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Abstract

During surgery for advanced epithelial ovarian cancer (EOC), the most important prognostic factor is the absence of residual tumor. Invisible microscopic peritoneal metastasis (mPM) are not removed during surgery and can be responsible of peritoneal recurrences. The aim of this current systematic review is to assess the role of fluorescence in evaluating mPM in EOC.

We performed a systematic review using bibliographic citations from PubMed, Clinical Trials.gov, Embase, Cochrane Library, and Web of Science databases. MeSH terms for fluorescence, EOC and peritoneal carcinomatosis were combined and not restricted to the English language. The final search was performed on September 1rst, 2021. The primary outcome was to determine the diagnostic accuracy of fluorescence. We also reviewed the different techniques used.

Eighty-seven studies were identified. Of these, 10 were included for analysis. The sensitivity and specificity of fluorescence ranged between 66.7-100% and 54.2-100%, respectively. Most importantly, the negative predictive value (NPV) ranged from 90-100% Due to the heterogeneity of the studies, no consensus was reached concerning the optimal use of fluorescence in terms of type of dye, type and timing of injection and imager to use. No adverse event was reported.

Fluorescence can safely be used in EOC to evaluate mPM with a high NPV. However, a randomized controlled trial is needed to homogenize current practice

Key words: Epithelial ovarian cancer; peritoneal carcinomatosis; fluorescent imaging; systematic review

Introduction

Surgery and chemotherapy constitute the cornerstone in the treatment of epithelial ovarian cancer (EOC). In advanced disease, the most powerful independent prognostic factor is the absence of residual tumor (1–5). The aim is therefore to obtain no residual disease after primary or interval cytoreductive surgery (CRS).

Nevertheless, despite clinical remission after chemotherapy and surgery, 63% of patients with advanced EOC still develop a recurrence, even if an optimal CRS is achieved (6). In 60% of cases, this recurrence is localized on the peritoneal surface (7). This could be explained by the persistence of microscopic peritoneal metastases (mPM) that are not seen and removed during surgery which could lead to secondary peritoneal recurrence (8).

Indeed, it has been shown that microscopic residual disease concerns almost all patient with high grade serous ovarian cancer after macroscopic complete CRS (9). A more thorough evaluation of the disease's spread is challenging because of the small size of metastatic lesions and the complexity of the peritoneal cavity. For this reason, there is an increasing interest for tools that could help surgeons recognize mPM intraoperatively.

In this specific setting, fluorescence imaging could be an ideal solution. A tumor-targeted fluorescence tracer is administered to the patient before or during surgery. The fluorescent dye, specific to the tumor, absorbs the light at a certain wavelength and emits light at a different wavelength. An imaging system is used to detect this fluorescence. The surgeon therefore has a real time intra operative feedback that can detect mPM and guide the surgery (10). However, one main difficulty persists: the correct fluorescent tracer must be specific to the tumor.

The aim of our work is to systematically review all existing data from human studies which investigated the use of fluorescence for the detection of peritoneal carcinomatosis in EOC.

72 The primary outcome was to assess the detection rate of fluorescence in diagnosing mPM in
73 EOC. We also aimed to describe the different techniques used for fluorescent detection of
74 mPM in EOC (type of fluorescent dye, injection, site and time of injection, dose/concentration
75 for injection, imager used and delay between injection and surgery).

76

Material and methods

This systematic review of literature was performed according to the guidelines established by the Preferred Reporting in Systematic Review and Meta-Analysis (PRISMA) and Assessing the Methodological quality of systematic reviews (AMSTAR) (11). It was registered in the International Prospective Register of Systematic Reviews (PROSPERO ID: CRD42021278978).

Sources and literature search

Eligible studies, with no language limitations, where retrieved through ClinicalTrials.gov, MEDLINE (PubMed), Cochrane library, Web of Science, Embase, Google Scholar and references among selected publications in 2021.

The following MeSH terms used were: Peritoneal Carcinomatosis [C04.588.033.513, C04.588.274.780, C06.301.780, C06.844.620], Fluorescence [G01.590.540.665.500], Ovarian Neoplasm [C04.588.322.455, C13.351.500.056.630.705, C13.351.937.418.685, C19.344.410, C19.391.630.705], Photosensitizing Agents, [D27.505.954.444.600, D27.505.954.600.710]. Free key terms used for search were: “epithelial ovarian cancer”, “fluorescence”, “photodynamic-guided surgery”, “peritoneal carcinomatosis”.

