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► To cite this version:

Safia Boussedra, Louise Benoit, Meriem Koual, Enrica Bentivegna, Huyen-Thu Nguyen-Xuan, et al.. Fluorescence guided surgery to improve peritoneal cytoreduction in epithelial ovarian cancer: A systematic review of available data. *EJSO - European Journal of Surgical Oncology*, 2022, 48 (6), pp.1217-1223. 10.1016/j.ejso.2022.02.022 . hal-03907017

HAL Id: hal-03907017

<https://hal.sorbonne-universite.fr/hal-03907017>

Submitted on 22 Jul 2024

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1 **Fluorescence guided surgery to improve peritoneal cytoreduction in epithelial ovarian**
2 **cancer: a systematic review of available data**

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21

22

23 **Funding:** None

24 **Declarations of interest:** None

25 **Abstract**

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

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

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

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

44

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

47

48 **Introduction**

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

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

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

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

70 The aim of our work is to systematically review all existing data from human studies which
71 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

77 **Material and methods**

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

83

84 *Sources and literature search*

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

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

94

95 *Eligibility*

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

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

103

104 *Risk of bias*

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

111

112 *Data extraction*

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

118

119 *Outcome*

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

123 sensitivity was defined as the number of true positive peritoneal nodules / (number of true
124 positive + false negative) x 100%; specificity the number of true negative peritoneal nodules /
125 (number of true negative peritoneal nodules / (number of true negatives + false positive) x
126 100%.

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

130

131

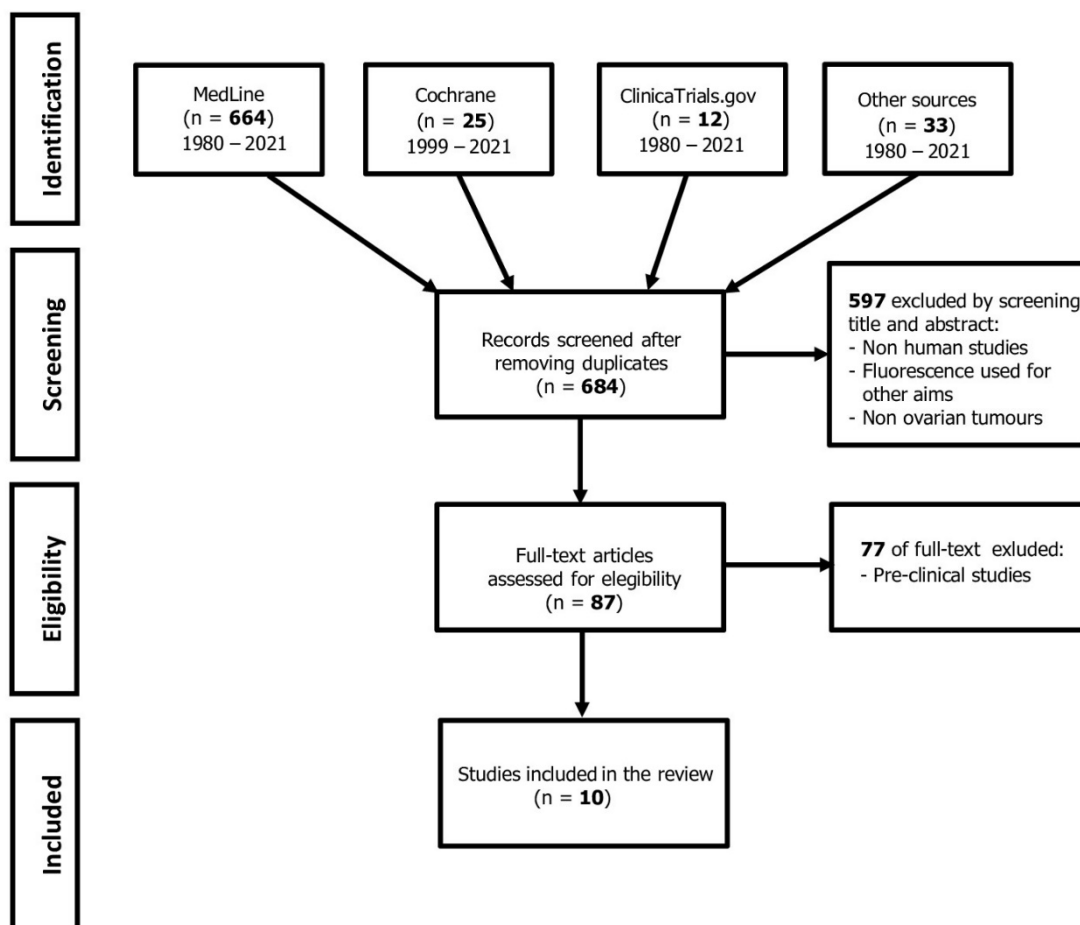
132 **Results**

133 *Study selection*

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

138 The process of study selection is reported in Figure 1.

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



141

142 *Figure 1:* Flow diagram illustrating the study selection process according to the PRISMA guidelines
143 (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).

