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Fluorescence-guided surgery in colorectal cancer; A review on clinical results and future perspectives

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ABSTRACT

Background: Colorectal cancer is the fourth most diagnosed malignancy worldwide and surgery is one of the cornerstones of the treatment strategy. Near-infrared (NIR) fluorescence imaging is a new and upcoming technique, which uses an NIR fluorescent agent combined with a specialised camera that can detect light in the NIR range. It aims for more precise surgery with improved oncological outcomes and a reduction in complications by improving discrimination between different structures.
Methods: A systematic search was conducted in the Embase, Medline and Cochrane databases with search terms corresponding to 'fluorescence-guided surgery', 'colorectal surgery', and 'colorectal cancer' to identify all relevant trials.
Results: The following clinical applications of fluorescence guided surgery for colorectal cancer were identified and discussed: (1) tumour imaging, (2) sentinel lymph node imaging, (3) imaging of distant metastases, (4) imaging of vital structures, (5) imaging of perfusion. Both experimental and FDA/EMA approved fluorescent agents are debated. Furthermore, promising future modalities are discussed.
Conclusion: Fluorescence-guided surgery for colorectal cancer is a rapidly evolving field. The first studies show additional value of this technique regarding change in surgical management. Future trials should focus on patient related outcomes such as complication rates, disease free survival, and overall survival.

1. Introduction

Colorectal cancer (CRC) is globally the fourth most common malignancy and the second cause of cancer related mortality with over 550 000 deaths annually [1]. In most CRC patients, surgery remains the cornerstone of treatment. Complete surgical resection of the tumour is associated with better overall survival and lower recurrence rates [2,3]. Minimal invasive surgery, laparoscopic or robot-assisted, is increasingly used in the last two decades. Despite its advantages, this application also brought new technical challenges as it lacks tactile feedback for tumour identification and identification of vital structures. These challenges sparked the interest in novel intraoperative visualisation techniques, such as near-infrared (NIR) fluorescence imaging.

NIR fluorescence imaging is a real-time imaging technique that combines a NIR fluorescent agent with a specialised imaging system (Fig. 1). These systems can capture light emitted by a fluorescent agent after excitation with an appropriate light source (Fig. 2). NIR light (650–900 nm) is favourable for intraoperative imaging compared to visible light because of its better depth penetration in tissue (up to 10 mm). Moreover, the fluorescent agents will not interfere with the standard surgical field, as the human eye is unable to detect light within these NIR wavelengths.

NIR fluorescent agents are predominantly injected

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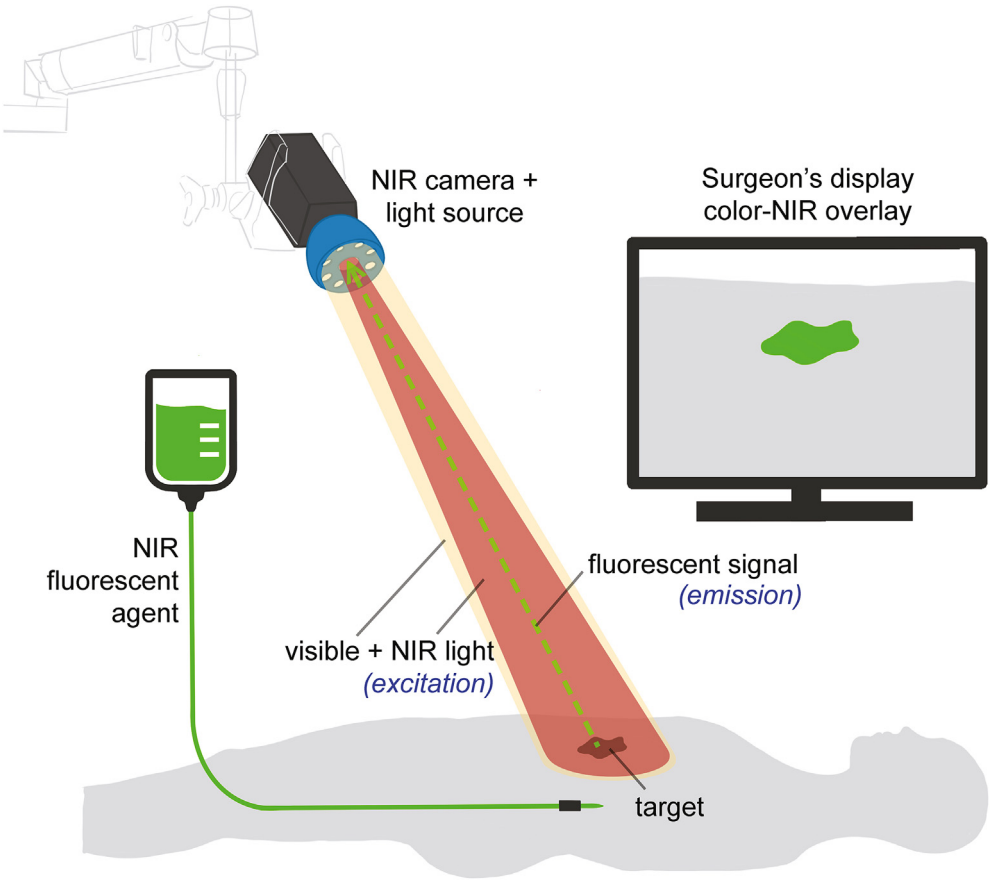

Fig. 1. The basic principles of fluorescence-guided surgery.
NIR fluorescent agents are administered intravenously or locally. Imaging of the agent is performed using a fluorescence imaging system. Besides a white light source and camera, this system includes a dedicated NIR excitation light, collection optics and filtration, and a camera dedicated to NIR fluorescence emission light. NIR fluorescence output is displayed on a screen in the operating theatre. A simultaneous visible light image, which can be merged with the NIR fluorescence image, is desirable.

intravenously and can be divided into two groups: targeted (binding to a specific ligand or activated by the tumour-specific environment) and non-targeted. Currently, various targeted fluorescent agents are tested in phase I-III clinical trials [4]. In the group of non-targeted agents, indocyanine green (ICG) and methylene blue (MB) are approved by the United States Food and Drug Administration (FDA) and the European Medicines Agent (EMA), for other purposes. ICG was first used in 1957 to determine hepatic function, but its fluorescent properties (excitation peak around 800 nm), and hence other applications, became known decades later [5]. MB on the other hand, is predominantly cleared renally and has its excitation peak around 700 nm [6]. Both agents have been proven to be safe for fluorescence utilisation.

There are many applications for NIR fluorescence imaging during colorectal surgery. This review provides an overview of the currently available clinical applications and promising future modalities of fluorescence-guided surgery in the treatment of CRC patients.

2. Methods

Due to heterogeneity in available literature and study phases between the several subjects, this study was not fully conducted according to the PRISMA guidelines.

2.1. Literature search and selection criteria

A systematic search was conducted in the Embase, Medline and Cochrane databases with search terms corresponding to 'fluorescence-guided surgery', 'colorectal surgery', and 'colorectal cancer'. The search strategy was expanded with terms to identify articles reporting on vital structure imaging, perfusion assessment, and colorectal metastases. Supplement 1 shows the search strategies per database and its corresponding hits. The last search was conducted on December 21st, 2020. All articles were independently screened based on title and abstract by two authors (HG and RM). Next, full article screening and reference screening was performed. Inconsistencies were discussed with an additional author (DH). Regarding experimental fluorescent agents, all clinical studies were included in the final reference list. Regarding ICG and MB, the final reference list was generated based on the quality of the article and the amount of scientific evidence available per subject. Articles on the following subjects were included: fluorescence-guided surgery for CRC for the imaging of the primary tumour, lymph nodes, metastases (peritoneal, liver, extra-abdominal), vital structures (nerve, ureter, urethra), and perfusion (anastomosis, omentoplasty). Only articles in English and published after the year 2000 were considered.

2.2. Data extraction

The following data was extracted: tumour type, fluorescent

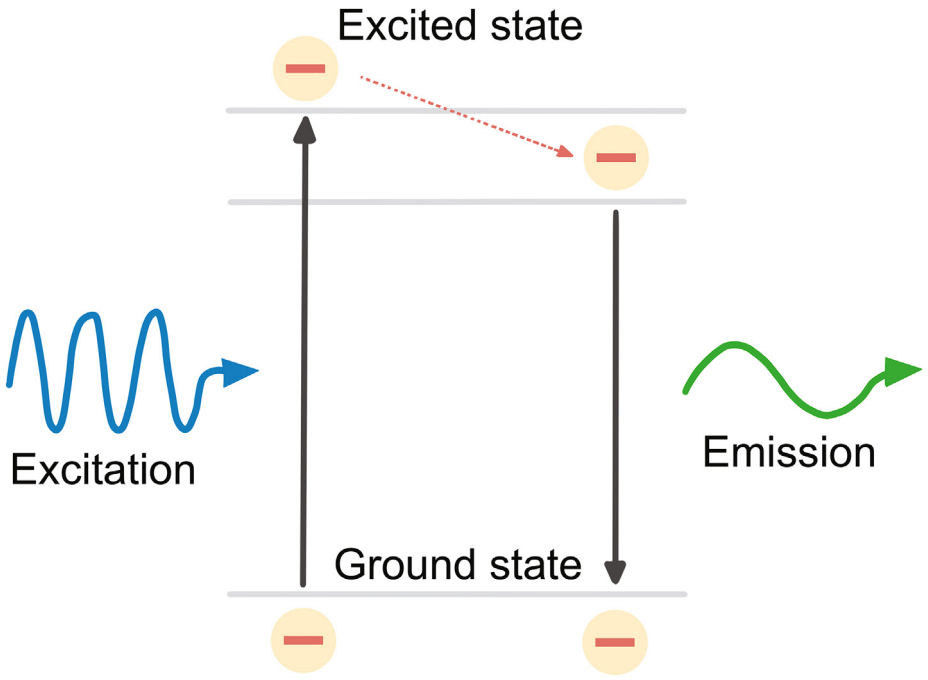

Fig. 2. The basic principles of fluorescence.
Photons emitted by the fluorescence imaging system are absorbed by the fluorescent agent. Subsequently, the electrons within the agent transition from their ground state to an excited state, and back to their ground state (Stokes shift). During this last step, a photon with a lower wavelength than the photon from the imaging system, is emitted as the energy from the electron gets released. This emitted fluorescence signal is captured by the dedicated fluorescence camera.

agent, fluorescence imaging application, (optimal) dose, (optimal) dosing interval, optimal TBR, sensitivity, specificity, change in surgical management, and other outcomes.