Eligibility

Prospective and retrospectives clinical studies assessing the diagnostic value of fluorescence in detecting peritoneal carcinomatosis in EOC were included. Studies using animals and laboratory-related models were excluded. Publications which investigated fluorescence in peritoneal carcinomatosis of non-ovarian origin were not included.

Two reviewers (SB and LB) independently assessed all studies in order to verify the inclusion criteria. In case of discrepancies, a third reviewer (HA) was consulted. Selection of studies was conducted by screening titles and abstracts.

Risk of bias

To assess the quality of the included studies, Study quality assessment tools were utilized (Quality assessment tool for before-after (pre-post) studies with no control group and Quality assessment tool for observational cohort and cross-sectional studies (*https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools*)). Studies were rated as "good" when at least 70% of the assessment criteria were met, "fair" when at least 50% of the criteria were met, and "poor" when less than 50% of the criteria were met.

Data extraction

Full text version for studies matching inclusion criteria were obtained for complete assessment. The following data was collected independently by LB and SB: year of publication, authors, country in which the study was conducted, study design, number of patients in each group, histological cancer type, fluorescence technique (timing, volume, concentration, localization of injection, dose) and detection rate.

Outcome

The primary outcome was to assess the detection rate of fluorescence in diagnosing mPM in epithelial ovarian cancer. Samples from fluorescent and non-fluorescent tissues were evaluated histologically. Diagnostic values are reported in terms of sensitivity and specificity:

sensitivity was defined as the number of true positive peritoneal nodules / (number of true positive + false negative) x 100%; specificity the number of true negative peritoneal nodules / (number of true negative peritoneal nodules / (number of true negatives + false positive) x 100%.

The secondary outcome was to describe the different techniques used for fluorescent detection of mPM in EOC: type of injection, site and time of injection, dose/concentration for injection, imager used and delay between injection and surgery.

Results

Study selection

Six hundred and eighty-four records were screened after removal of duplicated. Of these, 597 were excluded after reviewing the title and abstract. Among the 87 full texts assessed for eligibility, 77 were excluded and concerned pre-clinical studies. In total, 10 studies were included in the review for qualitative assessment.

The process of study selection is reported in Figure 1.

After quality assessment, 5 were rated as good, 3 were rated as fair and 2 were rated as poor (Table 1).

