REVIEW ARTICLE

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Molecular fluorescence-guided surgery of peritoneal carcinomatosis of colorectal origin: A narrative review

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Patients with peritoneal carcinomatosis (PC) from colorectal origin may undergo cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC) as a curative approach. One major prognostic factor that affects survival is completeness of cytoreduction. Molecular Fluorescence Guided Surgery (MFGS) is a novel intraoperative imaging technique that may improve tumor identification in the future, potentially preventing over- and under-treatment in these patients. This narrative review outlines a chronological overview of MFGS development in patients with PC of colorectal origin.

KEYWORDS
colorectal cancer, molecular fluorescence-guided surgery, peritoneal carcinomatosis, review

1 | INTRODUCTION

Colorectal cancer (CRC) is one of the most common cancers worldwide, with an incidence of 40 patients per 100 000 population and a mortality rate of 15 per 100 000 persons.[1,2] Of these patients, 8-25% develop peritoneal carcinomatosis (PC).[3–6] Over the past decades, the treatment of PC of colorectal origin has evolved considerably, from palliative care toward a more successful treatment approach with curative intent.[7,8] In particular, the introduction of cytoreductive surgery (CRS) combined with hyperthermic intraperitoneal chemotherapy (HIPEC) has contributed significantly to this change.[9,10] After surgical cytoreduction of all macroscopic tumor tissue, the abdominal cavity is perfused with heated chemotherapy in order to eliminate remaining microscopic disease. Up to date, only one randomized clinical trial has been performed studying patients with PC of colorectal origin. A median overall survival of 22 months was seen for patients after undergoing CRS in combination with HIPEC, compared to 13 months for patients receiving only systemic chemotherapy with or without palliative surgery.[11,12] The authors report a 5-years survival of 43% for patients in whom all macroscopic tumor was removed, compared to 0% for patients in whom residual lesions of more than 2.5 mm were left behind.[11] These findings emphasize the importance of patient selection and a macroscopically complete cytoreduction, mainly because incomplete cytoreduction followed by HIPEC does not contribute to a prolonged survival, but potentially does introduce a high risk of postoperative complications,

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an extensive rehabilitation period and subsequently decreased quality of life.[12–15]

Although the technical quality of the complete CRS/HIPEC procedure has improved, still up to 88% of the patients undergoing CRS and HIPEC for PC of CRC develop recurrent disease within 2 years.[16] Currently, many imaging modalities are available for preoperative staging, such as ultrasonography, computed tomography (CT), magnetic resonance imaging (MRI), or positron emission tomography (PET) scans. Unfortunately, all of these imaging modalities are insufficient for the preoperative assessment of tumor load, or determination of a preoperative Peritoneal Cancer Index (PCI), the most important staging system in PC. CT, MRI, and fluorodeoxyglucose (FDG-) PET scans have a poor sensitivity and specificity to estimate PCI by detection of individual tumor deposits, due to the limited spatial resolution.[17] For example, the detection of individual peritoneal deposits using a CT-scan varies from 9.1 to 24.3% for tumor sizes <1 cm, to up to 59.3-66.7% for tumor size of over 5 cm.[18] These results are in accordance with other previous studies.[19–21] Current hybrid PET/CT scanners have a limited spatial resolution of 5-8 mm,[22] whereas MRI seems to be more promising in detecting peritoneal lesions.[23]

For intraoperative differentiation between benign and malignant lesions, surgeons currently depend on visual and tactile inspection only. Unfortunately, the human eye and palpation are not competent enough to detect molecular changes in intra-abdominal lesions that have the same color and physical properties, or to distinguish tumor lesions from benign scar tissue originating from previous surgery. Today, to the best of our knowledge, no intraoperative imaging modalities provided by the more classical modalities like PET, are available to assist in the real-time identification of peritoneal cancer deposits, loco-regional metastases, and tumor-positive resection margins.

Considering the high tumor recurrence rates after the CRS and HIPEC procedure, there is a clear need for an imaging modality that can aid the oncological surgeon in the differentiation between tumor and benign tissue intraoperatively. In recent years, optical molecular imaging using tumor-targeted fluorescence tracers has emerged as a promising imaging technique for real-time guidance in oncological surgery.[24–26] This technique can be applied intraoperatively to serve as a "red-flag" imaging technique to assist in optimal tumor identification. Improved detection of tumor tissue could not only help attain a more complete cytoreduction, but might also facilitate tailored surgery, avoiding unnecessary resections of benign lesions and organs.

This narrative review explains the principles of intraoperative optical molecular imaging and provides a chronological overview of the development of Molecular Fluorescence Guided Surgery (MFGS) in patients with PC of colorectal origin.

