomosis. Intelligent theranostic equipment includes intelligent identification, analysis, diagnosis, intelligent minimally-invasive treatment, and theranostic methods. The most typical minimally-invasive theranostic methods are usually surgical navigation and IGS. The innovative research and development of surgical navigation and IGS technology effectively integrates minimally-invasive diagnosis and treatment schemes from the perspectives of

engineering and provides an image-guided surgery algorithm and specific steps for the implementation of image-guided therapy at the design level of LMIT.

The design of hardware structures and optical path structures provides equipment support for the integration of diagnosis and treatment [195,196], especially in light source characteristics (wavelength, power, energy density, radiation time, etc.), optical path compactness, equipment integration, and system safety. In addition, in terms of treatment equipment assistance, the switchable rigid-flexible robot [197] can realize wide-field optical imaging of biological tissues and efficient intelligent treatment of tumors. Research investigating the theory and application of these aspects lays a solid foundation for the design and development of intelligent optical theranostic equipment in the future. However, in intelligent MIT, the current lack of surgical methods for specific sites and tumor resection and the selection of treatment plans are still urgent directions of research necessary for the personalized and precise treatment of soft tissue carcinomas.

The endoscopic theranostic platform [198] is a future development direction in LMIT and could promote the rapid development of MIS. Given the versatile role of light in nature, the many ways that light-based theranostic approaches can sense, monitor, and manipulate treatment processes are not surprising. Endoscopic OCT, photoacoustic CT, confocal microscopy, and hyperspectral imaging are some convenient tools reflecting *in vivo* intraoperative information [199], including structural and functional situations, for presenting the effective biological states to monitor the process of cancer treatment. Optical molecular imaging [200] could be rapidly used to acquire tumor-to-tumor molecular heterogeneity, both dynamically and quantitatively. Optical imaging can be integrated into endoscopic theranostic platforms for real-time sensing of therapeutic states and monitoring the progress of light-induced therapy. Furthermore, minimized interventional theranostic probes integrating optical diagnosis and optical therapy for precision cancer treatments could be an important direction for translational clinics, such as natural orifices or minimal incisions and intraluminal interventions. This solution has wide clinical potential for interventional treatment in the future.

With the research of various technologies in LMIT, it has been widely developed in clinical applications, providing patients with less pain, shorter recovery time, and lower tissue trauma. Different optical methods can be selected based on the patient's disease type and specific situation to achieve the best treatment effect. Each technology has its own indications and limitations, and there may be multiple

diagnostic methods or collaborative diagnosis and treatment methods during the surgical process. Research on devices that integrate multiple diagnostic and treatment methods is still in the research stage, and further research is urgently needed to popularize them in clinical minimally invasive treatment.

6. Conclusions

Intelligent LMIT provides an optimized solution for the minimally-invasive treatment of tumorous tissues due to the excellent features of light-mediated theranostic strategies. This paper reviews the state-of-the-art light-mediated theranostics, which improve and update the treatment efficiency of tumorous tissues. Intelligent LMIT systems would been developed for use in clinical trials. Optical or light-mediated MIT equipment is an important developmental trend in future research and clinical practice. Such equipment provides the function of intraoperative imaging and diagnosis, surgical navigation, deep imaging-guided precision therapy, and intelligent minimally-invasive treatment. LMIT could provide great convenience, and improve and optimize the efficiency of cancer treatment.

Acknowledgements

Competing Interests

The authors have declared that no competing interest exists.

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