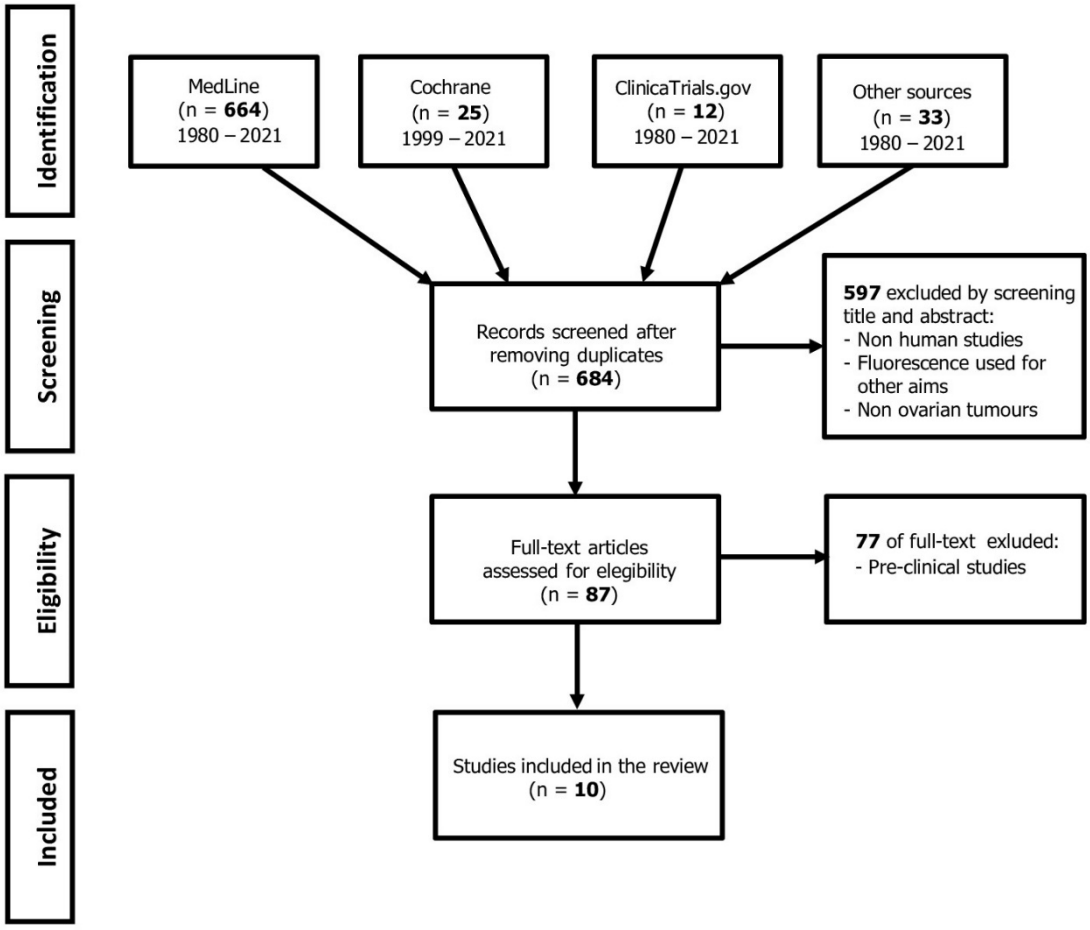

Figure 1: Flow diagram illustrating the study selection process according to the PRISMA guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analyses)

144

145 *Study characteristics*

146 All the series were based on clinical trials published between 2004 and 2016. Overall, 148
147 patients with EOC were included and, in most of cases, had advanced disease (FIGO III and
148 IV) at the time of diagnosis.

149

150 *Study population*

151 Among these clinical trials, 3 (12–14) investigated the role of fluorescence dye only in
152 women with high grade EOC and 7 included also patients with other histological findings.
153 When they were available, only data concerning patients with EOC were extracted for this
154 review. Löning et al. (n = 17) (12), Hillemanns et al. (n = 25) (13) and Veys et al. (n = 20)
155 (14) only included patients with EOC. In contrast, the other seven clinical trials included
156 patients with other histological findings such as borderline ovarian tumors, benign ovarian
157 cysts, sertoli-leyding tumor, primitive peritoneal cancer, gastrointestinal tumors
158 (cholangiocarcinoma, colorectal and gastric cancers), endometrial cancer, and breast cancer
159 (15–21). Hoogstins et al. tested the fluorescence dye among 42 subjects, of whom 12 had
160 EOC and 30 were healthy volunteers (21). A total of 148 EOC were included. Details are
161 presented Table 2.

162

163 *Surgical method*

164 Eight publications investigated the value of the fluorescence dyes in detecting peritoneal
165 metastases in CRS through median laparotomy (14,16–22), while 2 trials aimed to assess
166 peritoneal involvement by laparoscopy (12,15) .

Technique used for fluorescence detection

a- Fluorescent dye

Five clinical trials (12,15–17,23) examined the role of PpIX or 5-aminolevulinic acid (ALA) fluorescence in detection of MPM among 91 patients with EOC. PpIX is derived from the heme and is a fluorescent molecule produced by cells, in particular tumors, after administration of an oral or intraperitoneal precursor, ALA.

Two studies (14,18) analyzed the value of ICG (Indocyanine green) as fluorescence dye in peritoneal carcinomatosis by including globally 26 patients with EOC. Indocyanine green ICG is a water-soluble fluorophore, binding rapidly to plasma proteins after injection.

Two publications (19,20) focused on EC17 (a fluorescent agent targeting the folate receptor alpha, highly expressed in epithelial cancer, emitting at 500 nm), considering overall 16 women with EOC.