2 | PRINCIPLES OF INTRAOPERATIVE OPTICAL MOLECULAR IMAGING

In colorectal surgery, as in surgical oncology in general, radical surgery and tumor-free resection margins are essential for optimizing patient prognosis. Optical molecular imaging using fluorescence imaging agents can provide real-time intraoperative feedback with high resolution, that is in concordance with the natural surgical field of view of a surgeon and based on the molecular characteristics of the tissue (Figure 1). The technique makes use of non-ionizing imaging agents and can be implemented relatively easily in the current surgical workflow.

Over the past decades, there has been an increased interest in the clinical application of optical molecular imaging using fluorescence imaging agents. Fluorescence occurs when a photon or fluorescent dye absorbs light at a certain wavelength, subsequently triggering the release of a photon with a longer wavelength.[27] The quality of fluorescence imaging is influenced by different factors such as changes in photon directions (ie, scattering) and absorption of photons by the tissue. Multiple tissue components play an important role in fluorophore absorption, with the most relevant being hemoglobin, water, and lipids. As the scattering and absorption properties of tissue are lower in light with longer wavelengths, the near-infrared (NIR) light spectrum (700-900 nm) is considered the optimal clinical diagnostic window for fluorescence imaging.[28] These characteristics result in deeper penetration depths of up to one to three centimeters that can be obtained in the NIR light spectrum, leading to higher signal-to-background (SBR) ratios compared to the visible light spectrum (ie, red-green-blue white-light, 380-700 nm).[29,30]

NIR fluorescence light is invisible to the human eye and therefore special imaging devices are required to visualize fluorescence during surgery. In general, these camera systems are equipped with two different light sources: a white-light source and a NIR fluorescence light source. Due to the use of a dichroic mirror and specific filters installed in the camera system itself, the visible light derived from the tissue can be separated from NIR fluorescence light, which enables simultaneous imaging of both visible and NIR fluorescence light. Next to that, an overlay of fluorescence signals can be projected on the "normal" white-light images by use of computer software.[27] In the operating theatre, all three images can be displayed on monitors at the same time, providing real-time imaging related to the natural surgical field of view (Figure 2). Currently, there are several different intraoperative NIR fluorescence imaging devices available for research and clinical use.[31–38]

Fluorescence signals in tissue arise by either an endogenous tissue component (ie, autofluorescence), or an intravenously administered exogenous optical contrast agent. At present, various types of optical contrast agents are available enabling intraoperative imaging, which can roughly be divided into non-targeted and targeted imaging agents.

The effect of non-targeted imaging agents is mainly based on vascularization and perfusion (ie, also the so-called Enhanced Permeability and Retention (EPR) effect), whereas targeted imaging agents specifically bind to a receptor or protein that is present in a tumor cell. Due to genetic alterations that occur in cancer development, various receptors and proteins become upregulated, which can potentially be used as targets for imaging purposes.[39] Prior to developing such targeted imaging agents, it is essential to identify which genes or proteins become upregulated for each specific tumor type.[40,41]
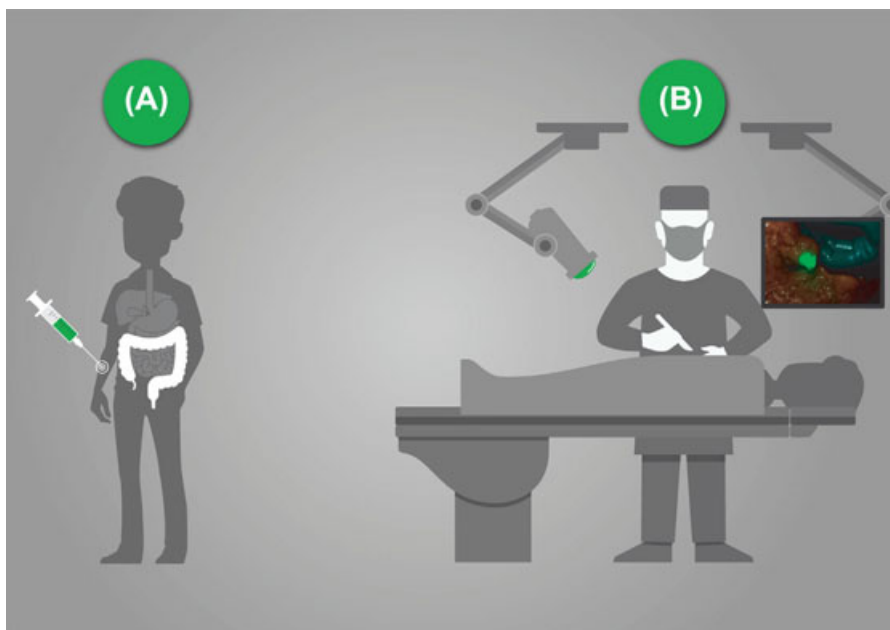
FIGURE 1 Concept of molecular fluorescence guided surgery (MFGS). Prior to surgery a fluorescent target tracer is injected intravenously (A). During the operation the surgeon will receive real-time feedback by a molecular fluorescence camera in the detection tumor tissue (B). Unpublished figure from previously published study Harlaar et al[107]