2.3. Quality assessment

Quality assessment was performed for all studies assessing experimental fluorescent agents. The Methodological index for non-randomized studies (MINORS score) was used for quality assessment. A total score of 16 (for non-comparative studies) or 24 (for comparative studies) could be obtained [7].

3. Results

A total of fourteen completed clinical studies (supplement 2) and eight ongoing trials (supplement 3) assessing experimental fluorescent agents for CRC surgery were identified. Fig. 3 gives an overview of all clinical applications of FGS for CRC, with the assessed fluorescent agents (Table 1). All 14 clinical studies regarding experimental fluorescence agents had a MINORS score of 11 or higher (supplement 4).

3.1. Imaging of the primary tumour and local recurrence

Achieving tumour-negative resection margins is of utmost importance in the surgical treatment of CRC patients, as tumour-positive resection margins are associated with a significant decrease in overall survival [2,8]. Tumour-positive resection margins are reported in 5% of all colon cancer cases, but occur more frequently with increasing tumour stage, with an occurrence of up to 14% in T4 colon cancer [2]. Moreover, in locally advanced rectal cancer the proportion of tumour-positive resection margins is 28% [8]. This rate is even higher in patients with recurrent rectal cancer, where up to 50% tumour-positive resection margins are reported [9]. These high rates in recurrent rectal cancer are likely a consequence of the distorted anatomy and treatment related fibrosis after previous resection and (re-)neoadjuvant treatment. Tumour identification is challenging in these cases due to the difficult distinction (both visual and tactile) between fibrosis and residual tumour tissue.

Preoperative endoscopic tattooing with India ink, a permanent marker injected distal to the tumour, is the current standard of care for intraoperative tumour identification in CRC, with an accuracy rate of 70–88% [10,11]. However, India ink can leak into the abdominal cavity and thereby interfere with the surgical procedure.

In 2009, the first NIR fluorescence imaging technique to identify the primary tumour in CRC was introduced by injecting ICG peritumoural via endoscopy. It has a high tumour identification rate (100%) and minimal adverse events [12,13]. However, a major drawback is the relatively rapid clearance of ICG, as detection rates tend to decrease two to seven days after injection [12]. Therefore, patients must undergo an additional endoscopy in the week before surgery, in contrast to the conventional injection of India ink that can be administered at the initial, diagnostic colonoscopy. Because of these drawbacks, peritumoural ICG injection has not been widely implemented for tumour identification. Moreover, this technique will not improve the tumour-negative resection margin rates because it does not differentiate between tumour- and benign tissue, nor does it enable the detection of additional lesions. A potential solution is the use of fluorescent agents that specifically bind to tumour cells.

The number of tumour-targeted fluorescent agents has substantially increased in the past two decades. The use of these agents is aimed to achieve complete tumour resection. This should lead to a decrease in the number of tumour-positive resection margins, detection of additional lesions and avoid unnecessary removal of

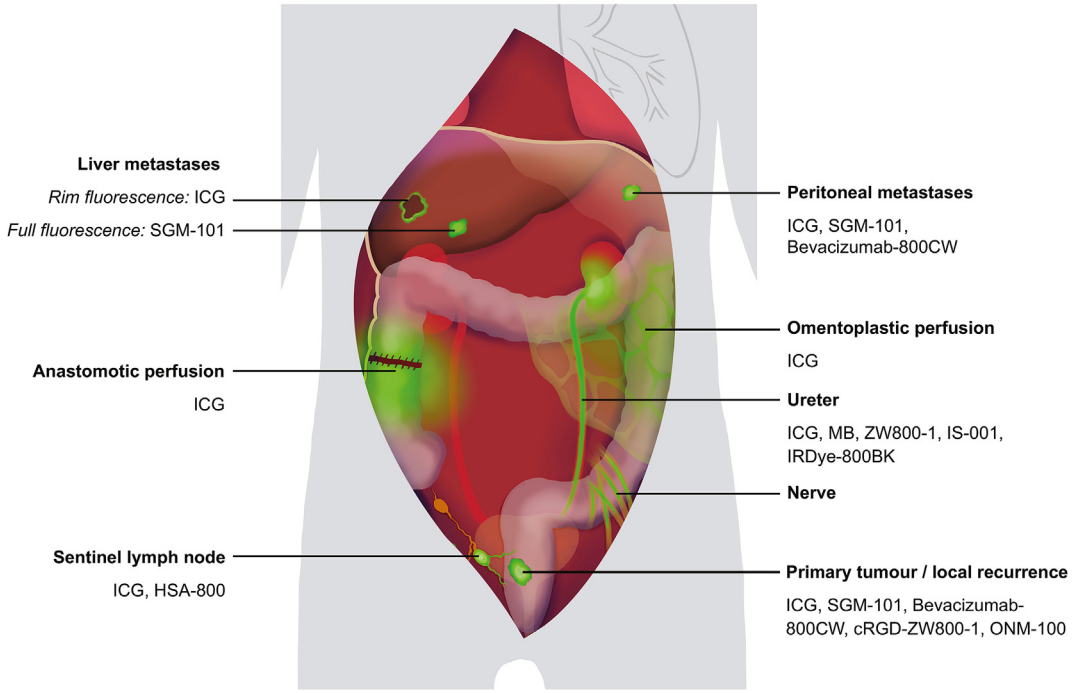

Fig. 3. A schematic overview of all clinical applications of fluorescence guided surgery for colorectal cancer.
Abbreviations: ICG indocyanine green, MB Methylene blue.

Table 1
An overview of all fluorescent agents used for colorectal cancer surgery and their optical properties.

Fluorescent Agent	Molecular target	Fluorophore	~Peak absorbance wavelength	~Peak emission wavelength	Ref
Bevacizumab-800CW	VEGF-A	IRDye-800CW	778 nm	794 nm	[21]
cRGD-ZW800-1	Integrins (αvβ6, αvβ3, αvβ5)	ZW800-1	785 nm	805–850 nm	[69]
HSA800	Na	IRDye-800CW	778 nm	795 nm	[21]
ICG	Na	ICG	780 nm	830 nm	[5]
IRDye-800BK	Na	IRDye-800BK	774 nm	790 nm	[72]
IS-001	Na	IS-001	780 nm	815 nm	[70]
LUM015	Cathepsins (K, L, S, B)	Cy5	650 nm	675 nm	[22]
MB	Na	MB	667 nm	685 nm	[6]
ONM-100	Metabolic acidosis*	ICG	780 nm	830 nm	[5]
SGM-101	CEA	BM-104	685 nm	705 nm	[19]
ZW800-1	Na	ZW800-1	785 nm	805–850 nm	[69]

* no molecular target but activated in tumour specific PH-environment

Abbreviations: VEGF-A vascular endothelial growth factor alpha | nm nanometre | ICG indocyanine green | MB methylene blue | CEA carcinoembryonic antigen | na not applicable.

benign tissue. To quantify fluorescence intensity, most studies use the signal-to-background ratio (SBR) or tumour-to-background ratio (TBR). This is a ratio of the mean fluorescence intensity of the tumour and the surrounding tissue (background). A TBR of at least 1.5 and preferably 2.0 is deemed sufficient for tumour identification. Currently, four tumour-targeted fluorescent agents have been tested in early phase clinical studies for CRC and have shown promising results: SGM-101, cRGD-ZW800-1, bevacizumab-800CW, and ONM-100 [14–18].

SGM-101 consists of a monoclonal antibody targeting the carcinoembryonic antigen (CEA) bound to the fluorophore BM-104 [19]. A phase II study of 37 patients showed an intraoperative TBR of 1.9. Importantly, based on fluorescence assessment, the surgical plan was changed in nine (24%) patients. In seven patients, fluorescence led to resection of malignant lesions that were not identified with white light only. In two patients, clinically suspected but non-fluorescent tissue was proven to be benign, which resulted in a less extensive resection [18]. These promising results have led to the initiation of two phase III trials using SGM-101 (NCT03659448, NCT04642924).

cRGD-ZW800-1 is a cyclic pentapeptide (cRGD) conjugated to the 800 nm zwitterionic NIR fluorophore ZW800-1. It targets various integrins that have been shown to be overexpressed on colorectal tumour cells. In the first-in-human study, twelve colon cancer patients were included. Intraoperative fluorescence imaging of the primary tumour was feasible in both open and minimal invasive surgeries (Fig. 4). The highest mean TBR of 1.6 was found in the highest dosing of 0.05 mg/kg [15].

