Cancer Nanotechnology

REVIEW Open Access

Opportunities and challenges of indocyanine green in gastrointestinal cancers for intraoperative and nano-medicine application

Liting Sun[1†], Cong Meng[1†], Zhongtao Zhang[1], Yao Luo[2*], Zhengyang Yang[1*] and Hongwei Yao[1*]

[†]Liting Sun and Cong Meng contributed equally to this work.

*Correspondence: luoyao@scu.edu.cn; doctoryangzy@163.com; yaohongwei@ccmu.edu.cn

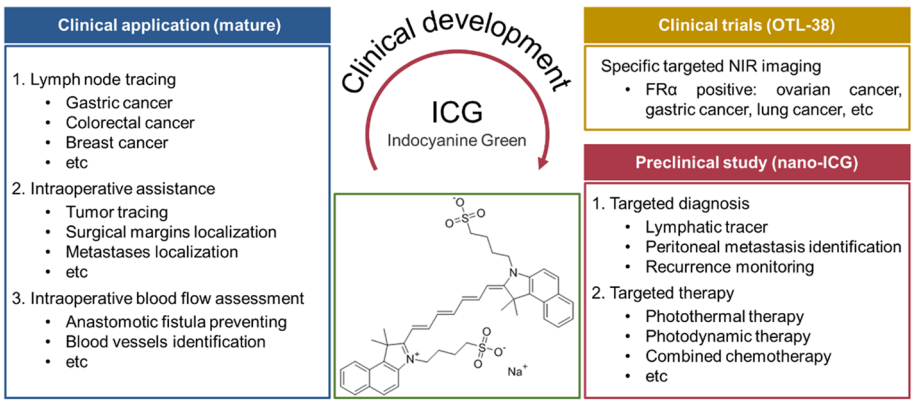
[1] Department of General Surgery, Beijing Friendship Hospital, Capital Medical University & National Clinical Research Center for Digestive Diseases, Beijing, China
[2] Department of Laboratory Medicine, West China Hospital, Sichuan University, Chengdu, China

Abstract

The morbidity and mortality of gastrointestinal tumours remain high worldwide. Surgical resection is currently the most critical radical therapeutic schedule, while postoperative complications and sentinel lymph node (SLN) identification are closely related to the outcome. Indocyanine green (ICG)-mediated fluorescence imaging is increasingly being used in gastrointestinal surgery. It has been embraced by various surgical disciplines as a potential method to improve lymph node detection and enhance surgical field visualization. ICG can passively concentrate in SLN because of enhanced permeation and retention effects. After excitation by near-infrared light devices, SLN can display higher intensity fluorescence, helping visualization for better lymph node dissection. In addition, visual assessment of intestinal blood flow through ICG may reduce the incidence of anastomotic leakage. Although it has good clinical application, ICG-imaging still faces some problems, such as a higher false-negative rate, poorly targeted biodistribution, and lower fluorescence contrast, due to the lack of active tumour targeting. Thus, different ICG-coupled nanoparticles with inherent characteristics or functional modification-enhanced SLN identification features for gastrointestinal cancers bring benefit through active tumour targeting, superior tumour-background ratio, and high resolution. Nano-ICG combined with potential substances, including enhanced imaging contrast and/or combination therapy (chemotherapy, targeted therapy, immunotherapy, etc.), have been packaged and accumulated in the tumour area through active targeting for multimodal imaging and treatment. In this review, we outline the intraoperative application and possible future nanodirections of ICG in gastrointestinal cancer. The prospects and challenges of nano-ICG diagnostic and therapeutic methods in clinical applications are also discussed.

Keywords: Gastrointestinal cancers, Indocyanine green, Sentinel lymph node, Nanoparticle, Target delivery

Graphical Abstract



Introduction

Gastrointestinal cancer has one of the highest incidence and mortality rates worldwide (Bray et al. 2018). A few early-stage patients have achieved endoscopic radical resection in recent years, but the majority still require surgery. For progressive gastrointestinal tumours, radical surgery combined with regional lymph node dissection remains the primary treatment (Adiamah et al. 2019). There are a large number of patients with advanced gastrointestinal tumours in China, many of whom have lymph node metastases (Wei et al. 2020). The sentinel lymph node (SLN) is acknowledged as the primary lymph node that drains a tumour, and its detection is frequently employed to identify cancer metastasis, determine cancer staging, predict prognosis, and select treatment options (Morita et al. 2007; Lee et al. 2009). Despite the reliance on preoperative imaging techniques such as computed tomography (CT) and magnetic resonance imaging (MRI) for SLN identification in clinical practice, the accuracy and sensitivity of these modalities are often inadequate for clinical purposes, and they lack intraoperative immediacy.

The utilization of near-infrared (NIR) fluorescence imaging has emerged as a novel approach for the real-time monitoring of tissue morphology and metabolism during surgical procedures, exhibiting considerable potential in the identification of crucial anatomical structures and tumour metastasis intraoperatively (Wakabayashi et al. 2022). Indocyanine green (ICG) is currently the most widely employed NIR photosensitizer in clinical settings and received approval from the US FDA in 1954 (Björnsson et al. 1982). Following intravenous administration, ICG exhibits a high degree of binding (approximately 98%) to plasma proteins, thereby remaining within the normal vascular structure and undergoing hepatic metabolism primarily (Keller et al. 2017). In recent times, this tool has been increasingly adopted by diverse surgical disciplines as a promising means to augment visualization of the surgical field and aid in the identification of diagnostic diseases and anatomical structures.

However, poor photostability, short half-life and concentration-dependent aggregation limit the use of ICG in actual clinical practice. The potential use of novel nano-ICG materials in the detection of tumour lymph nodes has attracted increasing attention

in recent years. Nanomedicine can offer many potential benefits for the diagnosis and treatment of gastrointestinal tumours. These include imaging and therapeutic advantages, including early detection of gastrointestinal tumours, passive and active focal targeting and improved drug biocompatibility as well as disease treatment and monitoring (Han et al. 2021; Liu et al. 2019; Zhang and Hao 2021). In recent years, ICG fluorescence imaging has been investigated in clinical trials, and a substantial number of studies have moved from nonspecific imaging to tumour marker-specific imaging. Although successfully developing safe and effective nanoparticles that can be used for targeted tumour imaging in vivo is challenging, some research has made progress in this area.

Various ICG-coupled nanoparticles with inherent or functional modification-enhanced SLN identification features for gastrointestinal cancers bring benefits through active tumour targeting, superior tumour–background ratio and high resolution. Nano-ICG combined with potential agents, including enhanced imaging contrast and/or combination therapy, have been packaged and accumulated in the tumour area through active targeting for multimodal imaging and treatment. With the objective of bringing more hope to patients in the future, this review is intended to provide an overview of the intraoperative use of indocyanine green and its derivatives in gastrointestinal cancers and possible future directions.

Clinical application

ICG-related imaging techniques have important clinical applications in the diagnosis and treatment of gastrointestinal tumours, showing good promise in assisting tumour localization, precise tracing of lymph nodes, distinguishing different tissues, and assessing anastomotic blood flow in real time (Wexner et al. 2022; Sherwinter et al. 2022; Villegas-Tovar et al. 2020). Several reviews have already summarized that the use of ICG as a free guidance tool in gastrointestinal surgery seems very promising (Sposito et al. 2022). The European Association for Endoscopic Surgery (EAES) has also reached a consensus on ICG fluorescence-guided surgery (Cassinotti et al. 2023). ICG fluorescence would therefore be beneficial in terms of patient-reported outcomes, detection rate, image quality, visualizations of perfusion, precision of surgical technique and separation/discrimination between healthy and unhealthy tissue. The use of ICG is thought to improve the precision of the surgical technique, the identification of blood vessels and the lymph node detection rate, as well as providing better image quality compared with standard white light. The application of ICG combined with other tracer methods, such as nuclear and single-photon emission CT, may provide a more reliable means to improve the detection rate of positive lymph nodes, thus enabling more personalized and precise surgical radical procedures for the treatment of gastrointestinal cancers (Xue et al. 2021; Xu et al. 2020).

Lymph node tracing

Accurate intraoperative localization of lymph nodes and guidance on the extent of clearance are helpful to detect more lymph nodes, provide more accurate pTNM staging, and guide patients' postoperative adjuvant therapy (Xu et al. 2020). Compared with other dyes, ICG near-infrared light imaging can have better tissue penetration in visible light and can better identify lymph nodes within hypertrophic fatty tissue,

Table 1 Clinical studies of ICG tracing of gastrointestinal tumours

Year	Tumour type	Sample size	*T* stage	Tumour diameter (mm)	Concentration (g/L)	Injection site	Mean SLN	Sensitivity (%)
2004 (Nimura et al. 2004)	GC	84	T1–T2	NA	5	SS	10.5	100
2006 (Nagata et al. 2006)	CRC	48	T1–T3	NA	5	SS	3.5	53.6
2007 (Ohdaira et al. 2007)	GC	52	T1	NA	5	SS	NA	100
2007 (Ishikawa et al. 2007)	GC	16	T1–T2	21	5	SS	2.9	50
2008 (Kusano et al. 2008)	CRC	26	T1–T3	NA	5	SM	2.6	33.3
2008 (Kusano et al. 2008)	GC	22	T1–T3	NA	5	SM	3.6	40
2008 (Noura et al. 2008)	CRC	25	T2–T3	58	5	SM	3	100
2008 (Noura et al. 2008)	CRC	25	T2–T3	58	5	SM	3	100
2009 (Ohdaira et al. 2009)	GC	30	T1–T2	42.6	5	SS	4.8	100
2009 (Tajima et al. 2009)	GC	30	T1–T3	NA	5	SS	7.2	64.7
2010 (Noura et al. 2010a)	CRC	25	T1–T3	45	5	SM	3	100
2010 (Kelder et al. 2010)	GC	212	T1	30	5	SS	6	97
2010 (Tajima et al. 2010)	GC	38	T1–T2	33.8	5	NA	7.9	75
2011 (Hutteman et al. 2010)	CRC	24	T1–T4	40	NA	SS/SM	3	NA
2011 (Miyashiro et al. 2011)	GC	10	T1	NA	NA	NA	3	100
2012 (Hirche et al. 2011)	CRC	26	T1–T4	NA	5	SS	1.7	82
2012 (Cahill et al. 2012)	CRC	18	T1–T3	NA	NA	SM	4.1	100
2012 (Yano et al. 2012)	GC	130	T1–T2	NA	0.5	SS	NA	100
2013 (Pas et al. 2013)	CRC	14	T2–T3	45	2.5	SS	4	NA
2013 (Schaafsma et al. 2013)	CRC	22	T1–T4	37	NA	SM	3.5	NA
2016 (Tummers et al. 2016)	GC	22	T1–T4	35	0.031	SM	3.1	75