3 | UPREGULATED GENES AND PROTEINS RELATED TO CRC

The potential application of targeted imaging agents for intraoperative tumor visualization is dependent on the expression levels of biomarkers. A biomarker is a specific component present on or secreted by the tumor cell itself.

Most colorectal cancers are thought to develop via the "adenoma-to-carcinoma sequence," arising from normal cells through the stepwise asset of different genetic alterations.[42,43] In these expressed
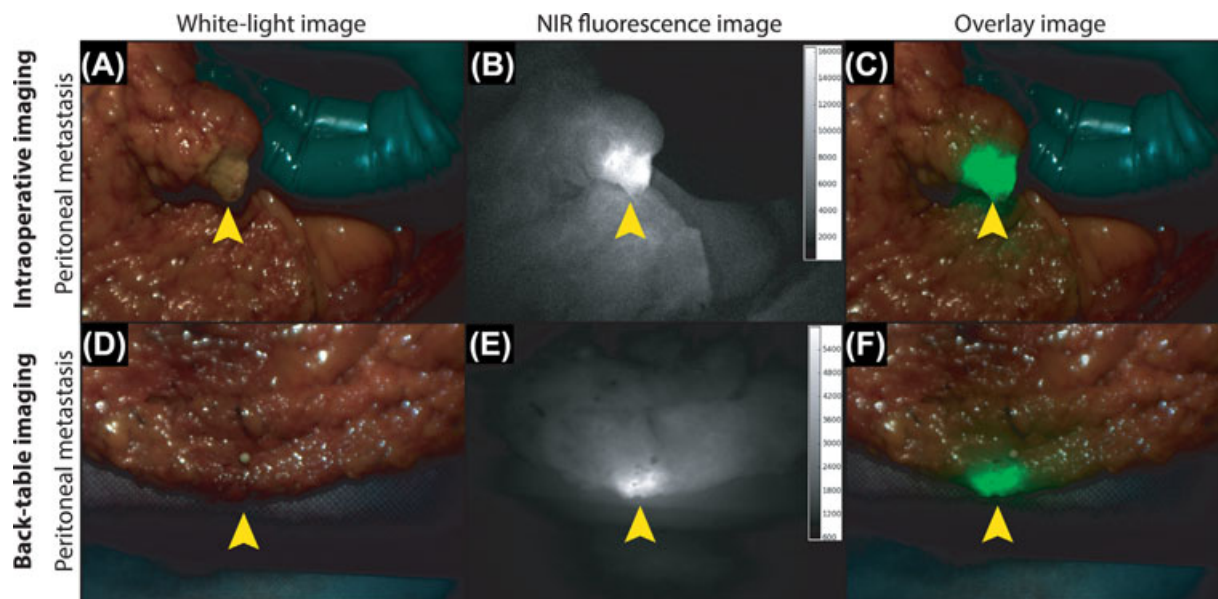

FIGURE 2 Intraoperative imaging with white-light, NIR fluorescence and the overlay of both. Intraoperative imaging of a patient with PC of colorectal origin following intravenous administration of 4.5 mg of the fluorescent tracer bevacizumab-800CW targeting VEGF-A. A white-light image (A), NIR fluorescence image (B), and overlay of both (C) clearly show fluorescent signals at the location of a clinically suspect peritoneal lesion. Back-table imaging directly after surgery of a different peritoneal lesion of the same patient is depicted (D-F). Both peritoneal lesions proved to be tumor metastasis upon final histopathology. Unpublished figures from previously published study Harlaar et al.[107]

genes different functional categories can be identified: genes related to proliferation and metabolic rates, to cell adhesion and communication, to transcription and mitosis regulation, or to apoptosis.[44,45] Knowing which biomarkers are encoded by which genes is important when searching for which target to develop a fluorescence imaging agent for.

Cardoso et al[44] presented a list of 128 different genes that were found to be upregulated in CRC compared to normal colorectal tissue. Since protein expression is not always synchronously upregulated, not all of these genes result in overexpression of the related proteins or receptors. Previously, an extensive literature search has been performed on this specific list of genes, in order to identify which genes gave an upregulation of the related proteins or receptors as confirmed by immunohistochemical analysis.[46] As a result, 29 targets were identified, that could be used for imaging purposes during CRC surgery.