Bevacizumab-800CW consists of a monoclonal antibody targeting vascular endothelial growth factor A (VEGF-A), bound to IRDye-800CW [20,21]. Bevacizumab-800CW has been studied in eight rectal cancer patients [16]. During back table fluorescence assessment of the resection margins on the surgical specimen, a tumour-positive margin was correctly identified in one out of two

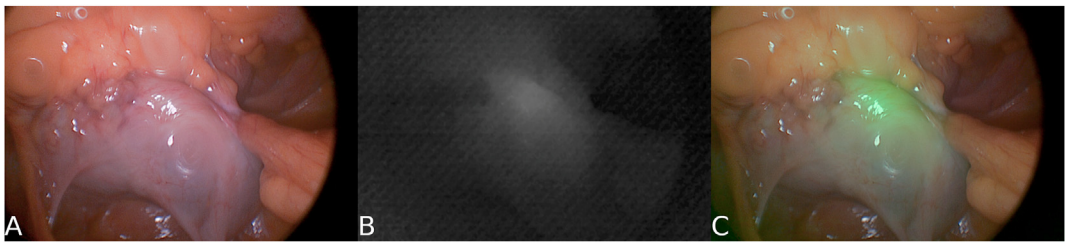

Fig. 4. Fluorescence imaging results of primary colon cancer.
Intraoperative fluorescence imaging result of an adenocarcinoma of the ascending colon (TBR 1.6) using cRGD-ZW800-1. Imaging was performed using the Quest Spectrum laparoscopic imaging system. It shows an image in white light (A), near-infrared (B) and merge of A and B (C).

patients. In the six patients with a tumour-negative resection margin, one (17%) showed a false-positive signal.

ONM-100 is a pH-activatable fluorescent agent that exploits the metabolic microenvironment of solid tumours [17]. It does not bind to specific tumour receptors but is activated in the acidic tumour environment. It is a conjugation of a pH-sensitive nanoparticle to ICG, which becomes fluorescent in environments with a pH below 6.9. Thirty patients were studied with this agent, of which three underwent surgery for CRC. All three CRC patients showed a sharply demarcated fluorescent signal during back table imaging. Currently, a phase II study using ONM-100 is ongoing in which patients undergoing surgery for CRC are also included (NCT03735680).

A phase I/II trial will be conducted using LUM015, a novel PEGylated protease-activated fluorescent imaging agent targeting cathepsins, which play a crucial role in mammalian cell turnover [22]. The first results of this study, which focuses on intraoperative imaging of CRC, are expected in 2022 (NCT02584244).

Altogether, these early phase clinical trials have shown that tumour-targeted fluorescence imaging is a feasible addition to CRC surgery. The fluorescent agents detected most of the known tumours and SGM-101 even detected additional lesions, which were not detected in white light. To assess the impact on patient related outcomes, future studies should focus on clinical endpoints like tumour-negative resection margin rate and change in surgical management.

3.2. Imaging of the sentinel lymph node

Adequate lymph node staging in CRC patients is crucial; it is an important prognostic factor and determines the need for (neo) adjuvant treatment. The sentinel lymph node (SLN) may be crucial in nodal staging, as it is defined as the first lymph node draining the tumour and is believed to be the first place for lymphogenic metastases. Moreover, one in three patients with stage I and II colon cancer, who are staged as lymph node-negative, still develop distant metastases [23]. This might be a consequence of understaging by histopathology, due to lymph nodes with occult malignant cells and micrometastases. Currently, a single paraffin embedded slide per lymph node is reviewed during routine histopathological analysis, increasing the chance of missing tumour cells away from the slide's cutting edge. More extensive histopathological analysis of all resected lymph nodes would improve nodal staging, but this process is time-consuming and expensive [24]. Extensive analysis of only the SLN is feasible, and thus unfolds a niche for SLN mapping in CRC. Moreover, tumour-negative SLNs create an opportunity for endoscopic or local resection of early stage tumours [25].

A reason for the absence of SLN mapping in the routine treatment of CRC patients might be a consequence of so-called skip metastases that are reported in up to 22% the patients [26]. In these cases, malignant cells are absent in the SLN, but present in other regional lymph nodes. Moreover, the use of blue dye for SLN mapping in CRC appears limited due to its minimal depth penetration in the mesocolic and mesorectal fat [27]. Therefore, the interest in fluorescent dyes, especially the peritumoural injection of ICG, has increased. These fluorescent dyes have already shown to be of additional value for the identification of complete lymph drainage patterns, including aberrant flow [28,29]. Nevertheless, the identification of only the SLN would be a valuable addition.

Various techniques have been used in studies assessing fluorescence-guided SLN mapping in CRC. Agent administration and SLN mapping can be performed before or during the procedure (*in vivo*) or after resection (*ex vivo*). Although *ex vivo* imaging might be easier to adapt in the current surgical or pathological workflow, it has drawbacks. Most importantly, *ex vivo* injection of an agent and identification of the SLN lacks the possibility of finding SLNs in patients with aberrant lymph node drainage patterns [30]. Another technical consideration is the site of injection. For *in vivo* SLN mapping, submucosal injection is done endoscopically, prior to surgery. Alternatively, subserosal injection can be performed during surgery, which in laparoscopic surgery demands transcutaneous needle placement. Submucosal injection is preferred over subserosal injection because of better accuracy of injection near the tumour and easier endoscopic needle positioning [31].

ICG is the only fluorescent dye that has been reported for *in vivo* SLN mapping in CRC with cohorts up to 48 patients and success rates of SLN detection ranging from 65.5 to 100% [31–35]. The accuracy of this technique seems to diminish with increasing tumour stage [34,36]. Which is most likely a result of the distorted drainage patterns caused by transmural growth of advanced tumours.

Ex vivo SLN mapping facilitates the use of experimental agents, like HSA800 (IRDye-800CW conjugated to human serum albumin). HSA800 has shown a potential advantage over ICG, due to its bigger hydrodynamic diameter that results in better retention in the SLN [37]. HSA800 has demonstrated successful identification of the SLN in 95–100% of 96 patients [38–40].

Despite high fluorescence-guided SLN identification rates, the SLN itself was associated with a relatively low negative predictive value (74–100%) in general, mainly as a result of high false-negative rates (when the SLN did not contain tumour tissue, but other regional lymph nodes did) [31–35,38,39]. This can be a result of the occurrence of skip metastases [26].

Correct staging is essential for treatment planning in CRC patients and may be improved with SLN mapping. A patient is upstaged when no tumour deposits were seen during conventional

histopathology of all lymph nodes, but the SLN showed malignant cells at advanced histopathological analysis using serial sectioning and immunohistochemistry. SLN mapping with ICG and subsequent advanced histopathology resulted in upstaging in 6–23% of the patients [31–33]. Although plausible, it is yet unknown whether upstaged patients with micrometastatic lymph nodes will benefit from subsequent adjuvant treatment.

Overall, it can be concluded that fluorescence-guided identification of the SLN is feasible and potentially of additional clinical value. However, a wide variety of techniques for fluorescence-guided SLN identification are currently used. It is recommended to first determine the optimal agent, injection technique and patient population. The high false-negative rate (tumour-negative SLN with tumour-positive regional nodes) remains a major drawback for SLN mapping in CRC in general. Nevertheless, its value in terms of upstaging and the consequence of adjuvant treatment seems enough reason to further explore this field.

3.3. Imaging of distant metastases

3.3.1. Peritoneal metastases

Approximately 10% of all CRC patients develop peritoneal metastases during the course of the disease [41]. In the past, this diagnosis was considered non-curable with a median overall survival of approximately 12 months [42]. These survival rates have improved with the introduction of cytoreductive surgery followed by intraoperative hyperthermic intraperitoneal chemotherapy (HIPEC) [3,43]. Studies have shown that in particular complete cytoreduction plays a major role as it prolongs the long-term survival of patients with peritoneal metastases [3]. However, identification of small peritoneal lesions can be challenging. An accurate PCI is essential as this score plays a crucial role in the decision to perform a HIPEC procedure or not [44]. Fluorescence imaging can potentially lead to more a precise PCI and complete cytoreductive surgery by more accurately identifying peritoneal lesions.

Intravenous injection of ICG and subsequent fluorescence imaging of peritoneal metastases is primary based on the enhanced permeability and retention (EPR) effect. The EPR effect is dependent on the porous nature of tumour vasculature and the extended circulation of the fluorescent agent, leading to accumulation in the tumour [45]. ICG is administered at the start of the surgical procedure and has shown good intraoperative imaging of peritoneal metastases, which has led to a modification of the surgical plan in 4 out of 14 patients (29%) solely based on the fluorescence assessment [46]. Nevertheless, the authors reported limited ability to assess fluorescence in areas with high physiological ICG accumulation such as the liver, as well as a sensitivity of 0% in patients with mucinous tumours [46]. Moreover, neoadjuvant treatment resulted in a higher false-negative rate (53.8% vs. 42.9%) and lower sensitivity (65.0% vs 76.3%) compared to patients who did not receive neoadjuvant treatment [47].