Table 1 (continued)

Year	Tumour type	Sample size	*T* stage	Tumour diameter (mm)	Concentration (g/L)	Injection site	Mean SLN	Sensitivity (%)
2016 (Kinami et al. 2016)	GC	72	T1–T3	27.6	0.05	SS	6	90.9
2016 (Takahashi et al. 2016)	GC	36	T1–T2	NA	5	SS	9.2	100
2016 (Liberale et al. 2016)	CRC	20	Tis, T1–T4	39	0.5	SS	7	57
2017 (Watanabe et al. 2016)	CRC	31	NA	NA	2.5	SM	NA	NA
2017 (Takahashi et al. 2017)	GC	44	T1	24.8	5	SS	7.9	100
2017 (Andersen et al. 2017)	CRC	29	T1–T4	NA	2.5	SS	1.8	33
2017 (Currie et al. 2017)	CRC	30	T1–T4	37	5	SM	3	33
2017 (Weixler et al. 2017)	CRC	50	T1–T4	NA	0.5	SS	4.4	64
2018 (Shida et al. 2018)	GC	60	T1	23	NA	SS	5	100
2018 (Okubo et al. 2018)	GC	17	T1–T2	19.6	NA	SS	4.5	100
2019 (Kim et al. 2019)	GC	28	T1	16	NA	SS	NA	100

GC gastric cancer, *CRC* colorectal cancer, *SLN* sentinel lymph node, *NA* not available, SM submucosal, *SS* subserosal

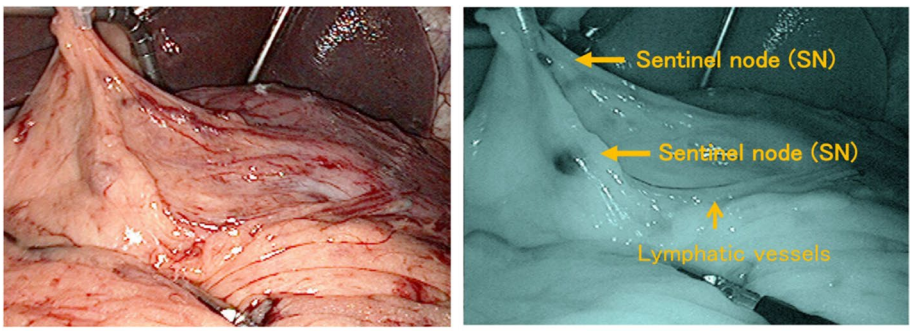


Fig. 1 As compared with ordinary light, lymphatic vessels and SNs can be easily detected using infrared ray electronic endoscopy (Miyashiro et al. 2011). Copyright 2018, Springer Nature

making the application of ICG fluorescence imaging in guiding procedures a new direction to explore (Villegas-Tovar et al. 2020). Table 1 summarizes the literature that we have retrieved on the use of ICG fluorescence mapping in operations for gastric cancer and colorectal cancer. Figure 1 illustrates ICG-stained lymphadenectomy.

The rate of lymph node metastasis in early gastric cancer is low (less than 10.6%) (Shen et al. 2013; Japanese Gastric Cancer Association 2021). In recent years, there have been several articles demonstrating that the application of ICG can detect more lymph nodes in patients with gastric cancer at an early stage. In addition to some of the studies summarized in Table 1, there are several studies of robotic surgery and ICG combined with other modalities that support this. The combination of ICG and radioisotope (dual method) by Kitagawa et al. led to a significant improvement in sensitivity and specificity for early gastric cancer lymph node detection (Kitagawa et al. 2005). Kwon et al. demonstrated in a prospective single-arm study of robotic ICG tracing in early gastric cancer patients that ICG tracing could improve lymph node retrieval and help complete lymph node dissection (Kwon et al. 2019). Huang and colleagues meta-analysed 54 studies that met their inclusion criteria and found that the number of lymph nodes detected was significantly higher with ICG-coupled techniques. Huang and colleagues meta-analysed 54 studies that met their inclusion criteria and found that the number of lymph nodes detected was markedly higher with the ICG-coupled method for several different dyes (Huang et al. 2021).

In patients with advanced gastric cancer, it is important to increase intraoperative nodal dissection and positive nodal findings to accurately stage patients and guide subsequent treatment (Smith et al. 2005). Extended lymphadenectomy confers a survival benefit in terms of both distant disease-free survival (DDFS) and overall survival (OS) in patients with node-negative gastric cancer (Deng et al. 2017). Evidence suggests that the use of ICG fluoroscopy allows the operator to effectively dissect more nodes and effectively reduce the rate of node dissection failure without increasing the operative time and postoperative complications of laparoscopic radical gastrectomy compared to conventional visual dissection (Tajima et al. 2010; Hutteman et al. 2010). The results of another study that included 514 patients showed that the sensitivity of overall visualization of station lymph node metastases was >80% in all patients with stage cT3-4a (Ankersmit et al. 2019). It was again shown that ICG fluorescence imaging using either the subserosal or submucosal approach helped to thoroughly dissect potentially metastatic lymphatic nodes.

Lymph node metastasis is also one of the most important metastatic routes for colorectal cancer. ICG NIR light imaging for radical colorectal cancer tracing lymph nodes is mostly performed by preoperative colonoscopic injection of ICG into the submucosa adjacent to the tumour at multiple points (Ankersmit et al. 2019). Compared with the conventional blue dye method, ICG NIR light imaging has the advantage of being able to precisely locate the metastatic lymph nodes and the distribution of the anterior lymph nodes, especially the extraregional lymph nodes, intraoperatively (Currie 2019). Nagata et al. reported that ICG fluorescent imaging detected up to 97.7% of sentinel nodes during colorectal cancer surgery, significantly higher than blue dye, and had a 55.0% sensitivity for diagnosing lymph node metastasis (Schaafsma et al. 2013). However, the literature also reported a false-negative rate of 46%, which was mainly in patients with stage T3.

In addition, ICG NIR light imaging has shown initial advantages in the detection of lateral anterior lymph nodes in rectal cancer. Lateral lymph node metastasis rates for low and intermediate rectal cancer vary widely, ranging from 8.6 to 49.0% (Yano and

Moran 2008; Kim et al. 2014). It is currently recommended that lateral lymph node dissection or preoperative chemotherapy be used to treat lateral lymph node metastases from rectal cancer. Unnecessary lateral pelvic lymph node dissection can be avoided if sentinel lymph node navigation can be used for low rectal cancer (Kim et al. 2014). A propensity score-matched study by Hiroki Ohya et al. showed that the total number of lateral pelvic lymph nodes retrieved was significantly higher in the NIR group than in the non-NIR group. The incidence of postoperative complications was not significantly different between groups (Ohya et al. 2022). Kawahara et al. located sentinel lymph nodes in the lateral rectal cancer region between the internal iliac vessels and pelvic plexus nerve and showed that 40 sentinel node-negative patients developed no lateral lymph node metastases (Kawahara et al. 2007). In a Japanese study, ICG was used for lateral lymph node dissection in patients with lower rectal cancer. The results showed that lateral sentinel nodes were successfully identified in 23 (92%) of 25 patients, with an average of 2.1 lateral sentinel nodes per patient (Noura et al. 2010b). ICG tracing is a more accessible technique that not only avoids the use of radioisotopes, but is also extremely cost-effective. Although there are few studies on the subject, the ICG method is both convenient and safe compared to the current lymph node radioisotope tracer method and holds great promise for the future.

Intraoperative assistance in tumour tracing, localization of surgical margins and metastases

In early-stage colorectal cancer, it is difficult to locate the tumour directly and accurately during laparoscopic surgery. It has been reported in the literature that after ICG injection around the tumour ring 1 day prior to surgery, intraoperative fluorescent margins were observed to be located approximately 2.5 cm from the tumour border (Miyoshi et al. 2009; Ushimaru et al. 2019). ICG is a safe and rapidly metabolized drug, and submucosal injection of ICG does not cause any tissue inflammation (Miyoshi et al. 2009). Park et al. reported that ICG fluorescence imaging can successfully visualize lymph node draining after endoscopic treatment with high sensitivity and negative predictive value (Park et al. 2021). It is now mostly accepted that mucosal injection around the tumour ring 1 day prior to surgery not only mimics the lymphatic drainage of the tumour but also functions to mark the location of the tumour.

For patients with intermediate to advanced gastrointestinal tumours, especially those with liver or peritoneal metastases, complete surgical removal of metastases is an effective treatment modality (Leporrier et al. 2006). However, the problem of a high rate of intrahepatic recurrence after resection of liver metastases still exists, probably due to the inability of current imaging methods to detect micrometastases. A comprehensive literature has reported the detection of nodules as small as 1 mm in diameter using ICG NIR imaging, suggesting that ICG NIR imaging may be suitable for the detection of microscopic metastases in the superficial part of the liver (Boogerd et al. 2017). In addition, this technique may improve the detection of peritoneal metastases in patients with nonmucinous adenocarcinoma. However, there is a paucity of literature in this area, which needs to be further confirmed.

Assist in intraoperative blood flow assessment

In addition to localizing tumours and lymph nodes, ICG-related techniques can also be used to visualize the blood supply intraoperatively. Anastomotic leakage is a common and hazardous postoperative complication of gastrointestinal surgery. Adequate tissue perfusion is a major factor in the success of gastrointestinal surgical reanastomosis (Zehetner et al. 2015). Using laparoscopic near-infrared fluorescence imaging has provided a new way to accurately assess anastomotic perfusion.