One clinical trial (21) investigated the role of OTL38 (a fluorescent agent targeting the folate receptor alpha , emitting at 796nm) among 12 patients with EOC. Details are presented Table 1.

b- *Optical devices and technology*

Systems used for fluorescence detection are detailed in Table 1. Wavelengths of excitation and detection are detailed as they are specific of each system and dye.

c- Administration protocol

In two studies (16,17) ALA was given orally 2-4 hours (h) before surgery at a dose of 20 mg/kg. Hillemanns et al. (23) also gave ALA orally, but randomizing different doses and timing among three groups of women. The aim was to establish the protocol administration that obtained the best results in term of fluorescence intensity and accuracy of the detection of mPM, in order to determine the optimal dosage range. After oral administration of ALA, in all these 3 publications patients underwent CRS through median laparotomy. In addition, Liu et al. performed also HIPEC (hyperthermic intraperitoneal chemotherapy) after debulking surgery. In contrast, in the other two clinical trials, ALA was administered intraperitoneally with a dose of 30 mg/kg, 5h before surgery, during a second-look laparoscopy.

Both Tummers et al. (18) and Veys et al. (14) administered ICG intravenously (IV) during surgery, respectively at a dose of 25 mg IV single bolus and 0.25 mg/kg IV.

Tummers et al.(19) and van Dam et al. (20) both administered EC17 IV at a dose of 0.1 mg/kg over 10 minutes, between 2 and 3 h before CRS.

Hoogstins et al. (21) administered the dye first among 30 healthy volunteers to explore the tolerability and pharmacokinetics of increasing doses of intravenous OTL38. They were randomized to receive a single dose of 0.025 mg/kg, 0.05 mg/kg, 0.1 mg/kg, and 0.2 mg/kg to find the optimal dosage range and the imaging time window. Then the authors used the results to administer OTL38 IV in 12 women with EOC, to evaluate its efficacy in detecting mPM, using different parameters like the TBR (tumor-to-background ratio), defined as the ratio between the fluorescent signal in tumor tissue and the fluorescent signal in the tissue surrounding the tumor. Each woman received a dose-escalating scheme with planned dose 0.025, 0.05 and 0.1 mg/kg over 1 h, between 2 and 3 h before surgery.

Efficacy

Data regarding performances of fluorescence to detect peritoneal lesions are presented in table 3. If available, the diagnostic value of these different techniques was assessed by sampling fluorescent and non-fluorescent tissues and comparing their sensibility, specificity, negative and positive predictive values.

ALA had an average sensibility of 94% and a specificity of 96%. In all these trials the smaller lesion detected measured 0.5 mm or less.

ICG: The authors demonstrated an average sensibility of 86.3%, while the specificity was available only in one study was 54.2% (14).

EC17: Sensibility was available only in one paper and was 94%, while there no data regarding specificity. The delay between EC17 injection and nodule resection ranged from 5 to 360 minutes and for peritoneal scars was between 5 and 240 minutes.

OTL38: An estimated sensitivity of 97% has been demonstrated and a total of 48.3% of patients had at least one additional lesion detected by OTL38 alone.

Side-effect and complication

No severe side effects have been observed (perioperative or intraoperative complications) related to the fluorescence protocol.

Discussion

To the best of our knowledge, this is the first study reviewing the role of fluorescence in the detection of mPM in EOC. Ten studies evaluated fluorescence tracing in EOC. We found that the sensitivity of fluorescence was high and most importantly, when assessed, fluorescence had a negative predictive value of 90-100%.

It is well known that the strongest prognostic factor in women with EOC is the absence of macroscopic residual tumor after CRS (4). Fluorescence guided surgery could therefore help surgeons remove mPM that would have been undetected (9). In this context, the role of fluorescence in the detection of mPM could represent an important step forward not only for accurate staging, but also for therapeutic intent, to recognize additional lesions that are not detected neither by naked eye, nor by palpation (24). In other terms, the use of this promising diagnostic imaging technique, could potentially increase the intraoperative detection of peritoneal metastasis allowing accurate complete surgical resection and possibly improving the prognosis of patients.