To date, two tumour-targeted agents have been used for *in vivo* detection of peritoneal metastases in CRC: bevacizumab-800CW and SGM-101. Bevacizumab-800CW was the first tumour-targeted fluorescent agent that was reported to yield promising results, identifying additional peritoneal metastases in two out of seven (29%) patients [48]. Similar results were achieved in a study with SGM-101, where fluorescence imaging led to a change in PCI in five out of twelve (42%) patients (Fig. 5). Four patients had a higher PCI and one patient a lower PCI, all confirmed by histopathology [49]. It is noteworthy that both studies reported a high false-positive rate (38% and 47%, respectively). This could be a result of non-specific localisation of the fluorescent agent or autofluorescence of collagen-rich structures and calcifications [50].

One clinical trial is currently ongoing using LUM015, including patients with peritoneal metastases of gastrointestinal cancer, ovarian cancer, and mesothelioma (NCT03834272). The aforementioned phase III study with SGM-101 will also include patients with peritoneal metastases (NCT03659448).

The feasibility of fluorescence-guided detection of peritoneal metastases has been demonstrated, allowing for detection of peritoneal deposits and potentially also of occult lesions. This is especially valuable knowing that treatment success is primarily determined by complete cytoreduction.

3.3.2. Liver metastases

Over the course of the disease, 20–30% of CRC patients develop liver metastases (CRLM) [51]. Complete resection of these metastases is an important treatment option, with positive resection margins being associated with a two-to three-fold decrease in 5-year survival compared to negative margins. However, positive resection margins occur in approximately 13% of patients [52]. In the past, the hepatic surface was palpated for superficial lesions during surgery. With minimal invasive surgery this has become challenging. Nowadays, preoperative magnetic resonance imaging (MRI), computed tomography (CT) and intraoperative ultrasound (IOUS) are the most frequently used imaging modalities for the identification of CRLM [53]. Fluorescence imaging offers surgeons another tool for detecting CRLM. It is suitable for detecting small superficial metastases (up to eight mm deep), but also for resection margin assessment. Intravenous ICG doses between 10 and 50 mg are described with injection windows of 1–14 days prior to surgery [54]. After intravenous injection, ICG is exclusively cleared by the liver. Immature hepatocytes, located at the transition zone between healthy and malignant liver cells, are unable to excrete ICG into bile due to down-regulation of anion transporters, resulting in an accumulation of ICG. This causes CRLM to show a rim of fluorescence (Fig. 6) [55].

Various studies have reported on fluorescence imaging with ICG for the detection of occult CRLM, but none were randomised [55–57]. In one systematic review, six out of nine studies reported a sensitivity exceeding 94% [54]. Furthermore, when fluorescence imaging was added to conventional imaging, extra metastases were found and resected in 20 out of 148 patients (13.5%). Tumour-targeted fluorescence identification of CRLM was previously reported in one study using SGM-101. SGM-101 provided visualisation of all twelve malignant lesions in eight patients with a mean *in vivo* TBR of 1.7 [58].

It is widely debated if additional resection of small superficial CRLM improves overall survival. One study has retrospectively assessed (disease-free) survival of 86 patients after ICG-guided resection of CRLM [59]. Significantly more additional lesions were found when fluorescence-guided resection with ICG was added compared to standard care (25% vs. 13%, $p = 0.04$). However, this was not associated with a significant decrease in local recurrence-free survival (HR: 0.74; 95% CI: 0.42–1.28), and overall survival (HR: 0.94; 95% CI: 0.50–1.76).

Besides detection of CRLM, fluorescence imaging can also be used for margin assessment and aiding in tumour delineation for CRLM resection. Two small case series with a total of 52 patients achieved 100% tumour-negative resection margins using ICG to determine the precise tumour border [56,57]. Recently, a systematic workflow was proposed to detect or prevent tumour positive margins in CRLM surgery [60]. In a selected group of eight patients with initial tumour positive resection margins, the surgeons were able to correctly identify seven out of eight positive margins by using the proposed surgical workflow. The currently ongoing prospective MIMIC-trial will assess whether this surgical workflow can lead to a decrease of tumour-positive resection margins in 186 patients with CRLM (Netherlands trial register: NL7674).

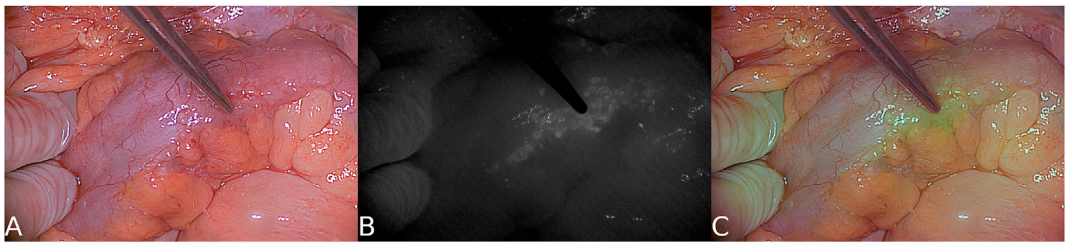

Fig. 5. Fluorescence imaging result of colorectal peritoneal metastases.
Intraoperative fluorescence imaging result of peritoneal metastases of a mucinous carcinoma with signet ring cell differentiation (TBR 1.8) using SGM-101. Imaging was performed using the Quest Spectrum open imaging system. It shows an image in white light (A), near-infrared (B) and merge of A and B (C).

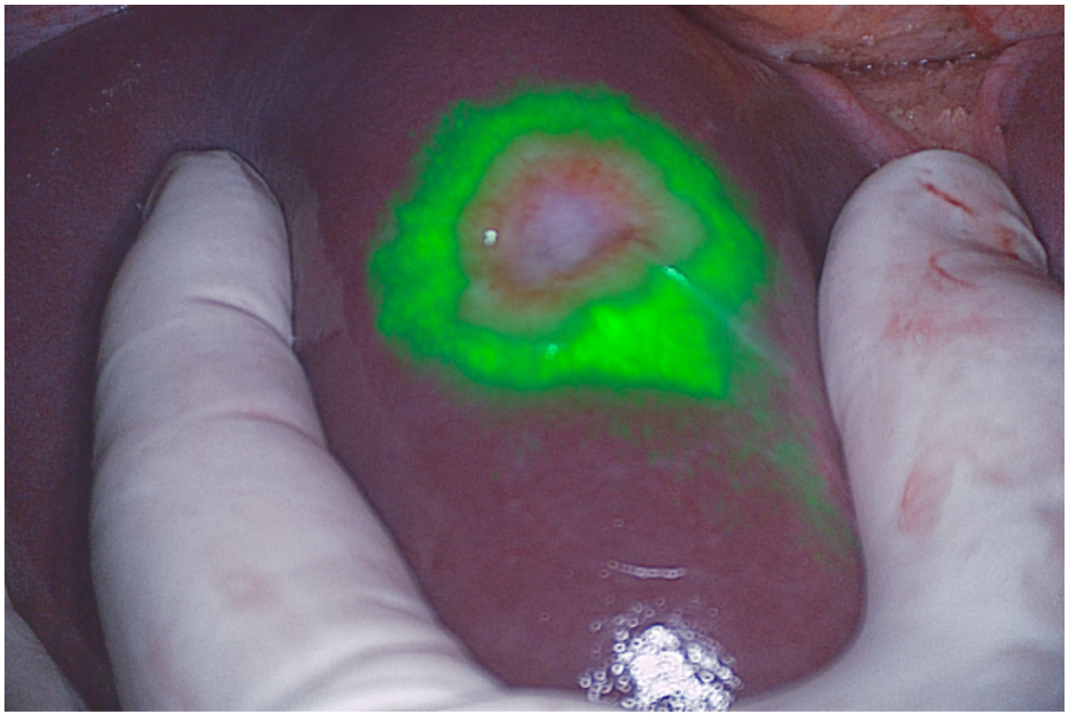

Fig. 6. Fluorescence imaging result of a liver metastasis.
A colorectal liver metastasis showing clear 'rim fluorescence' after intravenous injection of 10 mg indocyanine green 24 h prior to surgery. Imaging was performed using the Quest Spectrum open imaging system.

Fluorescence imaging with ICG has been demonstrated to improve intraoperative detection of CRLM. It can also be used for margin assessment and aiding in tumour delineation for CRLM resection. Future trials must confirm this potential and demonstrate whether this technique will improve patient survival.

3.3.3. Extra-abdominal metastases

A feasibility study with SGM-101 to identify colorectal lung metastases is currently recruiting (NCT04737213). A similar study with SGM-101 to identify colorectal brain metastases will be conducted soon (NCT04755920).

3.4. Imaging of vital structures

3.4.1. Ureters

Iatrogenic ureteral injury is a severe complication in abdominal surgery and has an incidence of up to 5.7% in colorectal surgery. Surgeries on the distal colon and rectum bear the highest risk for ureteral injury [61]. Depending on the time of diagnosis, location, and extent of the injury treatment ranges from minimal invasive transurethral procedures to complex surgical reconstruction. Consequences of (undiagnosed) iatrogenic ureteral injury include kidney failure, sepsis, ureteral stenosis, urinoma, and fistulas [62]. The ureter is usually identified through visual inspection and palpation, which can be difficult due to its retroperitoneal location. The introduction of minimal invasive surgery in the last decades has further increased this challenge [61]. Intraoperative fluorescence imaging can guide the surgeon in identification of the ureter, which could result in less ureteral injury. ICG and MB have both been studied for ureteral identification. Due to the hepatic clearance of ICG, retrograde intra-ureteral injection is needed, which makes ureteral identification with ICG a complex procedure [63]. Successful ureteral identification using ICG is reported in 94–100% of procedures [63–65]. As MB is cleared renally, intravenous injection

is possible for intraoperative identification of ureters. Outcomes of intravenous MB administration for ureteral identification show variable results [66–68]. Fluorescence of the ureters is reported in 50–100% of cases and usually between 10 and 90 min after injection of MB. Optimal visualisation is achieved with doses between 0.5 mg/kg and 1.0 mg/kg. Most important, in most cases, the ureter could only be identified with fluorescence after it was already adequately identified in white light, thus the clinical benefit was minimal. Overall, ICG and MB appear to be suboptimal for ureteral identification.