In radical laparoscopic gastric cancer surgery for cancer, the left hepatic collateral artery or alternative left hepatic artery is frequently encountered, and the decision to disconnect this vessel can be made by determining whether its blood supply interferes with hepatic blood flow (Diana et al. 2017). In addition, injury to some major supplying organs or tissue vessels (e.g., splenic artery trunk, superior splenic pole vessels, etc.) also requires intraoperative assessment of whether the corresponding organ is affected (Lee et al. 2021). In these cases, ICG fluorescence imaging can assist the operator in making better intraoperative decisions. In the PILLAR II study, 139 eligible colorectal cancer patients were assessed with fluorescence angiography (Stamos 2015). The results of this study showed that in the 11 patients who had a change in surgical plan due to intraoperative perfusion assessment with ICG NIR, there was a 1.4% incidence of anastomotic leakage and no anastomotic leaks. These results suggest that in laparoscopic surgery for colorectal cancer, ICG NIR imaging may reduce the incidence of anastomotic leakage. The Jafari team's research came to a similar conclusion (Jafari et al. 2021). Our centre is currently leading a multicentre, prospective randomized controlled trial in China, and we look forward to the results of our study as well.

ICG-related derivatives

The simple diffusion of free ICG and attenuation of fluorescence in SLN labelling requires rapid dissection of the SLN within 30 min. However, this period of time is not always sufficient for deep lymph node biopsy (Mok et al. 2012). In addition, the 'enhanced infiltration and retention' (EPR) effect, where ICG passively exudes into tumour tissue, can sometimes make it difficult to distinguish between inflammatory and cancerous tissue. Therefore, there is a need to develop durable ICG-loaded probes for efficient and long-lasting imaging. The resistance posed by this passive targeting mechanism is expected to be overcome by nano-ICGs that can actively bind.

Drugs already approved for clinical use: pafolacianine (OTL-38)

OTL-38 is a folate indole cyanine green-like conjugate to folate receptor alpha (FRa) (Hoogstins et al. 2016). Upon excitation, OTL-38 emits light with near-infrared spectral wavelengths, which can be detected from tumour tissue with an appropriate camera system. In 2016, the results of a study by Hoogstins' team validated the safety of OTL-38 for use in humans. Since then, several teams have begun phase II and III clinical drug studies related to OTL-38 (Hoogstins et al. 2016). Several previous studies have demonstrated overexpression of folate receptor alpha in various tumours, such as ovarian, lung, breast, and kidney cancers, and clinical studies related to OTL-38 have also been more frequently performed on these cancers.

Preliminary evidence suggests that folate receptor-targeted molecular imaging with OTL-38 is safe, according to a phase I study by Predina et al. (2017). Their data also suggest that OTL-38 accumulates in known lung cancers and may help to identify synchronous malignancies. In another study by Predina's team, intraoperative molecular imaging (IMI) identified 56 out of 59 (94.9%) malignant lung nodules identified by preoperative imaging. IMI detected a further 9 malignant lesions not detected preoperatively (Predina et al. 2018). The sensitivity of IMI and positron emission tomography (PET) was 95.6% and 73.5%, respectively ($P=0.001$). Subsequently, similar results were obtained in the phase 2 clinical trial by Gangadharan et al. (2021). The results from Randall's team's phase II ovarian cancer trial showed that a total of 48.3% (14/29) of patients had at least one additional lesion detected by OTL-38 alone (Randall et al. 2019). In this phase II study, these results demonstrate that OTL-38 is safe and effective regardless of folate expression levels and merits phase III evaluation. In a phase III clinical trial by Tanyi et al., 33.0% of patients who used pafolacianine with NIR imaging had additional cancers that were found in tissue that was not scheduled for excision and could not be detected by white light assessment and palpation (Tanyi et al. 2023).

Limited data indicate that FRα is also expressed in more than one-third of gastric adenocarcinomas (Low and Kularatne 2009). The first application of OTL-38 in gastric cancer was made by Newton et al. In their study, all four of the patients who underwent gastric resection had invasive gastric adenocarcinoma; three of them had fluorescent tumours, with a mean tumour-to-background ratio of 4.1 ± 2.9. Fluorescence was visible from the outside of the stomach in each fluorescent tumour. One patient with a non-fluorescing tumour had a T1a tumour with two 0.4 cm foci within a larger polyp. Two patients had fluorescent tumours expressing moderate FRα and not expressing CD68. One of the patients had a fluorescent tumour with a high level of CD68 expression and no FRα expression (Newton et al. 2021). Their research demonstrated that intraoperative molecular imaging of gastric adenocarcinoma with OTL-38 is feasible. Perhaps OTL-38 will have more applications in gastric cancer in the future, which needs to be confirmed by more clinical studies.

Targeted diagnosis and localization

Nanomedicine can offer many potential benefits for the diagnosis and treatment of gastrointestinal tumours, mainly including the following advantages: (1) nanoparticles can be functionalized by biomolecules, enabling them to target tumour tissue and localize to the target lesion; (2) nanoparticles can often be surface modified, wrapped or formulated to overcome problems of solubility and stability of common chemotherapeutic drugs; (3) nanoparticles have novel physical properties, such as near-infrared fluorescence imaging and photoacoustic imaging, which can be used for biological imaging; (4) nanoparticles usually consist of thousands of substances with high surface area and thus can carry higher therapeutic loads and kill tumour tissues more severely; and (5) nanoparticles can effectively accumulate at tumour sites through passive or active targeting, thus substantially reducing organ nonspecific toxicity. We summarize the ICG-related derivatives mentioned in the article in Table 2.

The findings of Tummers et al. offer a promising strategy for achieving early diagnosis and complete resection of cancer. His team first detected SLN in cancer patients by

Table 2 Representative ICG-relative nanoparticles mentioned in review

Name	Design of nanoparticles	Mechanism	Outcome	References
DSPE-PEG-RGD@ICG	Attaching RGD peptide to DSPE-PEGMal via a Michael addition reaction and encapsulated ICG	Active targeting to GC, and micelles were used to extend the circulation time in vivo	Active targeting of gastric cancer and micelles for prolongation of circulation time in vivo	Shao et al. 2020)
RGD-PEG-ss-PCL micelles	A drug nanocarrier PEG-ss-PCL with redox response, and grafted RGD peptide to the carboxyl modified PEG	EPR effect and the active targeting of RGD, in the tumour microenvironment and NIR laser irradiation, the disulfide bond cleavage releases DOC and ICG	Increase the solubility of drugs, improve the targeting of tumours and reduce systemic toxicity	Ren et al. 2021)
P(EF-PLLA) nanoparticles	Anti-CEA was covalently conjugated to the nanoparticles through the surface carboxylate groups	The encapsulation of the NIR fluorescent dye within the P(EF-PLLA) improves significantly the photostability of the dye	The anti-CEA-conjugated NIR fluorescent nanoparticles may be very useful for tumour diagnosis in vivo	Kolitz-Domb et al. 2014)
ssSM3E/800CW	CEA-targeted near-infrared fluorescent tracer, based on a disulphide stabilized single-chain antibody fragment	Cell and tissue binding characteristics and dosing using immunohistochemistry, flow cytometry, cell-based plate assays	Could clearly identify tumour tissue after injection	Boonstra et al. 2015)
ICNPs	A core–shell nanostructure consisting of an ICG-polymeric core and cancer cell membrane shell	Good monodispersity, preferable photothermal response, and excellent FL/PA imaging properties	Specific recognition, long blood circulation, and immune escaping	Chen et al. 2016)
RMDI	Composed of the RGD peptide, melanin-coated magnetic nanoparticles, DOX and ICG	Biological active targeting by RGD and physical magnetic targeting by an external magnetic field at tumour tissues	Synergistic PTT/chemotherapy, the dual-stimuli-responsive and dual-targeting nanotheranostic agent completely ablated tumour in vivo	He et al. 2021)
AuIP-RGD nanocapsules	Nanoparticles loaded with AuNCs, ICG and conjugate RGD peptides onto the surface	Actively targeted dual-modal imaging and photothermal therapy, one-photon and two-photon imaging techniques	A unique combination of the one-photon/two-photon fluorescence imaging and highly effective photothermal	Gu et al. 2016)
ICG-HANP/SWCNTs (IHANPT)	A CD44-targeted photoacoustic by conjugating ICG to hyaluronic acid nanoparticles encapsulated with carbon nanotubes	Photoacoustic imaging and photothermal and photodynamic therapy properties	Significant tumour growth inhibition and marked induction of tumour cell death and necrosis	Wang et al. 2016)
R&HV-Gd@ICG	RGD pentapeptide/hollow virus-like gadolinium-based ICG	Generated more reactive oxygen species under X-ray irradiation, improved RT sensitivity, and reduced tumour progression	Improved aqueous stability, tumour retention, target specificity of ICG, and achieves outstanding magnetic resonance	Yang et al. 2022)

Table 2 (continued)

Name	Design of nanoparticles	Mechanism	Outcome	References
CMCh-BAPE-RGD@ICG	Chemical link carboxymethyl chitosan and 4-hydroxymethyl pinacol phenyl borate for encapsulation of ICGs and linking with RGDs	RGD polypeptides are conjugated on the surface to achieve active targeting ability of the nanosystem	Illustrate the location and margin of the SGC7901 tumour through NIR imaging in comparison	Shao et al. 2021)
CSI@Ex-A	A biodegradable nanoplatform is fabricated by encapsulating catalase into silica nanoparticles for tumour hypoxia relief, and then loaded with ICG	Highly expressed glutathione triggers biodegradation of the nanoplatform and the released CAT catalyses hydrogen peroxide to relieve tumour hypoxia	The GSH depletion and O2self-supplying effectively enhances the SDT efficiency both in vitro and in vivo	Wu et al. 2022)
Cal/ICG@MPs	Tumour cell-derived microparticles co-delivering calcipotriol and ICG	Target tumour tissues and regulate CAFs to reduce tumour extracellular matrix, resulting in enhanced tumour accumulation and to generate strong PTT efficacy	Ameliorates CAF-induced antigen-mediated activation-induced cell death of tumour-specific CD8 + T cells in response to PTT	Li et al. 2022)

NIR fluorescence imaging using ICG combined with nanocolloids as a lymphatic tracer (Tummers et al. 2016). High accuracy was observed in patients with stage T1 and T2 gastric cancer, indicating that this technique can be used to identify tumour-positive lymph nodes outside of standard anatomical planes. Shao et al. constructed targeted fluorophore delivery micelles DSPE-PEG-RGD@ICG by attaching RGD peptide to DSPE-PEGMal via a Michael addition reaction and successfully encapsulated ICG (Fig. 2A). As reported, the RGD peptide is highly sensitive and has affinity for integrin αvβ3, which could be substantially targeted to gastric cancer cells. Thus, DSPE-PEG-RGD@ICG was used for active targeting of gastric cancer and micelles for prolongation of circulation time in vivo (Shao et al. 2020).