4 | TARGET SELECTION CRITERIA (TASC)

To select the most optimal target for imaging purposes from this large set of upregulated biomarkers, the TArget Selection Criteria (TASC) scoring system was developed.[46] The aim of the TASC was to improve the selection of suitable biomarkers for tumor-targeted imaging of all types of cancer. Seven of the most relevant target characteristics were identified based on literature, that each could be scored with 0-6 points. The following characteristics were identified by which a biomarker is validated: i) extracellular biomarker localization—either on the cell membrane or in close proximity of the tumor cell; ii) expression pattern; iii) tumor-to-healthy tissue ratio (T/N); iv) percentage of positive tumors; v) reported successful use of the biomarker in in vivo imaging studies; vi) enzymatic activity; and vii) internalization.[46] Based on extensive testing of the TASC on a variety of biomarkers, cut-off values were determined for target selection. A total score of 18 or more indicates that a biomarker can be considered a potential candidate for tumor-targeted imaging.

As mentioned before, 29 targets were identified that may be used as potential targets for intraoperative imaging of CRC.[46] Using the TASC-scoring system, six biomarkers were considered the most promising: Epithelial Cell Adhesion Molecule (EpCAM), CXC Chemokine Receptor 4 (CXCR4), Mucin 1 (Muc1), Matrix MetalloProteinases (MMPs), Epidermal Growth Factor Receptor (EGFR), and Carcino-Embryonic Antigen (CEA). Although the Vascular Endothelial Growth Factor-A (VEGF-A) scored a total of 17 points, it was still considered a suitable potential target as well, given the extensive experience there already is in VEGF-A targeted imaging. For the clinical translation of these seven suitable biomarkers, specific fluorescence imaging agents need to be available to facilitate MFGS of CRC and PC of colorectal origin.

5 | FLUORESCENCE IMAGING AGENTS

As stated before, fluorescence imaging agents or probes that can be used for MFGS can roughly be divided into two categories:

non-targeted fluorescent probes and targeted fluorescent probes. The main difference between these two categories is based on their mechanism of action (MOA).

5.1 | Non-targeted fluorescent probes

Non-targeted fluorescent probes accumulate "passively" in solid tumors due to physiological properties such as increased angiogenesis, pressure differences, and high metabolic activity (Figure 3A). It is commonly known that the majority of solid tumor cells stimulate angiogenesis and therefore are highly vascularized. This feature combined with the lack of efficient lymphatic drainage results in more accumulation in tumor tissue compared to normal surrounding tissue, thereby enhancing contrast and enabling a differentiation between the tumor and surrounding tissue. This phenomenon is also known as the enhanced permeability and retention (EPR) effect.

Many non-targeted fluorescent probes have already been used in humans to enhance contrast during surgery in a variety of different indications, such as for example fluorescein for retinal fluorescein angiography, indocyanine green (ICG) for liver perfusion[47–49] and lymph node detection,[50,51] or methylene blue for sentinel lymph node detection in breast cancer patients.[52,53]

ICG is the most commonly known fluorescent probe, which was already approved by the Food and Drug Administration (FDA) back in 1959. ICG has several advantages over to fluorescein as it only fluoresces in the NIR light spectrum (instead of the visible light spectrum) and therefore is less influenced by tissue optical properties such as scattering and absorption. As ICG binds to plasma proteins, it has a negligible toxicity and is excreted rapidly by the liver into the bile, with a plasma half-life of only 3-4 min.[54,55] These features make ICG a very attractive contrast agent for assessment of macro- and micro-circulatory status of different organs based on its intravascular distribution.[56]

Ever since its first clinical application in hepatology for liver condition monitoring in 1957,[57] it has been widely applied and studied to visualize perfusion in ophthalmology for identification of retinal blood vessels, in cardiac bypass surgery for evaluation of anastomoses and for monitoring cardiac output.[58–62] More recent studies have reported the potential application of ICG for intraoperative fluorescence angiography in a broad range of other indications such as neuro-, coronary-, reconstructive-, liver-, and vascular surgery.[59,63–70]