To date, three experimental fluorophores have been used in clinical studies to image the ureter: ZW800-1, IS-001, and IRDye-800BK [69–71]. These experimental fluorophores are all fluorescent dyes with peak emission around 800 nm. ZW800-1 is a zwitterionic molecule that shows low non-specific binding and is exclusively renally cleared. ZW800-1 was intravenously administered during abdominopelvic surgery in twelve patients. Using ZW800-1, all ureters became fluorescent within 10 min, without dissecting the peritoneum [69]. The SBR was 2.7 in the group with 2.5 mg throughout the first hour. The ureters remained visible with NIR during the whole procedure, with the longest procedure being over 3.5 h. The first clinical study assessing the safety and efficacy of IS-001 included 24 patients who underwent laparoscopic gynaecological surgery [70]. The ureters could be identified in all patients, the highest SBR (3.6) was observed with a dose of 20 mg. Signal intensity decreased rapidly over time, with the peak SBR occurring 30 min after injection. The third experimental fluorescent dye that was studied for ureter identification is IRDye-800BK, a hydrophilic dye [72]. In this trial, the optimal dose of 0.06 mg/kg was administered in 25 patients [71]. In all patients, the ureter was visualised within 10 min. After 90 min the ureter was still visible in 89% of the patients. Currently, another clinical trial is ongoing using IRDye800BK, including 40 patients undergoing laparoscopic surgery. (NCT03387410)

ZW800-1, IS-001, and IRDye-800BK appear suitable for ureter identification with NIR fluorescence imaging and have advantages over MB and ICG. Future clinical trials are needed to confirm the promising early results of these experimental fluorescent agents. However, large sample sizes are required for such studies due to relatively low incidence of iatrogenic ureteral injury. Therefore, phase III studies should focus on patients with high risk for intraoperative ureteral injury.

3.4.2. Urethra

Besides ureteral injury, the urethra is also at risk for injury during pelvic surgery. Especially perineal dissection in (low) rectal surgery is a high-risk step for urethral injury. One clinical study with urethral administration of ICG during prostatectomies in twelve patients has been published [73]. No intraoperative urethra injury occurred. In another study, ICG was injected in the urethra during a transanal total mesorectal excision in one patient, resulting in successful identification of the urethra [74].

3.4.3. Nerves

Sexual and urological dysfunction due to iatrogenic nerve injury are complications of rectal surgery, significantly affecting quality of life. Up to 79% of the patients undergoing rectal surgery acquire some sort of sexual or urological dysfunction [75]. The hypogastric, splanchnic, and levator ani nerves are at risk during (colo)rectal surgery [76]. Nerve targeted fluorescence-guided surgery has the potential to improve nerve identification, and therefore prevent injury. Although promising pre-clinical results of nerve specific fluorescence imaging have been reported, the translation to clinical studies has yet to be made [77–79]. The main difficulties include fluorescent agents not being able to pass the nerve-blood barrier, and relatively high nonspecific uptake of nerve targeted agents by fat and muscle [79].

3.5. Imaging of perfusion

3.5.1. Anastomotic perfusion

Anastomotic leakage is one of the most severe complications in CRC surgery. It often requires additional surgical or radiological intervention, leading to a prolonged hospital stay. Anastomotic leakage is reported up to 13% of patients undergoing CRC surgery with subsequent mortality rates of up to 27% [80,81]. Poor bowel perfusion is thought to play an important role in anastomotic leakage. ICG fluorescence-angiography can provide real-time feedback of bowel perfusion and aid the surgeon in determining the optimal location for the anastomosis. ICG doses between 2 and 20 mg have been reported [82,83]. In general, bowel perfusion can be assessed within 60 s after intravenous injection.

Over the years, several cohort studies have been published on the effect of ICG fluorescence angiography use on anastomotic leakage. Studies specifically addressing colonic anastomoses are sporadic and fail to show a significant decrease in anastomotic leakage rates when using ICG fluorescence angiography [84,85]. More data has been reported on rectal surgery. Song et al. published the most recent and complete meta-analysis on rectal anastomoses including 2088 patients from nine retrospective studies [86]. Their pooled analysis showed an odds ratio for anastomotic leakage of 0.34 (95% CI: 0.22–0.52) in favour of ICG fluorescence angiography over standard of care.

Recently, the first randomised controlled trials (RCTs) on ICG fluorescence angiography have been published. One study included 240 patients undergoing left-sided colon or rectal resection and failed to show a significant difference in anastomotic leakage rate between the ICG fluorescence angiography group and the control group (5% vs 9%; $p = 0.2$) [87]. The second study investigated the value of ICG fluorescence angiography on the occurrence of anastomotic leakage in 377 patients undergoing sigmoid or rectal resection. A significantly lower anastomotic leakage rate was found in the ICG fluorescence angiography group (9.1% vs 16.3%; $p = 0.04$) [88]. However, this difference was predominantly based on the occurrence of anastomotic leakage grade A, which does not alter patient management [89]. Thus, minimal clinical benefit was demonstrated as no difference was observed in the number of re-operations or the length of postoperative hospital stay. The third RCT also failed to report a significant decrease of anastomotic leakage in the ICG fluorescence angiography group compared to the control group (9.0% vs 9.6%; $p = 0.37$) [90]. It should be noted that the pre-determined sample size was not achieved due to a decrease in accrual rates. More RCTs have been registered that will include similar or higher amount of patients (NCT02598414, NCT04012645). Noteworthy are the INTACT-trial and the AVOID-trial, both planning to include up to 1000 patients (ISCRN: 13334746, NCT04712032). Also, the prospective IMARI trial is assessing a series of interventions, including ICG fluorescence angiography, and its influence on anastomotic leakage in rectal cancer surgery (Netherlands trial register: NL8261).

In conclusion, ICG fluorescence angiography has potential in the prevention of anastomotic leakage in a safe and simple way. Pooled analysis of cohort studies has demonstrated that ICG fluorescence angiography reduces anastomotic leakage, but high-quality evidence is currently lacking. RCTs with inclusion up to 1000 patients are currently ongoing and might provide with the answer if ICG fluorescence angiography prevents anastomotic leakage in CRC surgery.

3.5.2. Omentoplastic perfusion

Perineal wound bed complications occur in almost 50% of the patients undergoing abdominoperineal resection (APR) and carry major morbidity [91]. Omentoplasty can be performed for the prevention and management of these complications. It is hypothesised that the transferred omentum prevents dead space formation, has an anti-inflammatory and antibacterial effect, and provides excellent vascularisation to the wound bed [92]. However, its clinical benefit in rectal cancer surgery has been disputed. A meta-analysis of 1894 patients showed that omentoplasty did not reduce the risk of postoperative presacral abscesses or perineal complications [93]. ICG fluorescence angiography of the transferred omentum was recently assessed in a pilot study [94]. Remarkably, ICG fluorescence angiography led to a change in surgical management in 80% of the patients. A follow up study by the same group showed a decrease in pelviperineal non-healing in the ICG group compared to the control group (22% vs 42%; $p = 0.051$) [95]. However non-significant, this study showed a trend towards improved outcomes after ICG fluorescence angiography guided omentoplasty. The reported alteration of the surgical plan in 80% of cases suggests that 'standard' omentoplasty is vulnerable to poor omental perfusion. Further research on ICG fluorescence angiography for omentoplasty is therefore warranted.

4. Discussion and future perspectives

NIR fluorescence-guided surgery is a rapidly evolving technique with various clinical applications in CRC surgery. This review provides an overview of the clinical applications of all fluorescent agents for CRC surgery. ICG, the nonspecific FDA/EMA approved fluorescent agent, is already used in a variety of clinical applications of which CRLM resection and perfusion assessment show the most potential. However, no unequivocal benefits in relevant outcome measures have yet been reported. Over the past years, promising experimental fluorescent agents (targeted and non-targeted) have been investigated. These agents could potentially improve intraoperative fluorescence imaging, ultimately leading to improved detection of tumour tissue and vital structures. Improving intraoperative detection of tumour could not only lead to more complete resections, but can also lead to better patient selection, as unnecessary surgery could be refrained from if the disease is found to be too advanced. On the other hand, false-positive lesions would lead to unnecessary resection of healthy tissue which makes tumour-binding specificity of the fluorescent agent crucial.