Ren et al. combined optical molecular imaging with the RGD-ICG molecular probe (RGD-PEG-ss-PCL micelles) to study cancerous peritoneal carcinomas in a mouse model. These RGD-PEG-ss-PCL micelles were found to have a sensitivity and specificity of 93.93% and 100%, respectively (Ren et al. 2021). Through their research, Ren et al. have shown that such micelles can increase the solubility of drugs, improve the targeting of tumours and reduce systemic toxicity. In addition, their use significantly

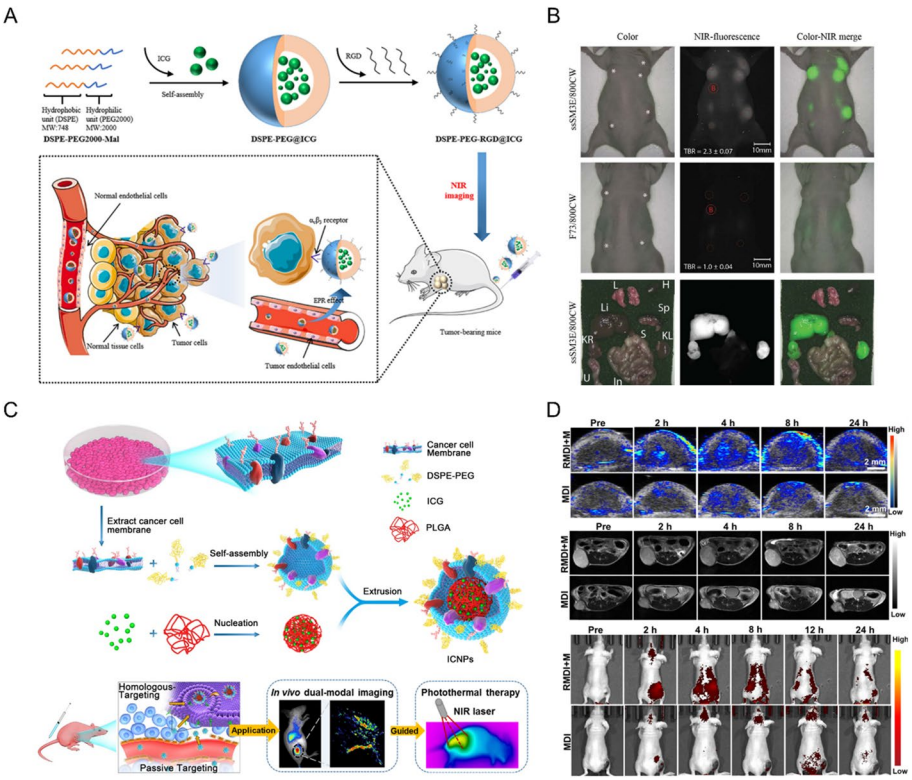


Fig. 2 Nano-ICG for targeted diagnosis and localization. **A** Schematic illustration of the RGD-modified ICG micelles for monitoring gastric cancer (Newton et al. 2021). Copyright 2020, Frontiers. **B** The in vivo and ex vivo of mice bearing subcutaneous tumours acquired 72 h after injection (Ren et al. 2021). Copyright 2015, John Wiley and Sons. **C** Illustration of the ICNPs for targeting tumour cells, dual-modal imaging, and photothermal therapy. Preparation procedure and schematic of ICNPs realizing tumour accumulation, dual-modal imaging, and effective photothermal therapy after intravenous injection (Kolitz-Domb et al. 2014). Copyright 2016, American Chemical Society. **D** In vivo multimodality imaging. Photoacoustic, T2-weighted MRI, and fluorescence images of U87MG tumour-bearing mice after RMDI and MDI injection (Boonstra et al. 2015). Copyright 2021, American Chemical Society

improves the combined antitumour effects of stable phase chemotherapy and photothermal therapy in ICG. In addition, a number of carcinoembryonic antigen (CEA)-targeted fluorescent probes have been preclinically tested in colon cancer models. Kolitz-Domb et al. reported anti-CEA-conjugated NIR fluorescent nanoparticles called P(EF-PLLA). The P(EF-PLLA) was suggested to have a significant advantage over colonoscopy (Kolitz-Domb et al. 2014). Boonstra's team reported a CEA-targeted NIR tracer based on a disulfide-stabilized single-chain antibody fragment called ssSM3E/800CW to visualize colorectal cancer lesions. As shown in Fig. 2B, the experiment showed that ssSM3E/800CW could clearly identify tumour tissue after injection. Additionally, histological assessment using fluorescence microscopy showed a clear correlation between CEA expression and near-infrared fluorescent signalling (Boonstra et al. 2015).

By modifying the surface of nanoparticles with targeting ligands, nanoparticles with targeting effects can be obtained, which can solve the problem of the lack of selectivity of traditional drugs to tumour tissues and realize targeted therapy of tumours. Nanoparticle-based drug delivery systems can increase the aqueous solubility of hydrophobic drugs, prolong circulation time, improve drug permeability to tumours and allow drugs to accumulate in the tumour. They have therefore attracted much attention from researchers.

Chen et al. reported a cancer cell membrane–cloaked nanoparticle system loaded with an ICG core and cancer cell membrane shell (ICNPs) (Chen et al. 2016). The preparation procedure of ICNPs is shown in Fig. 2C. Such ICNPs exhibited specific tumour targeting with preferable monodispersity, excellent photothermal response, and satisfactory fluorescence imaging properties. In addition, tumours could be completely eliminated after a single dose of laser therapy. A pilot study by HeTing et al. coloaded doxorubicin (DOX) and ICG for in vivo photoacoustic/magnetic resonance/fluorescence (PA/MR/FL) trimodal imaging of U87MG tumours (Fig. 2D). Through magnetic and RGD activity targeting, the prepared nanotherapeutics can preferentially accumulate in U87MG tumours in vivo. DOX/ICG can be released in a controlled manner, guided by PA/MR/FL trimodal imaging, stimulated by 808 nm laser irradiation and an acidic tumour microenvironment. Due to rapid tumour uptake, multimodal imaging guidance and synergistic photothermal enhanced tumour chemotherapy, RMDI nanotherapeutics completely ablated U87MG tumours in vivo without any tumour recurrence or biotoxicity (He et al. 2021).

Photothermal and photodynamic therapy

Photothermal therapy (PTT) and photodynamic therapy (PDT) use materials with high photothermal conversion efficiency or strong reactive oxygen species (ROS) yield to achieve therapeutic effects by exposing them to light sources of specific wavelengths and using their target recognition technology to make the materials phototoxic to specific cancer cells (Li et al. 2021a; Wang et al. 2018). Mitochondria damage by PDT and PTT can initiate apoptosis, a death pathway, along with the protective effect or mitophagy. The efficiency of PTT with nanoparticles as a mitochondrial targeting agent is improved by increasing the coefficient of light-to-heat conversion, reducing drug resistance, and overcoming hypoxia(Guo et al. 2021).The possible apoptotic and autophagic responses have been appraised that incident with photothermal therapy. Investigation of this

relationship might promote perspectives for the synergic treatment in different types of breast cancer with significant success (Kadkhoda et al. 2022). In recent years, there has been increasing interest in using ICG in PDT and PTT due to its strong absorbing band, which allows deeper tissue penetration and thus causes considerable heating.

Gu et al. loaded BSA-capped gold nanoclusters (AuNCs) and ICG on hybrid nanocapsules for bimodal imaging and PTT (Fig. 3A). They coupled GD peptides to the surface of hybrid nanocapsules to target cells overexpressing integrin αγβ3. It was shown through animal experiments that the hybrid nanocapsules exhibited low cytotoxicity. Single- and two-photon fluorescence imaging of tumour cells and subsequent efficient photothermal ablation can be achieved using such nanocapsules (Gu et al. 2016). Wang et al. developed a CD44-targeted photoacoustic nanophototherapeutic agent to produce a therapeutic nanocomplex of ICGHANP/SWCNTs (IHANPT) by coupling ICG with hyaluronic acid nanoparticles wrapped with single-walled carbon nanotubes (Fig. 3B). Compared to other phototherapeutic agents, IHANPT enhances tumour targeting through EPR effects and active CD44 targeting, which allows for effective delivery of