Fluorescence imaging-guided surgery needed to be investigated because, despite the improvement in imaging techniques, laparoscopy remains the cornerstone in evaluating the cancer extension. It helps address patients to the optimal treatment and is the best tool to evaluate the response after neoadjuvant chemotherapy (NACT) (31). However, during laparoscopy, tactile information of lesions cannot be obtained, and fluorescence imaging could add additional value. This is even more important in interval CRS in which it can be difficult to distinguish real mPM from cicatricial and necrotic lesions caused by NACT. In patients treated with NACT, residual cicatricial tissue represents a dilemma for surgeons because neither current imaging techniques nor the surgeon's eyes can distinguish tissue residual cancer cells from the fibrotic one caused by medical treatment. Veys et al. evaluated

the use of ICG in detecting mPM in scar tissue avec found a positive predictive value to detect tumor cells in scars of 57.1% (14).

One of the main setbacks of our work in the heterogeneity of the studies. It is difficult to conclude on the general efficiency of fluorescence in detecting mPM since all studies use a different protocol: type of dye, injection, imager… ALA is used by 5 studies and is not a photosensitizer but it is a precursor in the heme synthesis pathway (25). When it is administered exogenously it accumulates mostly in cancer cells where it is converted into a fluorescent dye named protoporphyrin IX (PpIX). PpIX fluoresces under blue light, absorbing light around 405 nm and emits red fluorescence that can be detected through camera system. ICG was evaluated in two studies and is a dye that fluoresces in the near infrared (NIR) range (700-900 nm) (26). After administration ICG binds to serum protein and, through circulation, it accumulates mainly in solid tumors through the "enhanced permeability and retention effect". This biological phenomenon is mainly observed among cancer tissues, and it is related to increased vascular permeability and reduced lymphatic drainage. EC17, assessed in two studies, also known as folate-FITC, is a folate analogue conjugated to 5-fluorescein isothiocyanate, which binds the folate receptors alpha (FRα). FRα are good target of dyes, because they are strongly expressed in epithelial cancers and only at low levels on the surface of normal cells (27). Over 90% of all EOC over-express FRα, and this percentage is even higher in serous cancers (90-100%). EC 17 fluoresces between the wavelengths of 520-530 nm. OTL38 was only evaluated in one work and shares with EC17 the same ligand (FRα), in fact it is defined as a folate-indocyanine green-like analogue conjugated to a NIR fluorescent dye. However, they contain different fluorochromes: EC17 contains a fluorescein dye in the visible wavelength, while OTL38 a cyanine dye in the NIR spectrum (28). It has high specificity and affinity for FRα.

Publications regarding folate-targeted dyes, EC17 and OTL38, showed great results allowing to detect respectively 16% and 29% more peritoneal lesions which have not been recognized by the naked eye. However, trials which used EC17, experienced the difficulty in developing new fluorescent probes labeled with target molecules feasible for clinical use.

Conversely, ICG has been widely used in different clinical context as a safe and effective in the identification of different tumors, such as hepatocellular carcinoma, and mPM from colorectal cancer. Nevertheless, in EOC, the two publications showed that ICG did not allow to detect more lesions compared to white light and naked eyes. However, scientists still aim to study the value of ICG as fluorescent dye in EOC. A parallel can be made between endometriosis and ovarian cancer: two illnesses with a peritoneal spread. In this benign gynecological pathology, the Gre-endo trial found that the sensitivity of NIR-ICG and white light was 85.6% and 82% and specificity was 95.2% and 97.9%, respectively (29).

Another promising field for fluorescence is the detection of sentinel lymph nodes. In endometrial, cervical and breast cancer, indocyanine green can be used as a detection tracer for the sentinel lymph node (30). In endometrial cancer, indocyanine green is even the preferred method for sentinel lymph node detection (31). Interest is emerging in the possibility of sentinel lymph node biopsy in early-stage ovarian cancer. Indeed, 14% of these patients are upstaged due to positive pelvic or para-aortic nodes after lymphadenectomy (32). Two major trials (SENTOV and SELLY) have evaluated the feasibility of a lymph node biopsy using fluorescence (33,34). The preliminary results of the SELLY trial, after injection of ICG in the ovarian pedicle, found a detection rate of 88.9% in women undergoing immediate staging (34,35).

No studies to date have assessed the impact on survival of using fluorescence during surgery.