The first potential application of ICG-based fluorescence imaging in patients with peritoneal metastases of colorectal origin was demonstrated in 2016.[71] In this study, peritoneal metastases from non-mucinous adenocarcinoma were accurately identified following the intravenous administration of free ICG during surgery, leading to an adjustment in clinical decision making in 29% of patients. However, the benefit was minimal in patients with mucinous adenocarcinoma. Despite the positive results demonstrated in this study, the main disadvantage still lies in the fact it is not tumor-specific and therefore leads to a low sensitivity and specificity.
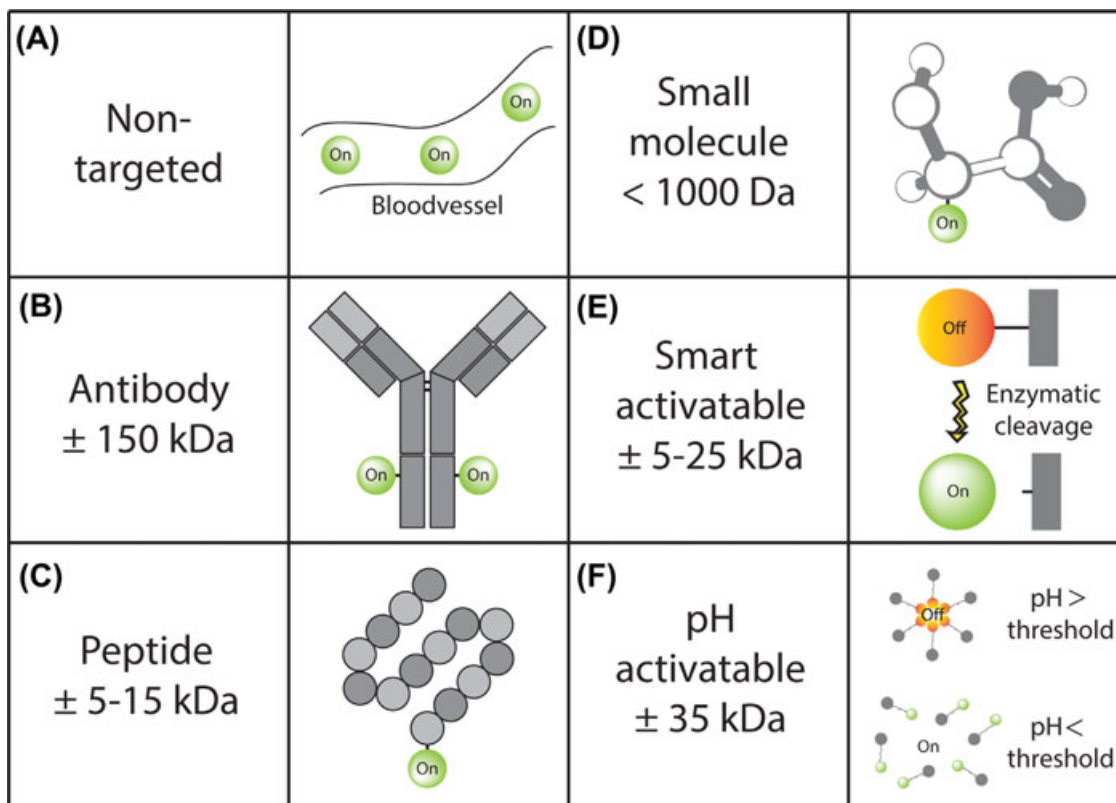
FIGURE 3 Fluorescence imaging probes. Overview of fluorescent imaging probes with different mechanisms of action. The effect of non-targeted fluorescent probes is based on tissue distribution by perfusion (A), whereas antibody-based (B), peptide-based (C), and small molecule- based (D) imaging enables targeted fluorescence imaging through binding to specific receptors or proteins overexpressed by the tumor. Smart activatable fluorescent probes are activated upon cleavage by specific enzymes or proteases secreted by the tumor (E), whereas pH activated probes becomes fluorescent through a change in molecular structure due to the characteristic acidotic environment of a tumor (F)

5.2 | Targeted fluorescent probes

Due to the low sensitivity and specificity of non-targeted fluorescence probes, its application in surgical oncology is still limited. Therefore, to increase contrast, this resulted in a shift toward the development and clinical translation of targeted optical imaging agents enhancing surgical vision based on the molecular characteristics of cancer cells.

The MOA of targeted fluorescent probes is based on the concept of a carrier molecule that is conjugated to a fluorescent dye, specifically binding to a certain tumor target. Carrier molecules can either be monoclonal antibodies, (small) peptides, small molecules, or other molecules that specifically target certain cell surface markers that become overexpressed due to genetic variances that occur in every tumor (Figure 3B).[72] Moreover, the increased metabolic activity that characterizes certain tumor types can be used as a target.[40]

Besides a suitable carrier molecule, the fluorescent dye itself also plays an important role. The development of new fluorescence probes is challenging since each agent needs separate regulatory approval, which is an expensive and time-consuming process.[73] As mentioned before, fluorescent dyes that emit light in the NIR light spectrum provide several advantages over dyes that emit light in the visible light spectrum. Although there is a wide variety of fluorescent dyes available for conjugation to carrier molecules, the most preclinical and clinical experience has been obtained with the NIR fluorescent dye IRDye800CW, developed by LI-COR Biosciences Inc. (Lincoln, NE). The IRDye800CW has a peak emission wavelength at 794 nm and is ideal for protein and antibody labeling, as conjugation to a carrier molecule is relatively easy and extensive toxicity studies have been performed.[74]