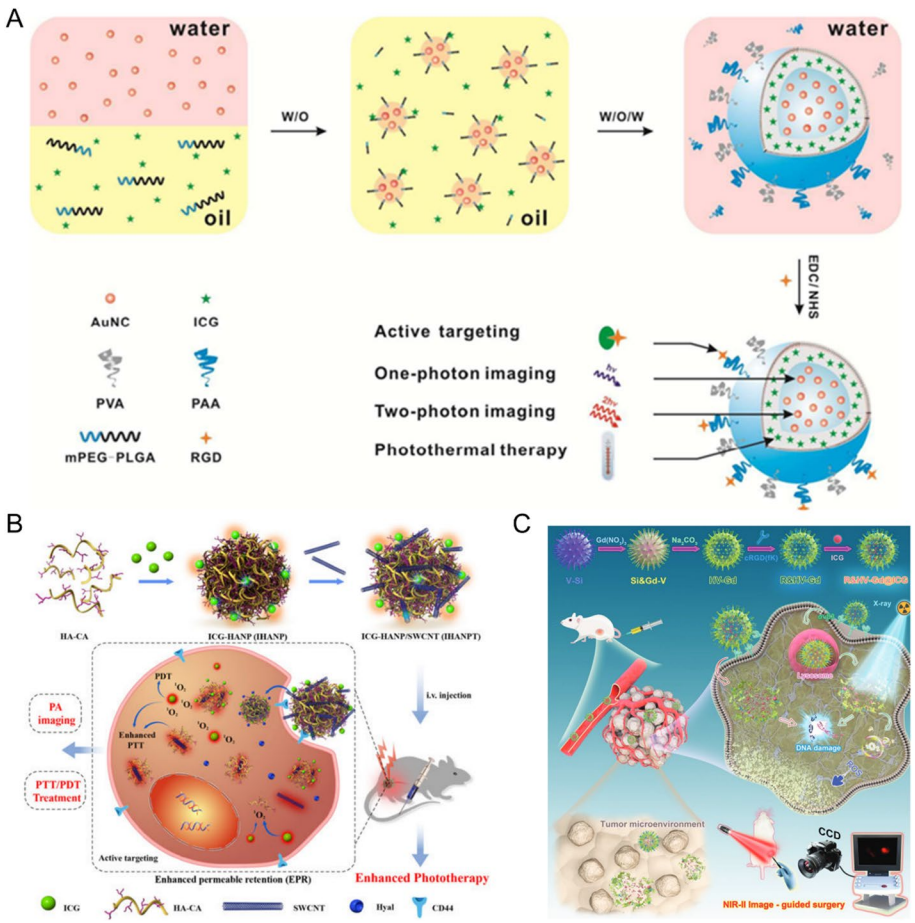


Fig. 3 **A** Schematic illustration of the formation of RGD-conjugated AuNC-ICG-mPEG-PLGA nanocapsules (Li et al. 2021a). Copyright 2016, Royal Society of Chemistry. **B** Design and intention of the dual targeted phototherapy agent, ICG-coupled threadlike nanoparticles (IHANPT) (Wang et al. 2018). Copyright 2016, American Chemical Society. **C** Schematic illustrating R&HV-Gd@ICG fabrication for NIR-II image-guided breast cancer surgery and enhanced RT efficacy (Guo et al. 2021). Copyright 2022, John Wiley and Sons

phototherapeutic agents at will in the tumour (Wang et al. 2016). Yang et al. developed a biodegradable cyclic RGD pentapeptide/hollow virus-like gadolinium-based indocyanine green (R&HV-Gd@ICG) nanoprobe to improve fluorescence image-guided surgery and breast cancer radiotherapy efficacy (Fig. 3C). Such nanoparticles exhibit remarkably improved aqueous stability, tumour retention, and target specificity of ICG and achieve outstanding magnetic resonance/second near-infrared window multimodal imaging in vivo. It is worth noting that nanoprobes are biodegradable in vivo and exhibit accelerated body clearance, which is expected to reduce potential long-term inorganic nanoparticle toxicity (Yang et al. 2022).

Combining several advantages of ICG is an even more promising option, not only for precise targeting and targeted delivery but also for facilitating drug action and combining to produce better efficacy. A promising reactive oxygen species (ROS)-responsive RGD-modified nanoparticle that can deliver ICG to cancer was successfully synthesized in a preclinical trial by Shao's team (Fig. 4A). The results show that these nanoparticles have a suitable size, improved water stability and outstanding photothermal conversion efficiency. Near-infrared fluorescence imaging can accurately show the location and margins of tumours in tumour-bearing mice and induce necrosis and apoptosis of cancer cells through PTT, which in turn effectively ablates tumours (Shao et al. 2021). The NIR supramolecular photosensitizer (RuDA) via self-assembly of an organometallic Ru(II)–arene complex in aqueous solution was reported (Fig. 4B). RuDA can generate singlet oxygen only in the aggregate state, showing distinct aggregation-induced singlet

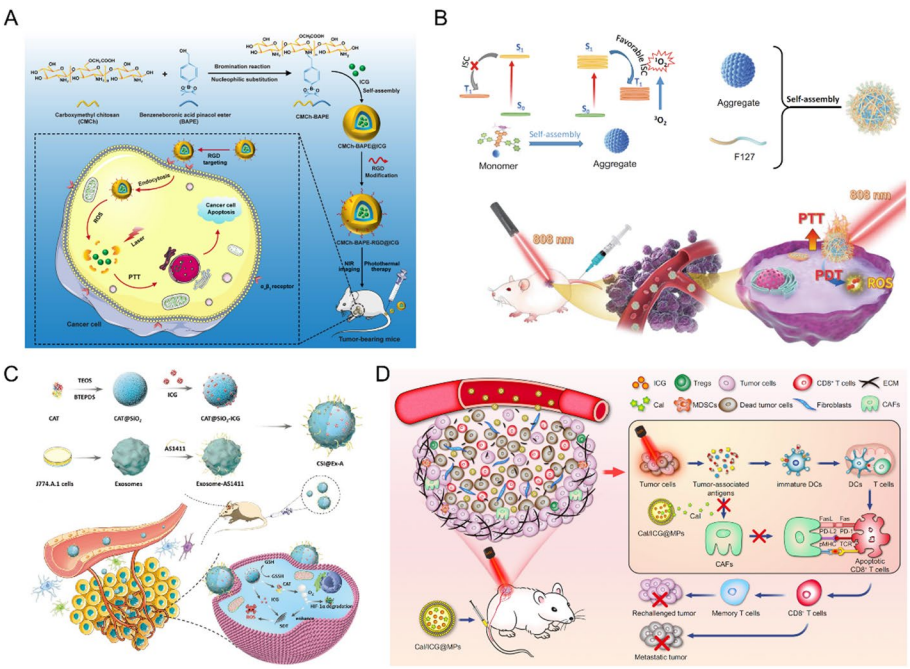


Fig. 4 **A** Schematic illustration of CMCh-BAPE-RGD@ICG for NIR imaging and photothermal therapy of gastric cancer (Kadkhoda et al. 2022). Copyright 2021, Taylor & Francis. **B** Schematic illustration of RuDA-NPs for phototherapy (Gu et al. 2016). Copyright 2022, Springer Nature. **C** Schematic illustration of CSI@Ex-A preparation and biodegradable CSI@Ex-A for enhanced SDT of glioblastoma (Wang et al. 2018). Copyright 2022, John Wiley and Sons. **D** Scheme of Cal/ICG@MPs as an efficient drug to regulate CAFs to enhance PTT efficacy (Yang et al. 2022). (Copyright 2022, Springer Nature)

oxygen generation behaviour because of the greatly increased singlet–triplet intersystem crossing process. After 808 nm laser irradiation, RuDA showed excellent photostability and displayed efficient singlet oxygen and heat generation in a singlet oxygen quantum yield of 16.4% together with a high photothermal conversion efficiency of 24.2%. In addition, RuDA with good biocompatibility can preferably accumulate in the tumour site and induce significant tumour regression with a 95.2% reduction in tumour volume during photodynamic therapy (Xu et al. 2022). Additionally, a biodegradable nanoplatform is fabricated by encapsulating catalase into silica nanoparticles and then loading with ICG. This nanoplatform was further coated with AS1411 aptamer-modified macrophage exosomes to form CSI@ Ex-A, which possesses efficient blood–brain barrier penetration and good cancer cell-targeting capability (Fig. 4C). Glutathione depletion and oxygen self-supply effectively enhance sonodynamic therapy efficiency both in vitro and in vivo (Wu et al. 2022). Tumour cell-derived microparticles co-delivering calcipotriol and indocyanine green (Cal/ICG@MPs) were also developed to modulate cancer-associated fibroblasts for improved PTT efficacy (Fig. 4D). The Cal/ICG@MP-triggered cancer-associated fibroblast regulation enhances tumour infiltration of CD8+ T cells and ameliorates cancer-associated fibroblast-induced antigen-mediated activation-induced cell death of tumour-specific CD8+ T cells in response to PTT (Li et al. 2022). Additionally, supramolecular nanofibrils fabricated through coassembly of clinically approved immunomodulatory thymopentin and ICG NIR were reported to localize photothermal immunotherapy of pancreatic tumours (Li et al. 2021b).

Summary and outlook

ICG has been widely used in surgery for gastrointestinal tumours as a safer dye. ICG-related NIR imaging has important clinical applications in the diagnosis and treatment of gastrointestinal tumours. Its use in evaluating anastomosis perfusion during colorectal resection has shown promising prospects in predicting and preventing anastomotic leakage. ICG-imaging has been widely studied in past years and has demonstrated safety and feasibility in gastric cancer resection not only for guiding limited surgery in early cancer, but also for precise lymph node resection in radical resection. Additionally, the application of ICG combined with other tracer methods, such as nanocarbon, may provide a more reliable means to improve the detection rate of positive lymph nodes, thus enabling more personalized and precise surgical radical procedures for the treatment of gastrointestinal cancers. However, the EPR effect, where ICG passively exudes into tumour tissue, can sometimes make it difficult to distinguish between inflammatory and cancerous tissue. Therefore, the resistance posed by this passive targeting mechanism is expected to be overcome by nano-ICGs that can actively bind.