167

168 Technique used for fluorescence detection

169 *a- Fluorescent dye*

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

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

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

180 One clinical trial (21) investigated the role of OTL38 (a fluorescent agent targeting the folate
181 receptor alpha , emitting at 796nm) among 12 patients with EOC. Details are presented Table
182 1.

183

184 *b- Optical devices and technology*

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

187

188 *c- Administration protocol*

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

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

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

202 Hoogstins et al. (21) administered the dye first among 30 healthy volunteers to explore the
203 tolerability and pharmacokinetics of increasing doses of intravenous OTL38. They were
204 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
205 find the optimal dosage range and the imaging time window. Then the authors used the results
206 to administer OTL38 IV in 12 women with EOC, to evaluate its efficacy in detecting mPM,
207 using different parameters like the TBR (tumor-to-background ratio), defined as the ratio
208 between the fluorescent signal in tumor tissue and the fluorescent signal in the tissue
209 surrounding the tumor. Each woman received a dose-escalating scheme with planned dose
210 0.025, 0.05 and 0.1 mg/kg over 1 h, between 2 and 3 h before surgery.

211

212 Efficacy

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

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

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

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

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

226

227 Side-effect and complication

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

230

231

232 Discussion

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

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

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

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

258 One of the main setbacks of our work in the heterogeneity of the studies. It is difficult to
259 conclude on the general efficiency of fluorescence in detecting mPM since all studies use a
260 different protocol: type of dye, injection, imager... ALA is used by 5 studies and is not a
261 photosensitizer but it is a precursor in the heme synthesis pathway (25). When it is
262 administered exogenously it accumulates mostly in cancer cells where it is converted into a
263 fluorescent dye named protoporphyrin IX (PpIX). PpIX fluoresces under blue light, absorbing
264 light around 405 nm and emits red fluorescence that can be detected through camera system.
265 ICG was evaluated in two studies and is a dye that fluoresces in the near infrared (NIR) range
266 (700-900 nm) (26). After administration ICG binds to serum protein and, through circulation,
267 it accumulates mainly in solid tumors through the “enhanced permeability and retention
268 effect”. This biological phenomenon is mainly observed among cancer tissues, and it is
269 related to increased vascular permeability and reduced lymphatic drainage. EC17, assessed in
270 two studies, also known as folate-FITC, is a folate analogue conjugated to 5-fluorescein
271 isothiocyanate, which binds the folate receptors alpha ($FR\alpha$). $FR\alpha$ are good target of dyes,
272 because they are strongly expressed in epithelial cancers and only at low levels on the surface
273 of normal cells (27). Over 90% of all EOC over-express $FR\alpha$, and this percentage is even
274 higher in serous cancers (90-100%). EC 17 fluoresces between the wavelengths of 520-530
275 nm. OTL38 was only evaluated in one work and shares with EC17 the same ligand ($FR\alpha$), in
276 fact it is defined as a folate-indocyanine green-like analogue conjugated to a NIR fluorescent
277 dye. However, they contain different fluorochromes: EC17 contains a fluorescein dye in the
278 visible wavelength, while OTL38 a cyanine dye in the NIR spectrum (28). It has high
279 specificity and affinity for $FR\alpha$.

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

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

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

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

303 Fluorescence diagnosis of mPM is not employed in current clinical practice, but the
304 increasing number of published studies and clinical trials demonstrate the interest in this
305 technique, which may be part of the future surgical management of peritoneal carcinomatosis
306 (36,37). Through ClinicalTrial.gov, we have discovered that, at the moment, there are 447
307 trials focused on use of ICG in many fields, underlying the huge interest of the scientific
308 community towards this fluorescence dye. However only two of them are conducted in
309 gynecological domain, and none is concentrated on the detection of mPM of ovarian cancer
310 origin, the specialty where it is most needed. Indeed, detecting mPM in ovarian cancer is of
311 paramount importance since it could help the surgeon achieve a complete surgery and
312 therefore possibly improve patient prognosis.

313

314

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317

318 **Tables**

319

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321

322

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, comorbid 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)	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Yonemura (2016)	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Tummers (2015)	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Veys (2017)	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Tummers (2016)	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Van Dam (2011)	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●

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 ($\lambda = 350\text{--}440$ 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 ($\lambda = 350\text{--}440$ nm)	<0.5	30 mg/kg IP 5 h before surgery
Liu (2014)	PpIX	20 (16)	III-IV	Laparotomy (CRS + HIPEC)	Blue light ($\lambda = 440$ 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 ($\lambda = 375\text{--}445$ 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 ($\lambda = 380\text{--}440$ 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 ($\lambda = 760$ nm)	NA	0,25 mg/kg IV Intraoperatively
Tummers (2016)	EC17	15 (12)	IIIB-IV	Laparotomy (CRS)	Artemis fluorescence imaging system (Quest Medical Imaging, The Netherlands) which generate 7.5 mW/cm ² 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/cm ² 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* Protoporphyrin 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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