Quantification of the fluorescence signal is challenging, with numerous factors such as scattering, absorption, camera angulation and distance, and background light influencing the signal intensity [96]. The latest studies on ICG fluorescence angiography for the prevention of anastomotic leakage focus on less subjective perfusion assessment by analysing time-dependent inflow parameters [97,98]. Real-time (*in vivo*) quantification of the fluorescence signal of tumour-targeted agents, aiding surgeons in deciding whether tissue is malignant or not, has not been reported yet. Most clinical studies report the SBR (or TBR) and change in surgical management as the main parameters in early phase studies. Eventually, trials should report on clinically significant events such as the tumour-negative resection margin rate, detection of occult lesions, surgical complications, and (disease free) survival [99].

Nowadays, a variety of fluorescence camera systems is available in clinical practice. It is important to keep in mind that these camera systems can influence imaging results [21]. This also counts for the difference between open- and laparoscopic cameras. Most laparoscopes that are currently clinically available are optimised for ICG at 830 nm. This wavelength is slightly too high for optimal imaging of most experimental fluorescent agents, which have peak emission wavelengths around 800 nm (Table 1). Therefore, there is a need for high-quality laparoscopes that are optimised for imaging of specific tumour-targeted fluorescent agents. Fluorescence imaging could account for the lack of tactile feedback in minimal invasive surgery, as it has the potential to improve visualisation of vital structures (e.g. the ureter, nerves) and tumours. Moreover, fluorescence imaging can be integrated in the laparoscopic field with an overlay view, which is an advantage over open surgery, where an additional handheld camera is needed. Especially in rectal surgery, in the conically shaped (male) pelvis, difficulties are experienced with optimal positioning due to the size of most open cameras. A laparoscope is much smaller and therefore easier to manoeuvre towards an optimal imaging angle.

5. Conclusion

In conclusion, the field of fluorescence-guided surgery is rapidly evolving with already several clinical applications in CRC surgery. ICG is widely used, and its use appears to be beneficial in specific applications. Many experimental fluorescent agents have been developed and several of these agents are currently being assessed in late phase clinical studies. The most promising applications of these experimental fluorescent agents in CRC surgery are distinguishing between fibrotic and tumour tissue after neo-adjuvant treatment, improving the rate of tumour-negative resection margins in locally advanced and recurrent rectal cancer, detection of occult metastases in cytoreductive surgery for peritoneal metastases, and ureteral imaging in high-risk cases. An essential next step for the implementation of these agents in clinical practice is to show direct patient benefit in terms of change in surgical management, surgical complications, recurrence-free survival, and overall survival.

Declaration of Competing Interest

Alexander L Vahrmeijer and Cornelis Verhoef are local principal investigators of several industry driven studies initiated by Surgimab (Montpellier, France) using SGM-101 without any personal financial interests. Surgimab was not involved in the process of creating this manuscript. The other authors declare no competing interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2021.10.005.

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References

[1] Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68(6):394–424.

[2] Amri R, Bordeianou LG, Sylla P, Berger DL. Association of radial margin positivity with colon cancer. JAMA Surg 2015;150(9):890–8.

[3] Elias D, Gilly F, Boutitie F, Quenet F, Bereder JM, Mansvelt B, et al. Peritoneal colorectal carcinomatosis treated with surgery and perioperative intraperitoneal chemotherapy: retrospective analysis of 523 patients from a multicentric French study. J Clin Oncol 2010;28(1):63–8.

[4] Hernot S, van Manen L, Debie P, Mieog JSD, Vahrmeijer AL. Latest developments in molecular tracers for fluorescence image-guided cancer surgery. Lancet Oncol 2019;20(7):e354–67.

[5] Fox IJ, Brooker LG, Heseltine DW, Essex HE, Wood EH. A tricarbocyanine dye for continuous recording of dilution curves in whole blood independent of variations in blood oxygen saturation. Proc Staff Meet Mayo Clin 1957;32(18):478–84.

[6] Ginimuge PR, Jyothi SD. Methylene blue: revisited. J Anaesthesiol Clin Pharmacol 2010;26(4):517–20.

[7] Slim K, Nini E, Forestier D, Kwiatkowski F, Panis Y, Chipponi J. Methodological index for non-randomized studies (minors): development and validation of a new instrument. ANZ J Surg 2003;73(9):712–6.

[8] Nagtegaal ID, Quirke P. What is the role for the circumferential margin in the modern treatment of rectal cancer? J Clin Oncol 2008;26(2):303–12.

[9] Holman FA, Bosman SJ, Haddock MG, Gunderson LL, Kusters M, Nieuwenhuijzen GA, et al. Results of a pooled analysis of IOERT containing multimodality treatment for locally recurrent rectal cancer: results of 565 patients of two major treatment centres. Eur J Surg Oncol 2017;43(1):107–17.

[10] Conaghan PJ, Maxwell-Armstrong CA, Garrioch MV, Hong L, Acheson AG. Leaving a mark: the frequency and accuracy of tattooing prior to laparoscopic colorectal surgery. Colorectal Dis 2011;13(10):1184–7.

[11] Feingold DL, Addona T, Forde KA, Arnell TD, Carter JJ, Huang EH, et al. Safety and reliability of tattooing colorectal neoplasms prior to laparoscopic resection. J Gastrointest Surg 2004;8(5):543–6.

[12] Satoyoshi T, Okita K, Ishii M, Hamabe A, Usui A, Akizuki E, et al. Timing of indocyanine green injection prior to laparoscopic colorectal surgery for tumor localization: a prospective case series. Surg Endosc 2020;35(2):763–9.

[13] Watanabe M, Tsunoda A, Narita K, Kusano M, Miwa M. Colonic tattooing using fluorescence imaging with light-emitting diode-activated indocyanine green: a feasibility study. Surg Today 2009;39(3):214–8.

[14] Boogerd LSF, Hoogstins CES, Schaap DP, Kusters M, Handgraaf HJM, van der Valk MJM, et al. Safety and effectiveness of SGM-101, a fluorescent antibody targeting carcinoembryonic antigen, for intraoperative detection of colorectal cancer: a dose-escalation pilot study. Lancet Gastroenterol Hepatol 2018;3(3):181–91.

[15] de Valk KS, Deken MM, Handgraaf HJM, Bhairosingh SS, Bijlstra OD, van Esdonk MJ, et al. First-in-Human assessment of cRGD-zw800-1, a zwitterionic, integrin-targeted, near-infrared fluorescent peptide in colon carcinoma. Clin Cancer Res 2020;26(15):3990–8.

[16] de Jongh SJ, Tjalma JJJ, Koller M, Linssen MD, Vonk J, Dobosz M, et al. Backtable fluorescence-guided imaging for circumferential resection margin evaluation using bevacizumab-800CW in patients with locally advanced rectal cancer. J Nucl Med 2020;61(5):655–61.

[17] Voskuil FJ, Steinkamp PJ, Zhao T, van der Vegt B, Koller M, Doff JJ, et al. Exploiting metabolic acidosis in solid cancers using a tumor-agnostic pH-activatable nanoprobe for fluorescence-guided surgery. Nat Commun 2020;11(1):3257.

[18] de Valk KS, Deken MM, Schaap DP, Meijer RP, Boogerd LS, Hoogstins CE, et al. Dose-finding study of a CEA-targeting agent, SGM-101, for intraoperative fluorescence imaging of colorectal cancer. Ann Surg Oncol 2020;28(3):1832–44.

[19] Gutowski M, Framery B, Boonstra MC, Garambois V, Quenet F, Dumas K, et al. SGM-101: an innovative near-infrared dye-antibody conjugate that targets CEA for fluorescence-guided surgery. Surg Oncol 2017;26(2):153–62.

[20] Lv W, Gao T, Wang S, Hou J, Liu M, Yang J, et al. Long-term tracking of cancer cell nucleus and identification of colorectal cancer with an aggregation-induced emission-based fluorescent probe. J Biomed Nanotechnol 2019;15(5):1033–42.

[21] Zhu B, Sevick-Muraca EM. A review of performance of near-infrared fluorescence imaging devices used in clinical studies. Br J Radiol 2015;88(1045):20140547.

[22] Whitley MJ, Cardona DM, Lazarides AL, Spasojevic I, Ferrer JM, Cahill J, et al. A mouse-human phase 1 co-clinical trial of a protease-activated fluorescent probe for imaging cancer. Sci Transl Med 2016;8(320). 320ra324.

[23] Figueredo A, Coombes ME, Mukherjee S. Adjuvant therapy for completely resected stage II colon cancer. Cochrane Database Syst Rev 2008;(3):CD005390.

[24] Yamamoto H, Murata K, Fukunaga M, Ohnishi T, Noura S, Miyake Y, et al. Micrometastasis volume in lymph nodes determines disease recurrence rate of stage II colorectal cancer: a prospective multicenter trial. Clin Cancer Res 2016;22(13):3201–8.

[25] Cahill RA, Leroy J, Marescaux J. Localized resection for colon cancer. Surg Oncol 2009;18(4):334–42.

[26] Bao F, Zhao LY, Balde AI, Liu H, Yan J, Li TT, et al. Prognostic impact of lymph node skip metastasis in Stage III colorectal cancer. Colorectal Dis 2016;18(9):O322–9.

[27] Bembenek AE, Rosenberg R, Wagler E, Gretschel S, Sendler A, Siewert JR, et al. Sentinel lymph node biopsy in colon cancer: a prospective multicenter trial. Ann Surg 2007;245(6):858–63.

[28] Chand M, Keller DS, Joshi HM, Devoto L, Rodriguez-Justo M, Cohen R. Feasibility of fluorescence lymph node imaging in colon cancer: FLICC. Tech Coloproctol 2018;22(4):271–7.