In recent years, with the development of nanotechnology, nanomedicines have been increasingly widely used in the medical field, and research related to some derivative nanoparticles of ICG has emerged, with excellent performance in tumour imaging and treatment. As shown in Fig. 5, ICG combined with potential substances, including enhanced imaging contrast (CT, MRI, PET, etc.) and/or combination therapy (chemotherapy, targeted therapy, immunotherapy, etc.), have been packaged into nanoparticles for further surface modification. After intravenous injection, such nanoplatforms accumulate in the tumour area through active targeting for multimodal imaging (NIR,

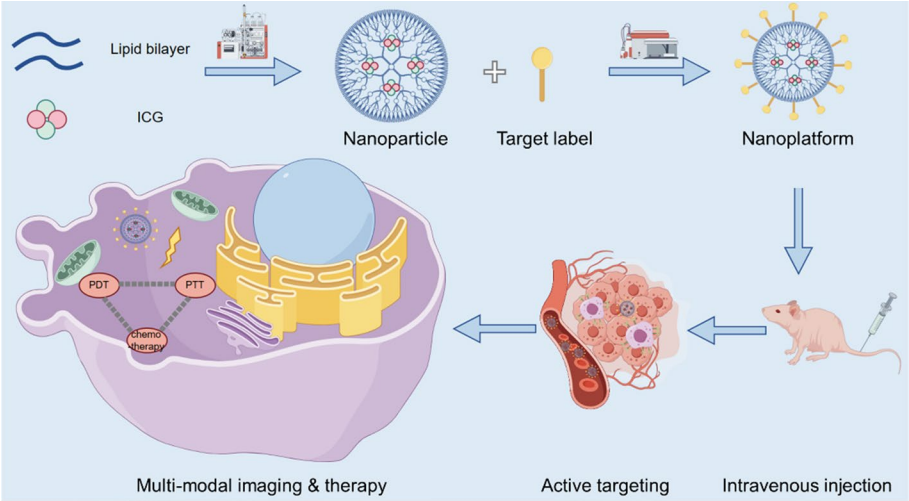


Fig. 5 Design and function of ICG-coupled nanoparticles. ICG and combined substance were packaged into nanoparticles for further surface modification. After intravenous injection, such nanoplatform accumulated in tumour area through active targeting for multimodal imaging and treatment

CT, MRI, etc.) and treatment (PDT, PTT, combined chemotherapy, etc.). Although there is an increasing number of studies on ICG, most of them are preclinical studies. Due to the limitations of internal metabolism, nanoparticle characteristics, and the highly heterogeneous nature of tumours, the biological distribution and targeting ability of nanoparticles may vary in clinical practice. The multifunctional nano-ICGs are endowed with additional expectations, such as targeted multimode therapy and enhanced contrast. However, additional functionality leads to additional synthesis steps and costs. In addition, more complex in-body behaviours and effects and greater dysregulation are involved.

Nanoparticles can be efficiently accumulated at the tumour site by passive or active targeting, greatly reducing nonspecific organ toxicity. Nanoparticles conjugated with ICG possess novel physical properties of ICG, such as near-infrared fluorescence imaging and photoacoustic imaging and can be used for bioimaging to target tumour tissue and localize to the target lesion. Typically, such nanoparticles are composed of multiple ICGs, which can also be linked by other biomolecules. When conjugated with chemotherapeutic agents, they not only overcome the solubility and stability problems of conventional chemotherapeutic agents, but also exploit the high specific surface area of the nanoparticles to carry a greater therapeutic load, thereby achieving greater lethality against tumour tissue.

Nanoparticle-targeted PTT can effectively ablate tumours by inducing necrosis and apoptosis in cancer cells. PTT works by using photothermal agents, which absorb light energy and convert it to heat energy when exposed to light. When PTT is applied, tumour cells undergo phenomena such as enzyme release and cytolysis, leading to cellular necrosis, initiation of protein denaturation and subsequent triggering of cancer cell death (Li et al. 2021a; Wang et al. 2018). ICG is also a photosensitizer with excellent photothermal conversion efficiency when exposed to a single wavelength of near-infrared light (Guo et al. 2021; Kadkhoda et al. 2022). Due to

the relative transparency of tissues under NIR illumination, ICG has several distinct advantages, including minimal interference from background fluorescence, deeper tissue penetration and real-time monitoring during the procedure. These attractive features suggest that ICG may be a promising dye for tumour imaging and PTT.

In conclusion, nanobased ICG is a promising strategy for the early diagnosis and image-oriented treatment of cancer. A range of materials with different imaging and therapeutic capabilities have been incorporated into the design and synthesis of nanoparticles with encouraging results. There is still a long way to go from preclinical research to clinical trials because of some hurdles. OTL-38 is currently available for clinical application, and while it was shown that FR alpha is expressed in more than one-third of gastrointestinal tumours, and the ratio of high cost to unsatisfactory efficacy needs to be further investigated (Low and Kularatne 2009). Heterogeneity in tumour cells and immune contexture among patients and even within individual tumours are the leading causes of inconsistent clinical response to these products. Therefore, it is crucial to improve sensitivity and specificity in the development of ICG nanoparticles coupled to other antigens expressed in gastrointestinal cancers (Aghanejad et al. 2022). In addition, with the increasing availability of nanomaterials, it should be possible to select individualized tumour-specific reagents based on antigen expression determined by preoperative biopsy. However, the many advantages and the encouraging research results to date lead us to believe that ICG-coupled nanomaterials will have major applications in gastrointestinal tumours in the future, bringing benefits to a wide range of patients.

Abbreviations

SLN	Sentinel lymph node
ICG	Indocyanine green
CT	Computed tomography
MRI	Magnetic resonance imaging
NIR	Near-infrared
DDFS	Disease-free survival
OS	Overall survival
EPR	Enhanced infiltration and retention
Fra	Folate receptor alpha
IMI	Intraoperative molecular imaging
PET	Positron emission tomography
CEA	Carcinoembryonic antigen
DOX	Doxorubicin
PA/MR/FL	Photoacoustic/magnetic resonance/fluorescence
PTT	Photothermal therapy
PDT	Photodynamic therapy
ROS	Reactive oxygen species

Acknowledgements
We thank Figdraw (www.figdraw.com) for supporting some figures drawing.

Author contributions
YL, ZY, and HY conceived and designed the review. LS and CM retrieved and reviewed literatures. LS, CM, and ZZ wrote the manuscript. YL, ZY, and HY reviewed and edited the manuscript. All authors contributed to the development and implementation of this protocol. All authors read and approved the final manuscript.

Funding
This work was supported by the National Natural Science Foundation of China (82202884), National Key Technologies R&D Program (No. 2015BAI13B09), National Key Technologies R&D Program of China (No. 2017YFC0110904), and Clinical Center for Colorectal Cancer, Capital Medical University (No. 1192070313).

Availability of data and materials
Not applicable.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

Received: 8 October 2023 Accepted: 24 January 2024
Published online: 07 February 2024

References

Adiamah A, Skořepa P, Weimann A (2019) The impact of preoperative immune modulating nutrition on outcomes in patients undergoing surgery for gastrointestinal cancer: a systematic review and meta-analysis. Ann Surg 270(2):247–256

Aghanejad A, Bonab SF, Sepehri M, Haghighi FS, Tarighatnia A, Kreiter C, Nader ND et al (2022) A review on targeting tumor microenvironment: The main paradigm shift in the mAb-based immunotherapy of solid tumors. Int J Biol Macromol 207:592–610

Andersen HS, Bennedsen ALB, Burgdorf SK, Eriksen JR, Eiholm S, Toxværd A, Riis LB, Rosenberg J, Gögenur I (2017) In vivo and ex vivo sentinel node mapping does not identify the same lymph nodes in colon cancer. Int J Colorectal Dis 32(7):983–990. https://doi.org/10.1007/s00384-017-2777-9. (**Epub 2017 Feb 16**)

Ankersmit M, Bonjer HJ, Hannink G et al (2019) Near-infrared fluorescence imaging for sentinel lymph node identification in colon cancer: a prospective single-center study and systematic review with meta-analysis. Tech Coloproctol 23(12):1113–1126

Björnsson OG, Murphy R, Chadwick VS (1982) Physiochemical studies of indocyanine green (ICG): absorbance/concentration relationship, pH tolerance and assay precision in various solvents. Experientia 38(12):1441–1442

Boogerd LS, Handgraaf HJ, Lam HD et al (2017) Laparoscopic detection and resection of occult liver tumors of multiple cancer types using real-time near-infrared fluorescence guidance. Surg Endosc 31(2):952–961

Boonstra MC, Tolner B, Schaafsma BE et al (2015) Preclinical evaluation of a novel CEA-targeting near-infrared fluorescent tracer delineating colorectal and pancreatic tumors. Int J Cancer 137(8):1910–1920

Bray F, Ferlay J, Soerjomataram I et al (2018) Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 68(6):394–424

Cahill RA, Anderson M, Wang LM, Lindsey I, Cunningham C, Mortensen NJ (2012) Near-infrared (NIR) laparoscopy for intraoperative lymphatic road-mapping and sentinel node identification during definitive surgical resection of early-stage colorectal neoplasia. Surg Endosc 26(1):197–204. https://doi.org/10.1007/s00464-011-1854-3.(Epub2011Aug19)

Cassinotti E, Al-Taher M, Antoniou SA, Arezzo A, Baldari L, Boni L et al (2023) European Association for Endoscopic Surgery (EAES) consensus on Indocyanine Green (ICG) fluorescence-guided surgery. Surg Endosc 37(3):1629–1648

Chen Z, Zhao P, Luo Z, Zheng M, Tian H, Gong P, Gao G, Pan H, Liu L, Ma A, Cui H, Ma Y, Cai L (2016) Cancer cell membrane-biomimetic nanoparticles for homologous-targeting dual-modal imaging and photothermal therapy. ACS Nano 10(11):10049–10057

Currie AC (2019) Intraoperative sentinel node mapping in the colon: potential and pitfalls. Eur Surg Res 60(1–2):45–52

Currie AC, Brigic A, Thomas-Gibson S, Suzuki N, Moorghen M, Jenkins JT, Faiz OD, Kennedy RH (2017) A pilot study to assess near infrared laparoscopy with indocyanine green (ICG) for intraoperative sentinel lymph node mapping in early colon cancer. Eur J Surg Oncol 43(11):2044–2051. https://doi.org/10.1016/j.ejso.2017.05.026. (**Epub 2017 Aug 23**)

Deng J, Yamashita H, Seto Y et al (2017) Increasing the number of examined lymph nodes is a prerequisite for improvement in the accurate evaluation of overall survival of node-negative gastric cancer patients. Ann Surg Oncol 24(3):745–753

Diana M, Liu YY, Pop R et al (2017) Superselective intra-arterial hepatic injection of indocyanine green (ICG) for fluorescence image-guided segmental positive staining: experimental proof of the concept. Surg Endosc 31(3):1451–1460