Fluorescence diagnosis of mPM is not employed in current clinical practice, but the increasing number of published studies and clinical trials demonstrate the interest in this technique, which may be part of the future surgical management of peritoneal carcinomatosis (36,37). Through ClinicalTrial.gov, we have discovered that, at the moment, there are 447 trials focused on use of ICG in many fields, underlying the huge interest of the scientific community towards this fluorescence dye. However only two of them are conducted in gynecological domain, and none is concentrated on the detection of mPM of ovarian cancer origin, the specialty where it is most needed. Indeed, detecting mPM in ovarian cancer is of paramount importance since it could help the surgeon achieve a complete surgery and therefore possibly improve patient prognosis.

Tables

Table 1. Quality assessment of studies analyzing image-guided surgery to detect peritoneal metastasis in epithelial ovarian cancer through fluorescence.

Quality Assessment of Controlled Intervention Studies															
	Was the study described as randomized, a randomized trial, a randomized clinical trial, or an RCT?	Was the method of randomization adequate (i.e., use of randomly generated assignment)?	Was the treatment allocation concealed (so that assignments could not be predicted)?	Were study participants and providers blinded to treatment group assignment?	Were the people assessing the outcomes blinded to the participants' group assignments?	Were the groups similar at baseline on important characteristics that could affect outcomes (e.g., demographics, risk factors, co-morbid conditions)?	Was the overall drop-out rate from the study at endpoint 20% or lower of the number allocated to treatment?	Was the differential drop-out rate (between treatment groups) at endpoint 15 percentage points or lower?	Was there high adherence to the intervention protocols for each treatment group?	Were other interventions avoided or similar in the groups (e.g., similar background treatments)?	Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?	Did the authors report that the sample size was sufficiently large to be able to detect a difference in the main outcome between groups with at least 80% power?	Were outcomes reported or subgroups analyzed prespecified (i.e., identified before analyses were conducted)?	Were all randomized participants analyzed in the group to which they were originally assigned, i.e., did they use an intention-to-treat analysis?	Total
Hillemanns (2017)	🟢	🔴	🔴	🔴	🔴	🟢	🟢	🟢	🟢	NA	🟢	🔴	🔴	🟢	🟡
Hoogstins (2016)	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	NA	🟢	🟡	🟡	🟢	🟢
Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies															
	Was the research question or objective in this paper clearly stated?	Was the study population clearly specified and defined?	Was the participation rate of eligible persons at least 50%?	Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	Was a sample size justification, power description, or variance and effect estimates provided?	For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?	Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Was the exposure(s) assessed more than once over time?	Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Were the outcome assessors blinded to the exposure status of participants?	Was loss to follow-up after baseline 20% or less?	Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	Total
Löning (2004)	🟢	🔴	🔴	🟡	🔴	NA	🟢	🟡	🟢	🔴	🟢	🔴	🟢	🟢	🔴
Löning (2006)	🟢	🔴	🔴	🟡	🔴	NA	🟢	🟢	🟢	🔴	🟢	🔴	🟢	🟢	🔴

Liu (2014)	●	●	●	●	●	NA	●	●	●	●	●	●	●	●	●
Yonemura (2016)	●	●	●	●	●	NA	●	●	●	●	●	●	●	●	●
Tummers (2015)	●	●	●	●	●	NA	●	●	●	●	●	●	●	●	●
Veys (2017)	●	●	●	●	●	NA	●	●	●	●	●	●	●	●	●
Tummers (2016)	●	●	●	●	●	NA	●	●	●	●	●	●	●	●	●
Van Dam (2011)	●	●	●	●	●	NA	●	●	●	●	●	●	●	●	●

Legend:
- Fair
- Good
- Poor

Table 2. Studies analyzing image-guided surgery to detect peritoneal metastasis in epithelial ovarian cancer through fluorescence.

