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REVIEW ARTICLE

Performance of Indocyanine green for sentinel lymph node mapping and lymph node metastasis in colorectal cancer: a diagnostic test accuracy meta-analysis

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Abstract

Background Indocyanine green has been widely employed as a secure and easy technique for sentinel lymph node mapping in different types of cancer. Nonetheless, the usage of Indocyanine green has not been fully implemented due to the heterogeneous results found in published studies. Thus, the objective of this meta-analysis is to evaluate the overall performance of Indocyanine green for sentinel lymph node mapping and node metastasis in patients undergoing colorectal cancer surgery.

Methods An extensive systematic search was performed to identify relevant studies in English and Spanish with no time limit restrictions. For the meta-analysis, a hierarchical summary receiver operating characteristic curve (HSROCs) was constructed, and quantitative data synthesis was performed using random effects models. Specificity, sensitivity, positive, and negative likelihood ratios were obtained from the corresponding HSROC. Between-study heterogeneity was visually evaluated using Galbraith plot, and publication bias was quantified using Deeks' method.

Results A total of 11 studies were included for analysis. The pooled detection rate for sentinel lymph node mapping was 91% (80–98%). Covariates significantly influencing the pooled detection rate were having colon cancer (estimate: 1.3001; 1.114 to 1.486; $p < 0.001$) and the usage of a laparoscopic approach (estimate: 1.3495; 1.1029 to 1.5961; $p < 0.001$). The performance of Indocyanine green for the detection of metastatic lymph nodes yielded an area under the roc curve of 66.5%, sensitivity of 64.3% (51–76%), and specificity of 65% (36–85%).

Conclusions Indocyanine green for the detection of sentinel lymph node mapping demonstrates better accuracy when used in colonic cancer and by a laparoscopic approach. Nevertheless, its overall performance for the detection of lymph node metastasis is poor.

Keywords Systematic review · Meta-analysis · Indocyanine green · Indocyanine green · Colorectal cancer · Sentinel lymph node mapping

In colorectal cancer, the removal of the tumor along with the lymph nodes related to the lesion is the current standard treatment. Thus, an adequate assessment of the sentinel lymph nodes during surgery is important due to the contribution it makes to the staging of the disease and its prognostic value [1–4].

Experience gained from other types of cancer, such as breast cancer, demonstrates the importance of the search for the sentinel lymph node in colorectal cancer. If the sentinel lymph node is located and proven to be positive, a complete lymph node dissection would be indicated [5–12]. This underlines the importance of a highly sensitive method that would allow us to map those sentinel lymph nodes adequately, helping us to detect the implicated metastatic lymph

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nodes. It has been suggested that a more extensive nodal dissection could help to improve the survival time of patients undergoing colorectal cancer surgery [13, 14]. Therefore, the purpose of node mapping does not fall only on the detection of the sentinel lymph node, but also in identifying the vast majority of lymph nodes with suspected metastases in order to perform a limited lymphatic dissection.

For several years, Indocyanine green has been widely employed as a secure and easy technique for node mapping in patients with multiple types of cancer [3, 5, 6, 11]. Still, due to the heterogeneity found in published studies, the usage of Indocyanine green has not been fully implemented for all procedures [9, 15]. The objective of this meta-analysis is to evaluate the overall performance of Indocyanine green for sentinel lymph node mapping and mapping of node metastasis in patients undergoing colorectal cancer surgery.

Methods

Eligibility criteria, information sources, search strategy

An extensive systematic search was performed using databases PubMed, ISI Web of Science, and SCOPUS to identify relevant studies published in English and Spanish, with no time limit restrictions, utilizing combinations of relevant MeSH term, keywords, and word variants for "Indocyanine green," "indocyanine," "colorectal neoplasms," "colorectal," "cancer," "colonic," "colonic cancer". Other sources were manually searched for potentially relevant published studies. The first search was run on December 5th, 2017. Afterward, an update was extended until January 2019. No institutional research board approval nor informed consents are needed for systematic reviews and meta-analysis in our institution.