[29] Nishigori N, Koyama F, Nakagawa T, Nakamura S, Ueda T, Inoue T, et al. Visualization of lymph/blood flow in laparoscopic colorectal cancer surgery by ICG fluorescence imaging (Lap-IGFI). Ann Surg Oncol 2016;23(Suppl 2):S266–74.

[30] Tuech JJ, Pessaux P, Regenet N, Bergamaschi R, Colson A. Sentinel lymph node mapping in colon cancer. Surg Endosc 2004;18(12):1721–9.

[31] Ankersmit M, Bonjer HJ, Hannink G, Schoonmade LJ, van der Pas MHGM, Meijerink WJHJ. 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 2019;23(12):1113–26.

[32] Andersen HS, Bennedsen ALB, Burgdorf SK, Eriksen JR, Eiholm S, Toxværd A, et al. In vivo and ex vivo sentinel node mapping does not identify the same lymph nodes in colon cancer. Int J Colorectal Dis 2017;32(7):983–90.

[33] Hirche C, Mohr Z, Kneif S, Doniga S, Murawa D, Strik M, et al. Ultrastaging of colon cancer by sentinel node biopsy using fluorescence navigation with indocyanine green. Int J Colorectal Dis 2012;27(3):319–24.

[34] Nagata K, Endo S, Hidaka E, Tanaka JI, Kudo SE, Shiokawa A. Laparoscopic sentinel node mapping for colorectal cancer using infrared ray laparoscopy. Anticancer Res 2006;26(3 B):2307–11.

[35] Cahill RA, Anderson M, Wang LM, Lindsey I, Cunningham C, Mortensen NJ. Near-infrared (NIR) laparoscopy for intraoperative lymphatic road-mapping and sentinel node identification during definitive surgical resection of early-stage colorectal neoplasia. Surg Endosc Interv Tech 2012;26(1):197–204.

[36] Burghgraef TA, Zweep AL, Sikkenk DJ, van der Pas M, Verheijen PM, Consten ECJ. In vivo sentinel lymph node identification using fluorescent tracer imaging in colon cancer: a systematic review and meta-analysis. Crit Rev Oncol Hematol 2021;158:103149.

[37] Ohnishi S, Lomnes SJ, Laurence RG, Gogbashian A, Mariani G, Frangioni JV. Organic alternatives to quantum dots for intraoperative near-infrared fluorescent sentinel lymph node mapping. Mol Imag 2005;4(3):172–81.

[38] Schaafsma BE, Verbeek FPR, Van Der Vorst JR, Hutteman M, Kuppen PJK, Frangioni JV, et al. Ex vivo sentinel node mapping in colon cancer combining blue dye staining and fluorescence imaging. J Surg Res 2013;183(1):253–7.

[39] Hutteman M, Choi HS, Mieog JSD, Van Der Vorst JR, Ashitate Y, Kuppen PJK, et al. Clinical translation of ex vivo sentinel lymph node mapping for colorectal cancer using invisible near-infrared fluorescence light. Ann Surg Oncol 2011;18(4):1006–14.

[40] Weixler B, Rickenbacher A, Raptis DA, Viehl CT, Guller U, Rueff J, et al. 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 2017;41(9):2378–86.

[41] Koppe MJ, Boerman OC, Oyen WJ, Bleichrodt RP. Peritoneal carcinomatosis of colorectal origin: incidence and current treatment strategies. Ann Surg 2006;243(2):212–22.

[42] Razenberg LG, Lemmens VE, Verwaal VJ, Punt CJ, Tanis PJ, Creemers GJ, et al. Challenging the dogma of colorectal peritoneal metastases as an untreatable condition: results of a population-based study. Eur J Cancer 2016;65:113–20.

[43] Simkens GA, van Oudheusden TR, Nieboer D, Steyerberg EW, Rutten HJ, Luyer MD, et al. Development of a prognostic nomogram for patients with peritoneally metastasized colorectal cancer treated with cytoreductive surgery and HIPEC. Ann Surg Oncol 2016;23(13):4214–21.

[44] Faron M, Macovei R, Goere D, Honore C, Benhaim L, Elias D. Linear relationship of peritoneal cancer index and survival in patients with peritoneal metastases from colorectal cancer. Ann Surg Oncol 2016;23(1):114–9.

[45] Maeda H. Tumor-selective delivery of macromolecular drugs via the EPR effect: background and future prospects. Bioconjugate Chem 2010;21(5):797–802.

[46] Liberale G, Vankerckhove S, Gomez Caldon M, Ahmed B, Moreau M, El Nakadi I, et al. Fluorescence imaging after indocyanine green injection for detection of peritoneal metastases in patients undergoing cytoreductive surgery for peritoneal carcinomatosis from colorectal cancer: a pilot study. Ann Surg 2016;264(6):1110–5.

[47] Filippello A, Porcheron J, Klein JP, Cottier M, Barabino G. Affinity of indocyanine green in the detection of colorectal peritoneal carcinomatosis. Surg Innovat 2017;24(2):103–8.

[48] Harlaar NJ, Koller M, de Jongh SJ, van Leeuwen BL, Hemmer PH, Kruijff S, et al. Molecular fluorescence-guided surgery of peritoneal carcinomatosis of colorectal origin: a single-centre feasibility study. Lancet Gastroenterol Hepatol 2016;1(4):283–90.

[49] Schaap DP, de Valk KS, Deken MM, Meijer RPJ, Burggraaf J, Vahrmeijer AL, et al. Carcinoembryonic antigen-specific, fluorescent image-guided cytoreductive surgery with hyperthermic intraperitoneal chemotherapy for metastatic colorectal cancer. Br J Surg 2020;107(4):334–7.

[50] Kobayashi H, Watanabe R, Choyke PL. Improving conventional enhanced permeability and retention (EPR) effects; what is the appropriate target? Theranostics 2013;4(1):81–9.