Author	Dye	Patients (EOC)	FIGO stage	Surgical approach and indication	Detection system	Smallest lesion detected (mm)	Administration protocol
Löning (2004)	PpIX	30 (27)	I-IV	Second-look laparoscopy	10-mm 0 ° Combilight PDD 5133 laparoscope (Richard Wolf GmbH) that can switch from white to blue light mode (λ = 350–440 nm)	<0.5	30 mg/kg IP 5 h before surgery
Löning (2006)	PpIX	17 (17)	NA	Second-look laparoscopy	Combilight PDD 5133 (Richard Wolf GmbH, Knittlingen, Germany) blue light (λ = 350–440 nm)	<0.5	30 mg/kg IP 5 h before surgery
Liu (2014)	PpIX	20 (16)	III-IV	Laparotomy (CRS + HIPEC)	Blue light (λ = 440 nm)	0.5	20 mg/ kg PO 2 h before surgery
Yonemura (2016)	PpIX	115 (9)	NA	Laparotomy (CRS + HIPEC)	Xenon lamp (300 W) with blue light (λ = 375-445 nm)	0.5	20 mg/ kg PO 4 h before surgery
Hillemanns (2017)	PpIX	25 (25)	I-IV	Laparotomy (CRS)	Fixed endoscope connected to a D-Light system (Karl Storz GmbH und Co. KG, Tuttlingen, Germany) that that can switch from white to blue light (λ = 380–440 nm)	NA	A) 1 mg/kg PO 3-14 h before surgery B) 10 mg/kg PO 4-9 h before surgery C) 10 mg/kg PO 10-16 h before surgery

Tummers (2015)	ICG	10 (6)	IA-IIIC	Laparotomy (CRS)	Mini-FLARE system	NA	25 mg IV single bolus Intraoperatively
Veys (2017)	ICG	20 (20)	IIA-IVB	Laparotomy (CRS)	NIR camera system Photodynamic Eye, PDE; Hamamatsu Photonics, Hamamatsu, Japan (λ =760 nm)	NA	0,25 mg/kg IV Intraoperatively
Tummers (2016)	EC17	15 (12)	IIB-IV	Laparotomy (CRS)	Artemis fluorescence imaging system (Quest Medical Imaging, The Netherlands) which generate 7.5 mW/cm2 at 490 nm light	NA	0.1 mg/kg IV over 10 min 2-3 h BS
Van Dam (2011)	EC17	10 (4)	III	Laparotomy (CRS)	Multispectral fluorescence camera system developed by the Technical University Munich/Helmholtz Center Munich	NA	0.3 mg/kg IV over 10 min
Hoogstins (2016)	OTL38	42 (12)	IIIB-IV	Laparotomy (CRS)	Artemis fluorescence imaging system Camera and light designed to generate 7.5 mW/cm2 at 760-nm light	NA	Healthy volunteers randomized to receive an IV single dose between : 0.025, 0.05, 0.1 or 0.2 mg/kg All patients with EOC received dose-escalating scheme with planned dose: 0.025, 0.05 and 0.1 mg/kg over 1 h, 2-3 before surgery

Abbreviations: CRS cytoreductive surgery, *EC17* folate analogue conjugated to 5-fluorescein isothiocyanate, *FIGO* International Federation of Obstetrics and Gynecology, *HIPEC* hyperthermic intraperitoneal chemotherapy, *ICG* Indocyanine green, *Mini-FLARE* Mini-Fluorescence

assisted resection and exploration, *IP* intraperitoneal, *IV* intravenous, *NPV* negative predictive value, *PpIX* Protoporhyrin IX, *PO* per os, , λ wavelength.

Table 3. Studies analyzing the diagnostic accuracy of fluorescence in detecting peritoneal metastasis in epithelial ovarian cancer.

Author		Patients (EOC)	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
Löning	**(2004)**	30 (27)	92	95	*NA*	*NA*
Löning	**(2006)**	17 (17)	100	88	91	100
Liu	**(2014)**	20 (16)	95	100	NA	NA
Yonemura	**(2016)**	115 (9)	89	100	100	90
Hillemanns	**(2017)**	25 (25)	A) NA B) 66.7 C) 36.4	A) NA B) 94.1 C) 91.7	*NA*	*NA*
Tummers	**(2015)**	10 (6)	100	*NA*	*NA*	*NA*
Veys	**(2017)**	20 (20)	72.6%	54.2%	76.80%	NA

Abbreviations: NA: not applicable, EOC: epithelial ovarian cancer

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