The increasing clinical application of therapeutic monoclonal antibodies specifically targeting certain biomarkers of cancer is an interesting development in the perspective of optical molecular imaging. Targeting certain tumor-specific receptors with fluorescently labeled antibodies seems to have great potential for visualization of cancer during interventions, also in CRC.[72,75–78] Multiple targeted probes have already been testes successfully in several preclinical studies.[75,77–84]

The first in-human proof-or-principle of targeted optical molecular imaging using a fluorescent probe was provided by van Dam et al[24] in 2011, demonstrating the potential of MFGS in patients with PC originating from ovarian cancer using the fluorescent tracer

folate-FITC, targeting the folate receptor α. Ever since, targeted optical imaging has been applied for many different indications.

6 | POTENTIAL FLUORESCENCE IMAGING AGENTS FOR DETECTION OF COLORECTAL CANCER

As mentioned before, using the TASC scoring system, seven potential targets for optical molecular imaging of PC of colorectal origin have been identified: CXCR4, EpCAM, EGFR, CEA, Muc1, MMPs, and VEGF-A.[46] The specifics of these proteins and receptors are summarized in Table 1.[85–109] Several fluorescent imaging probes targeting these biomarkers have already been investigated in humans in a broad variety of indications.

For example, the NIR fluorescent tracer cetuximab-800CW targeting EGFR has been applied in humans for surgical navigation in head-and-neck squamous cell carcinoma.[92] Moreover, cetuximab-800CW is being used in a phase-I clinical trial in the University Medical Center Groningen in patients with head and neck squamous cell carcinoma (NCT03134846).

Besides, the NIR fluorescent tracer bevacizumab-800CW targeting VEGF-A has been applied for detection of a variety of different tumor types, among which locally advanced rectal cancer (NCT01972373), pancreatic cancer (NCT02743975), breast cancer[109] (NCT02583568), and esophageal cancer.[108] The feasibility of MFGS using bevacizumab-800CW is also being investigated for intra-operative guidance in benign diseases such as endometriosis (NCT02975219) or for endoscopic detection of familial adenomatous polyposis (NCT02113202).

In CRC and specifically peritoneal metastases of colorectal origin, so far two phase-I feasibility studies have been performed in humans.

7 | FEASABILITY STUDIES IN PC OF COLORECTAL ORIGIN

In 2016, Harlaar et al[107] used the NIR fluorescent tracer bevacizumab-RDye800CW targeting VEGF-A for MFGS in seven patients with PC from CRC origin, that were scheduled to undergo CRS and HIPEC. Intravenous administration of bevacizumab-800CW 3 days prior to surgery proved to be safe, as no (serious) adverse events that were related to tracer administration occurred in any of the patients. Fluorescence signals were observed in all patients during surgery. Additional tumor tissue that had not been identified by the surgeons using only visual and tactile inspection was detected in two patients using fluorescence imaging. The fresh surgical specimens were imaged back-table at the operating theatre. A total of 80 peritoneal areas were imaged using the intraoperative camera system and analyzed by a pathologist. All 29 resected, but non-fluorescent areas proved to be benign on final histopathology, thus potentially indicating a sensitivity of 100%. In 27 out of 57 fluorescent areas in the fresh surgical specimen, tumor tissue was

identified. Although the authors state that their study was not powered to investigate the sensitivity and specificity, the results are very promising. In conclusion, in this study MFGS using bevacizumab-800CW was safe and feasible and could potentially improve CRS and patient selection.

The second feasibility study was performed in 2018 by Boogerd et al,[96] in which SGM-101, a fluorescent anti-CEA monoclonal antibody, was administered intravenously 2–4 days before surgery, to investigate the feasibility of MFGS in CRC and PC of colorectal origin. Patients with PC of colorectal origin that were scheduled for open surgical removal were included. First, a dose-finding study was performed in the first nine patients. Subsequently, the most optimal dose of SGM-101 was investigated in another 17 patients. SGM-101 showed no treatment-related (serious) adverse events. However, a total of eight possibly related mild adverse events occurred throughout the study. Using MFGS, in six patients a total of 19 additional peritoneal lesions were identified as potentially tumor-positive, and therefore treatment strategies were changed. The authors report a sensitivity of 98% and a specificity of 62%.