Gangadharan S, Sarkaria IN, Rice D et al (2021) Multiinstitutional phase 2 clinical trial of intraoperative molecular imaging of lung cancer. Ann Thorac Surg 112(4):1150–1159

Gu W, Zhang Q, Zhang T et al (2016) Hybrid polymeric nano-capsules loaded with gold nanoclusters and indocyanine green for dual-modal imaging and photothermal therapy. J Mater Chem B 4(5):910–919

Guo X, Yang N, Ji W, Zhang H, Dong X, Zhou Z (2021) Mito-bomb: targeting mitochondria for cancer therapy. Adv Mater 33(43):e2007778

Han Y, Yang Y, Sun Q et al (2021) Dual-targeted lung cancer therapy via inhalation delivery of UCNP-siRNA-AS1411 nanocages. Cancer Biol Med 19(7):1047–1060

He T, He J, Younis MR et al (2021) Dual-stimuli-responsive nanotheranostics for dual-targeting photothermal-enhanced chemotherapy of tumor. ACS Appl Mater Interfaces 13(19):22204–22212

Hirche C, Mohr Z, Kneif S, Doniga S, Murawa D, Strik M, Hünerbein M (2012) Ultrastaging of colon cancer by sentinel node biopsy using fluorescence navigation with indocyanine green. Int J Colorectal Dis 27(3):319–324. https://doi.org/10.1007/s00384-011-1306-5. (**Epub 2011 Sep 13**)

Hoogstins CE, Tummers QR, Gaarenstroom KN et al (2016) A novel tumor-specific agent for intraoperative near-infrared fluorescence imaging: a translational study in healthy volunteers and patients with ovarian cancer. Clin Cancer Res 22(12):2929–2938
Huang Y, Pan M, Chen B (2021) A systematic review and meta-analysis of sentinel lymph node biopsy in gastric cancer, an optimization of imaging protocol for tracer mapping. World J Surg 45(4):1126–1134
Hutteman M, Choi HS, Mieog JS, van der Vorst JR, Ashitate Y, Kuppen PJ, van Groningen MC, Löwik CW, Smit VT, van de Velde CJ, Frangioni JV, Vahrmeijer AL (2011) Clinical translation of ex vivo sentinel lymph node mapping for colorectal cancer using invisible near-infrared fluorescence light. Ann Surg Oncol 18(4):1006–1014. https://doi.org/10.1245/s10434-010-1426-0. (**Epub 2010 Nov 16**)
Ishikawa K, Yasuda K, Shiromizu A et al (2007) Laparoscopic sentinel node navigation achieved by infrared ray electronic endoscopy system in patients with gastric cancer. Surg Endosc 21(7):1131–1134
Jafari MD, Pigazzi A, McLemore EC et al (2021) Perfusion assessment in left-sided/low anterior resection (PILLAR III): a randomized, controlled, parallel, multicenter study assessing perfusion outcomes with PINPOINT near-infrared fluorescence imaging in low anterior resection. Dis Colon Rectum 64(8):995–1002
Japanese Gastric Cancer Association (2021) Japanese gastric cancer treatment guidelines 2018 (5th edition). Gastric Cancer 24(1):1–21
Kadkhoda J, Tarighatnia A, Tohidkia MR, Nader ND, Aghanejad A (2022) Photothermal therapy-mediated autophagy in breast cancer treatment: Progress and trends. Life Sci 298:120499
Kawahara H, Nimura H, Watanabe K et al (2007) Where does the first lateral pelvic lymph node receive drainage from? Dig Surg 24(6):413–417
Kelder W, Nimura H, Takahashi N et al (2010) Sentinel node mapping with indocyanine green (ICG) and infrared ray detection in early gastric cancer: an accurate method that enables a limited lymphadenectomy. Eur J Surg Oncol 6:552–558
Keller DS, Ishizawa T, Cohen R, Chand M (2017) Indocyanine green fluorescence imaging in colorectal surgery: overview, applications, and future directions. Lancet Gastroenterol Hepatol 2(10):757–766
Kim DJ, Chung JJ, Yu JS et al (2014) Evaluation of lateral pelvic nodes in patients with advanced rectal cancer. AJR Am J Roentgenol 202(6):1245–1255
Kim DW, Jeong B, Shin IH et al (2019) Sentinel node navigation surgery using near-infrared indocyanine green fluorescence in early gastric cancer. Surg Endosc 33(4):1235–1243
Kinami S, Oonishi T, Fujita J et al (2016) Optimal settings and accuracy of indocyanine green fluorescence imaging for sentinel node biopsy in early gastric cancer. Oncol Lett 11(6):4055–4062
Kitagawa Y, Kubota T, Kumai K et al (2005) Recent studies of sentinel lymph node. Multicenter prospective clinical trials of SN biopsy for gastric cancer. Gan to Kagaku Ryoho 32(5):695–698 (**Japenese**)
Kolitz-Domb M, Grinberg I, Corem-Salkmon E, Margel S (2014) Engineering of near infrared fluorescent proteinoid-poly(L-lactic acid) particles for in vivo colon cancer detection. J Nanobiotechnol 12:30
Kusano M, Tajima Y, Yamazaki K et al (2008) Sentinel node mapping guided by indocyanine green fluorescence imaging: a new method for sentinel node navigation surgery in gastrointestinal cancer. Dig Surg 25(2):103–108
Kwon IG, Son T, Kim HI et al (2019) Fluorescent lymphography-guided lymphadenectomy during robotic radical gastrectomy for gastric cancer. JAMA Surg 154(2):150–158
Lee JH, Ryu KW, Nam BH et al (2009) Factors associated with detection failure and false-negative sentinel node biopsy findings in gastric cancer: results of prospective single center trials. J Surg Oncol 99(3):137–142
Lee JH, Son T, Chung YE et al (2021) Real-time identification of aberrant left hepatic arterial territories using near-infrared fluorescence with indocyanine green during gastrectomy for gastric cancer. Surg Endosc 35(5):2389–2397
Leporrier J, Maurel J, Chiche L et al (2006) A population-based study of the incidence, management and prognosis of hepatic metastases from colorectal cancer. Br J Surg 93(4):465–474
Li R, Chen Z, Dai Z, Yu Y (2021a) Nanotechnology assisted photo- and sonodynamic therapy for overcoming drug resistance. Cancer Biol Med 18(2):388–400
Li S, Zhang W, Xing R, Yuan C, Xue H, Yan X (2021b) Supramolecular nanofibrils formed by coassembly of clinically approved drugs for tumor photothermal immunotherapy. Adv Mater 33(29):e2103733
Li X, Yong T, Wei Z et al (2022) Reversing insufficient photothermal therapy-induced tumor relapse and metastasis by regulating cancer-associated fibroblasts. Nat Commun 13(1):2794
Liberale G, Vankerckhove S, Galdon MG, Larsimont D, Ahmed B, Bouazza F, Moreau M, El Nakadi I, Donckier V, Bourgeois P, R&D Group for the Clinical Application of Fluorescence Imaging at the Jules Bordet Institute (2016) Sentinel lymph node detection by blue dye versus indocyanine green fluorescence imaging in colon cancer. Anticancer Res 36(9):4853–4858. https://doi.org/10.21873/anticanres.11048
Liu Y, Bhattarai P, Dai Z et al (2019) Photothermal therapy and photoacoustic imaging via nanotheranostics in fighting cancer. Chem Soc Rev 48(7):2053–2108
Low PS, Kularatne SA (2009) Folate-targeted therapeutic and imaging agents for cancer. Curr Opin Chem Biol 13(3):256–262
Miyashiro I, Kishi K, Yano MT et al (2011) Laparoscopic detection of sentinel node in gastric cancer surgery by indocyanine green fluorescence imaging. Surg Endosc 25(5):1672–1676
Miyoshi N, Ohue M, Noura S et al (2009) Surgical usefulness of indocyanine green as an alternative to India ink for endoscopic marking. Surg Endosc 23(2):347–351
Mok H, Jeong H, Kim SJ et al (2012) Indocyanine green encapsulated nanogels for hyaluronidase activatable and selective near infrared imaging of tumors and lymph nodes. Chem Commun (camb) 48(69):8628–8630
Morita D, Tsuda H, Ichikura T et al (2007) Analysis of sentinel node involvement in gastric cancer. Clin Gastroenterol Hepatol 5(9):1046–1052
Nagata K, Endo S, Hidaka E et al (2006) Laparoscopic sentinel node mapping for colorectal cancer using infrared ray laparoscopy. Anticancer Res 26(3B):2307–2311
Newton AD, Predina JD, Frenzel-Sulyok LG et al (2021) Intraoperative molecular imaging utilizing a folate receptor-targeted near-infrared probe can identify macroscopic gastric adenocarcinomas. Mol Imaging Biol 23(1):11–17