[51] Manfredi S, Lepage C, Hatem C, Coatmeur O, Faivre J, Bouvier AM. Epidemiology and management of liver metastases from colorectal cancer. Ann Surg 2006;244(2):254–9.
[52] Nierop PMH, Höppener DJ, van der Stok EP, Galjart B, Buisman FE, Balachandran VP, et al. Histopathological growth patterns and positive margins after resection of colorectal liver metastases. HPB (Oxford) 2020;22(6):911–9.
[53] Elfrink AKE, Pool M, van der Werf LR, Marra E, Burgmans MC, Meijerink MR, et al. The Dutch Hepato-Biliary Audit G. Preoperative imaging for colorectal liver metastases: a nationwide population-based study. BJS Open 2020;4(4):605–21.
[54] Liberale G, Bourgeois P, Larsimont D, Moreau M, Donckier V, Ishizawa T. Indocyanine green fluorescence-guided surgery after IV injection in metastatic colorectal cancer: a systematic review. Eur J Surg Oncol 2017;43(9):1656–67.
[55] Van Der Vorst JR, Schaafsma BE, Hutteman M, Verbeek FPR, Liefers GJ, Hartgrink HH, et al. Near-infrared fluorescence-guided resection of colorectal liver metastases. Cancer 2013;119(18):3411–8.
[56] Peloso A, Franchi E, Canepa MC, Barbieri L, Briani L, Ferrario J, et al. Combined use of intraoperative ultrasound and indocyanine green fluorescence imaging to detect liver metastases from colorectal cancer. HPB 2013;15(12):928–34.
[57] Aoki T, Murakami M, Koizumi T, Matsuda K, Fujimori A, Kusano T, et al. Determination of the surgical margin in laparoscopic liver resections using infrared indocyanine green fluorescence. Langenbecks Arch Surg 2018;403(5):671–80.
[58] Meijer RPJ, de Valk KS, Deken MM, Boogerd LSF, Hoogstins CES, Bhairosingh SS, et al. Intraoperative detection of colorectal and pancreatic liver metastases using SGM-101, a fluorescent antibody targeting CEA. Eur J Surg Oncol 2020;47(3 Pt B):667–73.
[59] Handgraaf HJM, Boogerd LSF, Höppener DJ, Peloso A, Sibinga Mulder BG, Hoogstins CES, et al. Long-term follow-up after near-infrared fluorescence-guided resection of colorectal liver metastases: a retrospective multicenter analysis. Eur J Surg Oncol 2017;43(8):1463–71.
[60] Achterberg FB, Sibinga Mulder BG, Meijer RPJ, Bonsing BA, Hartgrink HH, Mieog JSD, et al. Real-time surgical margin assessment using ICG-fluorescence during laparoscopic and robot-assisted resections of colorectal liver metastases. Ann Transl Med 2020;8(21):1448.
[61] Gild P, Kluth LA, Vetterlein MW, Engel O, Chun FKH, Fisch M. Adult iatrogenic ureteral injury and stricture-incidence and treatment strategies. Asian J Urol 2018;5(2):101–6.
[62] Blackwell RH, Kirshenbaum EJ, Shah AS, Kuo PC, Gupta GN, Turk TMT. Complications of recognized and unrecognized iatrogenic ureteral injury at time of hysterectomy: a population based analysis. J Urol 2018;199(6):1540–5.
[63] White LA, Joseph JP, Yang DY, Kelley SR, Mathis KL, Behm K, et al. Intraureteral indocyanine green augments ureteral identification and avoidance during complex robotic-assisted colorectal surgery. Colorectal Dis 2020;23(3):718–23.
[64] Mandovra P, Kalikar V, Patankar RV. Real-time visualization of ureters using indocyanine green during laparoscopic surgeries: can we make surgery safer? Surg Innovat 2019;26(4):464–8.
[65] Cabanes M, Boria F, Hernández Gutiérrez A, Zapardiel I. Intra-operative identification of ureters using indocyanine green for gynecological oncology procedures. Int J Gynecol Cancer 2019;30(2). https://doi.org/10.1136/ijgc-2019-000895.
[66] Al-Taher M, Van Den Bos J, Schols RM, Bouvy ND, Stassen LPS. Fluorescence ureteral visualization in human laparoscopic colorectal surgery using methylene blue. J Laparoendosc Adv Surg Tech 2016;26(11):870–5.
[67] Barnes TG, Hompes R, Birks J, Mortensen NJ, Jones O, Lindsey I, et al. Methylene blue fluorescence of the ureter during colorectal surgery 2018;32(9):4036–43.
[68] Verbeek FPR, Van Der Vorst JR, Schaafsma BE, Swijnenburg RJ, Gaarenstroom KN, Elzevier HW, et al. Intraoperative near infrared fluorescence guided identification of the ureters using low dose methylene blue: a first in human experience. J Urol 2013;190(2):574–9.
[69] de Valk KS, Handgraaf HJ, Deken MM, Sibinga Mulder BG, Valentijn AR, Terwisscha van Scheltinga AG, et al. A zwitterionic near-infrared fluorophore for real-time ureter identification during laparoscopic abdominopelvic surgery. Nat Commun 2019;10(1).
[70] Farnam RW, Arms RG, Klaassen AH, Sorger JM. Intraoperative ureter visualization using a near-infrared imaging agent. J Biomed Opt 2019;24(6):1–8.
[71] Huh WK, Johnson JL, Elliott E, Boone JD, Leath CA, Kovar JL, et al. Fluorescence imaging of the ureter in minimally invasive pelvic surgery. J Minim Invasive Gynecol 2020;28(2):331–41.
[72] Al-Taher M, van den Bos J, Schols RM, Kubat B, Bouvy ND, Stassen LPS. Evaluation of a novel dye for near-infrared fluorescence delineation of the ureters during laparoscopy. BJS Open 2018;2(4):254–61.
[73] Simone G, Misuraca L, Anceschi U, Minisola F, Ferriero M, Guaglianone S, et al. Urethra and ejaculation preserving robot-assisted simple prostatectomy: near-infrared fluorescence imaging-guided madigan technique. Eur Urol 2019;75(3):492–7.
[74] Nitta T, Tanaka K, Kataoka J, Ohta M, Ishii M, Ishibashi T, et al. Novel technique with the IRIS U kit to prevent urethral injury in patients undergoing transanal total mesorectal excision. Ann Med Surg 2019;46:1–3.
[75] Lange MM, Marijnen CA, Maas CP, Putter H, Rutten HJ, Stiggelbout AM, et al. Cooperative clinical investigators of the D. Risk factors for sexual dysfunction after rectal cancer treatment. Eur J Cancer 2009;45(9):1578–88.
[76] Lange MM, van de Velde CJ. Urinary and sexual dysfunction after rectal cancer treatment. Nat Rev Urol 2011;8(1):51–7.
[77] Gonzales J, Pirovano G, Chow CY, de Souza Franca PD, Carter LM, Klint JK, et al. Fluorescence labeling of a NaV1.7-targeted peptide for near-infrared nerve visualization. EJNMMI Res 2020;10(1).
[78] Hingorani DV, Whitney MA, Friedman B, Kwon JK, Crisp JL, Xiong Q, et al. Nerve-targeted probes for fluorescence-guided intraoperative imaging. Theranostics 2018;8(15):4226–37.
[79] Wang LG, Barth CW, Kitts CH, Mebrat MD, Montaño AR, House BJ, et al. Near-infrared nerve-binding fluorophores for buried nerve tissue imaging. Sci Transl Med 2020;12(542).
[80] Sparreboom CL, Komen N, Rizopoulos D, Verhaar AP, Dik WA, Wu Z, et al. A multicentre cohort study of serum and peritoneal biomarkers to predict anastomotic leakage after rectal cancer resection. Colorectal Dis 2020;22(1):36–45.
[81] Angeramo CA, Dreifuss NH, Schlottmann F, Bun ME, Rotholtz NA. Postoperative outcomes in patients undergoing colorectal surgery with anastomotic leak before and after hospital discharge. Updates Surg 2020;72(2):463–8.
[82] van Manen L, Handgraaf HJM, Diana M, Dijkstra J, Ishizawa T, Vahrmeijer AL, et al. A practical guide for the use of indocyanine green and methylene blue in fluorescence-guided abdominal surgery. J Surg Oncol 2018;118(2):283–300.
[83] Watanabe J, Ishibe A, Suwa Y, Suwa H, Ota M, Kunisaki C, et al. Indocyanine green fluorescence imaging to reduce the risk of anastomotic leakage in laparoscopic low anterior resection for rectal cancer: a propensity score-matched cohort study. Surg Endosc 2020;34(1):202–8.
[84] Kin C, Vo H, Welton L, Welton M. Equivocal effect of intraoperative fluorescence angiography on colorectal anastomotic leaks. Dis Colon Rectum 2015;58(6):582–7.
[85] Kudszus S, Roesel C, Schachtrupp A, Höer JJ. Intraoperative laser fluorescence angiography in colorectal surgery: a noninvasive analysis to reduce the rate of anastomotic leakage. Langenbeck's Arch Surg 2010:1–6.
[86] Song M, Liu J, Xia D, Yao H, Tian G, Chen X, et al. Assessment of intraoperative use of indocyanine green fluorescence imaging on the incidence of anastomotic leakage after rectal cancer surgery: a PRISMA-compliant systematic review and meta-analysis. Tech Coloproctol 2020;25(1):49–58.
[87] De Nardi P, Elmore U, Maggi G, Maggiore R, Boni L, Cassinotti E, et al. Intraoperative angiography with indocyanine green to assess anastomosis perfusion in patients undergoing laparoscopic colorectal resection: results of a multicenter randomized controlled trial. Surg Endosc 2020;34(1):53–60.
[88] Alekseev M, Rybakov E, Shelygin Y, Chernyshov S, Zarodnyuk I. A study investigating the perfusion of colorectal anastomoses using fluorescence angiography: results of the FLAG randomized trial. Colorectal Dis 2020;22(9):1147–53.
[89] Rahbari NN, Weitz J, Hohenberger W, Heald RJ, Moran B, Ulrich A, et al. Definition and grading of anastomotic leakage following anterior resection of the rectum: a proposal by the International Study Group of Rectal Cancer. Surgery 2010;147(3):339–51.
[90] Jafari MD, Pigazzi A, McLemore EC, Mutch MG, Haas E, Rasheid S, et al. 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 2021;64(8):995–1002.
[91] Musters GD, Klaver CEL, Bosker RJI, Burger JWA, van Duijvendijk P, van Etten B, et al. Biological mesh closure of the pelvic floor after extralevator abdominoperineal resection for rectal cancer: a multicenter randomized controlled trial (the BIOPEX-study). Ann Surg 2017;265(6):1074–81.
[92] Chandra A, Srivastava RK, Kashyap MP, Kumar R, Srivastava RN, Pant AB. The anti-inflammatory and antibacterial basis of human omental defense: selective expression of cytokines and antimicrobial peptides. PLoS One 2011;6(5):e20446.
[93] Blok RD, Hagemans JAW, Klaver CEL, Hellinga J, van Etten B, Burger JWA, et al. A systematic review and meta-analysis on omentoplasty for the management of abdominoperineal defects in patients treated for cancer. Ann Surg 2020;271(4):654–62.
[94] Slooter MD, Blok RD, Wisselink DD, Buskens CJ, Bemelman WA, Tanis PJ, et al. Near-infrared fluorescence angiography for intra-operative assessment of pedicled omentoplasty for filling of a pelvic cavity: a pilot study. Tech Coloproctol 2019;23(8):723–8.
[95] Slooter MD, Blok RD, de Krom MA, Buskens CJ, Bemelman WA, Tanis PJ, et al. Optimizing omentoplasty for management of chronic pelvic sepsis by intraoperative fluorescence angiography: a comparative cohort study. Colorectal Dis 2020;22(12):2252–9.
[96] Keereweer S, Van Driel PB, Snoeks TJ, Kerrebijn JD, Baatenburg de Jong RJ,

Vahrmeijer AL, et al. Optical image-guided cancer surgery: challenges and limitations. Clin Cancer Res 2013;19(14):3745–54.
[97] Lütken CD, Achiam MP, Svendsen MB, Boni L, Nerup N. Optimizing quantitative fluorescence angiography for visceral perfusion assessment. Surg Endosc 2020;34(12):5223–33.
[98] Goncalves LN, van den Hoven P, van Schaik J, Leeuwenburgh L, Hendricks CHF, Verduijn PS, et al. Perfusion parameters in near-infrared fluorescence imaging with indocyanine green: a systematic review of the literature. Life 2021;11(5):433.
[99] Lauwerends LJ, van Driel P, Baatenburg de Jong RJ, Hardillo JAU, Koljenovic S, Puppels G, et al. Real-time fluorescence imaging in intraoperative decision making for cancer surgery. Lancet Oncol 2021;22(5):e186–95.