Interestingly, although both studies used different fluorescent tracers, more or less the same conclusions were drawn. Most importantly, both bevacizumab-800CW and SGM-101 were deemed safe in combination with MFGS. Moreover, it appeared that with both fluorescent tracers, a very high sensitivity could be obtained. If these results are validated in a larger patient cohort and indeed clinically suspect, but non-fluorescent lesions turn out to be benign, non-fluorescent lesions may be left in situ in the future and subsequently decrease morbidity. Interestingly, this might also imply that currently visual and tactile inspection-based surgery leads to unnecessary resections when compared to MFGS. The majority of complications and revalidation time is probably related to the extent of the cytoreduction itself. This might also improve the current morbidity of 22-34% and mortality of 0.8-4.1%.[110–115]

The specificity in these two feasibility studies appears to be relatively low, with a substantial amount of false positive lesions when applying intraoperative fluorescence imaging. This might be due to technical limitations of the fluorescence camera system that still need to be improved, such as the multispectral substration techniques. Currently, quantification of fluorescence with most of the present generation of clinically approved fluorescence camera systems is still limited, making the interpretation of fluorescence signals subjective. If a threshold could be set to give the surgeon a "yes" or "no" answer to the question whether a peritoneal lesion is tumor-positive with a certain sensitivity and specificity, this could potentially improve interpretation of fluorescence signals. Last, for some tracers, the optimal dose might still need further optimization.[107]

Additional research and studies need to be performed to investigate novel fluorescence imaging agents in humans for MFGS of PC of colorectal origin. Theoretically, multiple fluorescence imaging agents can be intravenously administered to the same patients simultaneously, a so-called "tracer cocktail," in order to improve sensitivity and specificity. Therefore, novel fluorescence imaging agents need to be validated in a standardized way, with the emphasis

TABLE 1 Potential targets for optical molecular imaging in PC of colorectal origin using the TASC scoring system

Target	Name	Location	Function	Over-expression in CRC	Carrier molecule clinically available	GMP-labeled fluorescent tracer	Clinical trials in humans
CXCR4	Chemokine Receptor 4	Cell surface	Homing of hematopoietic stem cells to the bone-marrow	±70%[85]	AMD3100 (molecule)[86] SDF-1a (peptide)[86] 12G5 (mAb)[86]	-	-
EpCAM	Epithelial Cell Adhesion Molecule	Cell surface	Cell adhesion	>80%[87,88]	Edrecolomab Catumaxomab	323/A3-800CW[89]	-
EGFR	Epidermal Growth Factor Receptor	Cell surface	Cell proliferation, differentiation, adhesion and migration	±80%[90,91]	Cetuximab Panitumumab	Cetuximab-800CW Panitumumab-800CW	NCT03134846[92]
CEA	Carcino-embryogenic antigen	Cell surface	Cell adhesion	>90%[93-95]	Arcitumomab	SGM-101[96]	-
Muc1	Mucin-1	Cell surface	Forming protective mucous barriers on epithelial surfaces, intracellular signaling (cell adhesion and anti-adhesion)	±50%[97,98]	Muc1-targeting peptide C595 (mAb) Bispecific anti-Muc1 antibody	-	-
MMP	Matrix Metalloproteinases	Tumor micro-environment	Degrading proteins in extracellular matrix	30-95% depending on the type[97,99-102]	-	-	-
VEGF-A	Vascular Endothelial Growth Factor-A	Tumor micro-environment	Angiogenesis	Up to 96%[103,104]	Bevacizumab	Bevacizumab-800CW[105]	NCT02113202 NCT01972373 NCT02583568 NCT02975219 NCT02743975 NCT01691391 [106-109]

on the determination of the safety, feasibility, optimal agent dose, and optimal timing for surgical intervention in phase-I feasibility studies.

8 | FUTURE PERSPECTIVES

8.1 | Target selection for MFGS

Currently, there are many carrier molecules that seem promising for potential validation in phase-I feasibility studies according to the TASC scoring system.[46] Additionally, new strategies have been developed recently to identity biomarkers that are upregulated in cancer development, such as functional genomic mRNA (FGM) profiling.[116] This method corrects expression data of numerous genes for relevant non-genetic variables. It is likely that in the near future new promising targets will be identified by this gene expression analysis, that may be used as targets, providing new possibilities for imaging of PC of colorectal origin.