Nimura H, Narimiya N, Mitsumori NY et al (2004) Infrared ray electronic endoscopy combined with indocyanine green injection for detection of sentinel nodes of patients with gastric cancer. Br J Surg 91(5):575–579
Noura S, Ohue M, Seki Y, Yamamoto T, Idota A, Fujii J, Yamasaki T, Nakajima H, Murata K, Kameyama M, Yamada T, Miyashiro I, Ohigashi H, Yano M, Ishikawa O, Imaoka S (2008) Evaluation of the lateral sentinel node by indocyanine green for rectal cancer based on micrometastasis determined by reverse transcriptase-polymerase chain reaction. Oncol Rep 20(4):745–750
Noura S, Ohue M, Seki Y, Tanaka K, Motoori M, Kishi K, Miyashiro I, Ohigashi H, Yano M, Ishikawa O, Miyamoto Y (2010a) Feasibility of a lateral region sentinel node biopsy of lower rectal cancer guided by indocyanine green using a near-infrared camera system. Ann Surg Oncol 17(1):144–151. https://doi.org/10.1245/s10434-009-0711-2. (**Epub 2009 Sep 23**)
Noura S, Ohue M, Seki Y et al (2010b) Feasibility of a lateral region sentinel node biopsy of lower rectal cancer guided by indocyanine green using a near-infrared camera system. Ann Surg Oncol 17(1):144–151
Ohdaira H, Nimura H, Mitsumori N et al (2007) Validity of modified gastrectomy combined with sentinel node navigation surgery for early gastric cancer. Gastric Cancer 10(2):117–122
Ohdaira H, Nimura H, Fujita T et al (2009) Tailoring treatment for early gastric cancer after endoscopic resection using sentinel node navigation with infrared ray electronic endoscopy combined with indocyanine green injection. Dig Surg 26(4):276–281
Ohya H, Watanabe J, Suwa H et al (2022) Near-infrared imaging using indocyanine green for laparoscopic lateral pelvic lymph node dissection for clinical stage II/III middle-lower rectal cancer: a propensity score-matched cohort study. Dis Colon Rectum 65(7):885–893
Okubo K, Uenosono Y, Arigami T et al (2018) Quantitative assessment of fluorescence intensity of ICG in sentinel nodes in early gastric cancer. Gastric Cancer 21(5):776–781
Park SH, Lee HJ, Park JH et al (2021) Clinical significance of intra-operative gastroscopy for tumor localization in totally laparoscopic partial gastrectomy. J Gastrointest Surg 25(5):1134–1146
Predina JD, Newton AD, Keating J et al (2017) Intraoperative molecular imaging combined with positron emission tomography improves surgical management of peripheral malignant pulmonary nodules. Ann Surg 266(3):479–488
Predina JD, Newton AD, Keating J et al (2018) A phase I clinical trial of targeted intraoperative molecular imaging for pulmonary adenocarcinomas. Ann Thorac Surg 105(3):901–908
Randall LM, Wenham RM, Low PS et al (2019) A phase II, multicenter, open-label trial of OTL38 injection for the intraoperative imaging of folate receptor-alpha positive ovarian cancer. Gynecol Oncol 155(1):63–68
Ren L, Nie J, Wei J et al (2021) RGD-targeted redox responsive nano micelle: co-loading docetaxel and indocyanine green to treat the tumor. Drug Deliv 28(1):2024–2032
Schaafsma BE, Verbeek FP, van der Vorst JR, Hutteman M, Kuppen PJ, Frangioni JV, van de Velde CJ, Vahrmeijer AL. Ex vivo sentinel node mapping in colon cancer combining blue dye staining and fluorescence imaging. J Surg Res. 2013;183(1):253-7. doi: https://doi.org/10.1016/j.jss.2013.01.003. (Epub 2013 Jan 25). Erratum in: J Surg Res. 2014;189(1):192.
Shao J, Zheng X, Feng L et al (2020) Targeting Fluorescence imaging of RGD-modified indocyanine green micelles on gastric cancer. Front Bioeng Biotechnol 8:575365
Shao J, Liang R, Ding D et al (2021) A smart multifunctional nanoparticle for enhanced near-infrared image-guided photothermal therapy against gastric cancer. Int J Nanomedicine 16:2897–2915
Shen L, Shan YS, Hu HM et al (2013) Management of gastric cancer in Asia: resource-stratified guidelines. Lancet Oncol 14(12):e535–e547
Sherwinter DA, Boni L, Bouvet M et al (2022) Use of fluorescence imaging and indocyanine green for sentinel node mapping during gastric cancer surgery: Results of an intercontinental Delphi survey. Surgery 172(6S):S29–S37
Shida A, Mitsumori N, Fujioka S et al (2018) Sentinel node navigation surgery for early gastric cancer: analysis of factors which affect direction of lymphatic drainage. World J Surg 42(3):766–772
Smith DD, Schwarz RR, Schwarz RE (2005) Impact of total lymph node count on staging and survival after gastrectomy for gastric cancer: data from a large US-population database. J Clin Oncol 23(28):7114–7124
Sposito C, Maspero M, Belotti P, Simonotti N, Altomare M, Ciana P et al (2022) Indocyanine green fluorescence-guided surgery for gastrointestinal tumors: a systematic review. Ann Surg Open 3(3):e190
Stamos MJ (2015) Perfusion assessment in laparoscopic left-sided/anterior resection (PILLAR II): a multi-institutional study. J Am Coll Surg 220(1):82-92.e81
Tajima Y, Yamazaki K, Masuda Y et al (2009) Sentinel node mapping guided by indocyanine green fluorescence imaging in gastric cancer. Ann Surg 249(1):58–62
Tajima Y, Murakami M, Yamazaki K et al (2010) Sentinel node mapping guided by indocyanine green fluorescence imaging during laparoscopic surgery in gastric cancer. Ann Surg Oncol 17(7):1787–1793
Takahashi N, Nimura H, Fujita T et al (2016) Quantitative assessment of visual estimation of the infrared indocyanine green imaging of lymph nodes retrieved at sentinel node navigation surgery for gastric cancer. BMC Surg 16(1):35
Takahashi N, Nimura H, Fujita T et al (2017) Laparoscopic sentinel node navigation surgery for early gastric cancer: a prospective multicenter trial. Langenbecks Arch Surg 402(1):27–32
Tanyi JL, Randall LM, Chambers SK et al (2023) A phase III study of pafolacianine injection (OTL38) for intraoperative imaging of folate receptor-positive ovarian cancer (study 006). J Clin Oncol 41(2):276–284
Tummers QR, Boogerd LS, de Steur WO et al (2016) Near-infrared fluorescence sentinel lymph node detection in gastric cancer: a pilot study. World J Gastroenterol 22(13):3644–3651
Ushimaru Y, Omori T, Fujiwara Y et al (2019) The feasibility and safety of preoperative fluorescence marking with indocyanine green (ICG) in laparoscopic gastrectomy for gastric cancer. J Gastrointest Surg 23(3):468–476

van der Pas MH, Ankersmit M, Stockmann HB, Silvis R, van Grieken NC, Bril H, Meijerink WJ (2013) Laparoscopic sentinel lymph node identification in patients with colon carcinoma using a near-infrared dye: description of a new technique and feasibility study. J Laparoendosc Adv Surg Tech A 23(4):367–371. https://doi.org/10.1089/lap.2012.0407. (**Epub 2013 Mar 11**)
Villegas-Tovar E, Jimenez-Lillo J, Jimenez-Valerio V et al (2020) Performance of Indocyanine green for sentinel lymph node mapping and lymph node metastasis in colorectal cancer: a diagnostic test accuracy meta-analysis. Surg Endosc 34(3):1035–1047
Wakabayashi T, Cacciaguerra AB, Abe Y et al (2022) Indocyanine green fluorescence navigation in liver surgery: a systematic review on dose and timing of administration. Ann Surg 275(6):1025–1034
Wang G, Zhang F, Tian R, Zhang L et al (2016) Nanotubes-embedded indocyanine green-hyaluronic acid nanoparticles for photoacoustic-imaging-guided phototherapy. ACS Appl Mater Interfaces 8(8):5608–5617
Wang H, Li X, Tse BW, Yang H et al (2018) Indocyanine green-incorporating nanoparticles for cancer theranostics. Theranostics 8(5):1227–1242
Watanabe J, Ota M, Suwa Y, Ishibe A, Masui H, Nagahori K (2017) Evaluation of lymph flow patterns in splenic flexural colon cancers using laparoscopic real-time indocyanine green fluorescence imaging. Int J Colorectal Dis 32(2):201–207. https://doi.org/10.1007/s00384-016-2669-4. (**Epub 2016 Oct 1**)
Wei W, Zeng H, Zheng R et al (2020) Cancer registration in China and its role in cancer prevention and control. Lancet Oncol 21(7):e342–e349
Weixler B, Rickenbacher A, Raptis DA, Viehl CT, Guller U, Rueff J, Zettl A, Zuber M (2017) Sentinel lymph node mapping with isosulfan blue or indocyanine green in colon cancer shows comparable results and identifies patients with decreased survival: a prospective single-center trial. World J Surg 41(9):2378–2386. https://doi.org/10.1007/s00268-017-4051-2
Wexner S, Abu-Gazala M, Boni L et al (2022) Use of fluorescence imaging and indocyanine green during colorectal surgery: results of an intercontinental Delphi survey. Surgery 172(6S):S38–S45
Wu T, Liu Y, Cao Y, Liu Z (2022) Engineering macrophage exosome disguised biodegradable nanoplatform for enhanced sonodynamic therapy of glioblastoma. Adv Mater 34(15):e2110364
Xu H, Ohulchanskyy TY, Qu J et al (2020) Co-encapsulating indocyanine green and CT contrast agent within nanoliposomes for trimodal imaging and near infrared phototherapy of cancer. Nanomedicine 29:102269
Xu G, Li C, Chi C et al (2022) A supramolecular photosensitizer derived from an Arene-Ru(II) complex self-assembly for NIR activated photodynamic and photothermal therapy. Nat Commun 13(1):3064
Xue Y, Gao Y, Meng F, Luo L (2021) Recent progress of nanotechnology-based theranostic systems in cancer treatments. Cancer Biol Med 18(2):336–351
Yang RQ, Wang PY, Lou KL et al (2022) Biodegradable nanoprobe for NIR-II fluorescence image-guided surgery and enhanced breast cancer radiotherapy efficacy. Adv Sci (weinh) 9(12):e2104728
Yano H, Moran BJ (2008) The incidence of lateral pelvic side-wall nodal involvement in low rectal cancer may be similar in Japan and the West. Br J Surg 95(1):33–49
Yano K, Nimura H, Mitsumori N et al (2012) The efficiency of micrometastasis by sentinel node navigation surgery using indocyanine green and infrared ray laparoscopy system for gastric cancer. Gastric Cancer 15(3):287–291
Zehetner J, DeMeester SR, Alicuben ET et al (2015) Intraoperative assessment of perfusion of the gastric graft and correlation with anastomotic leaks after esophagectomy. Ann Surg 262(1):74–78
Zhang N, Hao X (2021) Epigenetic modulation of the tumor immune microenvironment by nanoinducers to potentiate cancer immunotherapy. Cancer Biol Med 19(1):1–3

Publisher's Note