8.2 | Novel fluorescence imaging probes

Next to the validation of potential targets for imaging, novel fluorescent probes are being developed.[72,117] Different types of carrier molecules have different pharmacokinetics. The substantial molecular weight of monoclonal antibodies (generally ± 150 kDa, Figure 3B) results in a relatively long blood circulation time of several days up to weeks. Although there is extensive experience with the use of monoclonal antibodies, even smaller molecules may provide favorable pharmacokinetic properties, such as nano-bodies.[118] A faster clearance from background tissue results in sufficient signal-to-background ratios that occur within a much shorter period of time. Therefore, peptides or small molecules might be logistically favorable compared to antibodies for MFGS (Figures 3C and D).[118] On the other hand, smaller molecules are in general more difficult to conjugate to a fluorescence dye, as even small structural changes can influence pharmacokinetics and binding efficacy significantly.[118,119]

Another subgroup of imaging probes has come forward in recent years: targeted smart-activatable probes (Figure 3E).[119] The working mechanism of these probes is based on the principle of photochemical quenching or ligand-targeted activation. Smart activatable probes only fluoresce when bound to the tumor or cleaved by specific proteases or peptidases excreted by the tumor, which improves signal-to-back-ground ratios due to limited background fluorescence.[118,120] The first clinical studies to investigate smart activatable probes have been performed already.[117] However, to the best of our knowledge, this has not yet been done for intraoperative imaging of CRC or PC of colorectal origin.

A similar "on-or-off" concept has been applied in the development of a pH-activatable fluorescent probe. This probe becomes activated upon contact with a certain threshold pH (pH ≤ 6.9), as the majority of solid tumors are acidic. Although this probe does not target a tumor biomarker, it is still highly specific due to the pH transistor concept.[121] The benefit of such a probe is that it can be applied in a broad range of oncological indications. However, the first proof-of-concept in human study using a pH-activated probe still needs to be conducted.

8.3 | Phase II/III clinical studies

Although different fluorescent probes are being developed, so far only two phase-I feasibility studies have been finalized in relatively small numbers of patients with PC of colorectal origin.[96,107] The ability of fluorescence imaging to detect peritoneal metastases that are missed by visual and tactile inspection and to aid in the differentiation between malignant and benign tissue, may have the potential to change clinical decision making. Although these results seem promising, further validation in phase-II clinical studies is required, with larger patient cohorts that are sufficiently powered to estimate the diagnostic accuracy. Eventually, in phase-III studies, the impact of MFGS in CRS and HIPEC surgery on clinical endpoints such as progression-free and overall survival need to be evaluated, hoping to improve the current median progression-free survival of only 12.6 months.[11]

8.4 | Photodynamic therapy

Although current clinical studies are mainly aimed to investigate the feasibility of optical imaging for cancer detection, in the future intraoperative imaging may also be used as a therapeutic modality. Carrier molecules that specifically target the tumor can also be labeled to a photoactive dye (ie, photosensitizer), to allow targeted photodynamic therapy (tPDT). When excited with light of a specific wavelength, photosensitizers not only fluoresce, but also form reactive oxygen species that oxidize the cells they target, thereby killing them.[122] Potentially, tPDT may be applied after CRS, to assist in the elimination of microscopic peritoneal lesions. As there is only superficial activation of the targeted photosensitizers, side-effects are estimated to be limited. The first clinical trials have already been performed to investigate the safety and feasibility of tPDT using a variety of different photosensitizers. Phase I and II clinical trials have been conducted for treatment of colorectal cancer,[123] pelvic recurrence of CRC,[124] colorectal liver metastases (NCT00068068),[125] and locally advanced rectal cancer.[126] Moreover, tPDT has also been applied for the treatment of peritoneal metastases originating from ovarian cancer and sarcomas,[127] and different gastrointestinal tumors[128] with promising results. These studies demonstrate that tPDT could potentially be used as an effective treatment for both CRC and PC. However, future studies are required to determine the effect on PC of colorectal origin, when combined with MFGS.

9 | CONCLUSION

In conclusion, treatment of PC of colorectal origin with curative intent consists of CRS followed by HIPEC. Up to date, surgeons still rely on visual and tactile inspection for intraoperative differentiation between tumor and benign tissue. The ultimate goal during cytoreduction is to

obtain a macroscopically complete cytoreduction by resecting malignant tissue only. Therefore, there is a clear need for an intraoperative imaging technique improving tumor detection. The first phase-I clinical trials have been performed showing the potential benefit of MFGS for patients with PC of colorectal origin. Even though no conclusions can be drawn with regard to the impact of these studies on clinical decision making, it appears MFGS has the potential to improve both cytoreduction and patient selection, facilitating patient-tailored surgery. However, to reliably determine the sensitivity and specificity of MFGS during CRS and HIPEC, subsequent phase-II studies are required.

CONFLICTS OF INTEREST

None.

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SYNOPSIS

This paper gives a chronological overview in the development of Molecular Fluorescence Guided Surgery during Cytoreductive Surgery and HIPEC treatment in patients with Peritoneal Carcinomatosis of colorectal origin.