This review was done adhering to the recommendation on "Synthesizing Evidence from Diagnostic Accuracy Test (SEDATE) guidelines" [16] and PRISMA [17] guidelines for systematic reviews and meta-analysis. The study protocol was agreed between the authors, and one of them (A.L) being external to the group acted as a reviewer of it. Also, before running the analysis, the protocol was registered at the prospective international registry of systematic reviews (PROSPERO: CDR42018084841).

All abstracts identified were assessed by two independent evaluators (E.V. and J.J.), both blinded to authorship, authors' institutions, and study results. Studies meeting inclusion criteria were full-text reviewed. The external author (A.L.) independently resolved any disagreement between evaluators. In cases of relevant studies with missing information, corresponding authors were reached by email. Annex 1 in the supplementary material details the search strategy and query syntaxes.

The primary endpoint of this review was to assess the performance of Indocyanine green for sentinel lymph node mapping, defined as the staining of the sentinel node that was confirmed by direct observation during the surgical procedure. The secondary endpoint was to evaluate the performance of Indocyanine green for the detection of lymph node metastasis.

Study selection

Criteria for inclusion in this systematic review were observational studies and case series of patients with colorectal cancer undergoing open or laparoscopic surgery using Indocyanine green injection as the primary technique for sentinel lymph node mapping. Exclusion criteria were studies with less than five patients, no adequately described surgical procedure, studies evaluating other types of cancer differently than colorectal cancer, reviews, and studies with not enough information to obtain the 2×2 tables.

Data extraction

The following data were extracted on a datasheet: author, year of publication, country where the study was conducted, study design, original inclusion criteria, exclusion criteria, total number of patients included in the study, mean age at surgery, number of lymph nodes detected by indocyanine green, In vivo or ex vivo assessment of the nodes, number of metastatic lymph nodes identified at histological analysis, type of near-infrared light and camera used for node mapping, latency time from Indocyanine green injection to the observation of the sentinel lymph node, and the surgical technique performed.

Quality assessment

Two reviewers (D.G.G. and F.P.R) independently assessed the quality of the selected studies. Quality assessment was carried out using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool. This tool evaluates the quality of the included studies concerning biases affecting their applicability in four principal branches: patient selection, index test, reference standard, and flow and timing [18]. Results from these questions were graphed and assessed using Review Manager.

Statistical analysis

For the primary outcome, a single proportion meta-analysis with Arcsine transformation for small studies was performed using random effects modeling (weighting by the inverse of the variance). Between-study heterogeneity was assessed using tau^2, χ^2 (Cochrane Q), and I^2 statistics. Results were

presented using forest plots. For the secondary outcome, each article extracted information that was used to produce a 2×2 table for calculation of sensitivity and specificity [18, 19]. Obtained results were pooled in a meta-analysis using hierarchical summary receiver–operating characteristics (hSROC) curve. The model was fitted using a generalized linear mixed model approach that corresponds to the empirical Bayes fitting for the HSROC model [20–22]. Results were presented using pooled sensitivity, specificity, positive and negative likelihood ratios, and hSROC curves. Between-study heterogeneity was visually assessed using the Galbraith plot (Diagnostic log odds ratio against the inverse of the sensitivity) to visually identify outliers [23]. A formal investigation of heterogeneity was performed using various meta-regressions to evaluate the contribution of several covariates on the pooled detection rate and sensitivity. The possibility of publication bias was assessed using Deeks' funnel plot asymmetry test [25, 26], where $p < 0.05$ was considered as significant asymmetry [24, 25]. All statistical analysis was conducted using the Meta-Analysis of Diagnostic Accuracy (mada) package [R project] [18, 19], MIDAS [26], and METANDI [27] from STATA v.15.0 (Texas College Station).

Results

Study selection

A total of 282 studies were identified by database searching, with three additional studies included manually (Fig. 1). Of them, 25 studies were eligible for full-text review. After

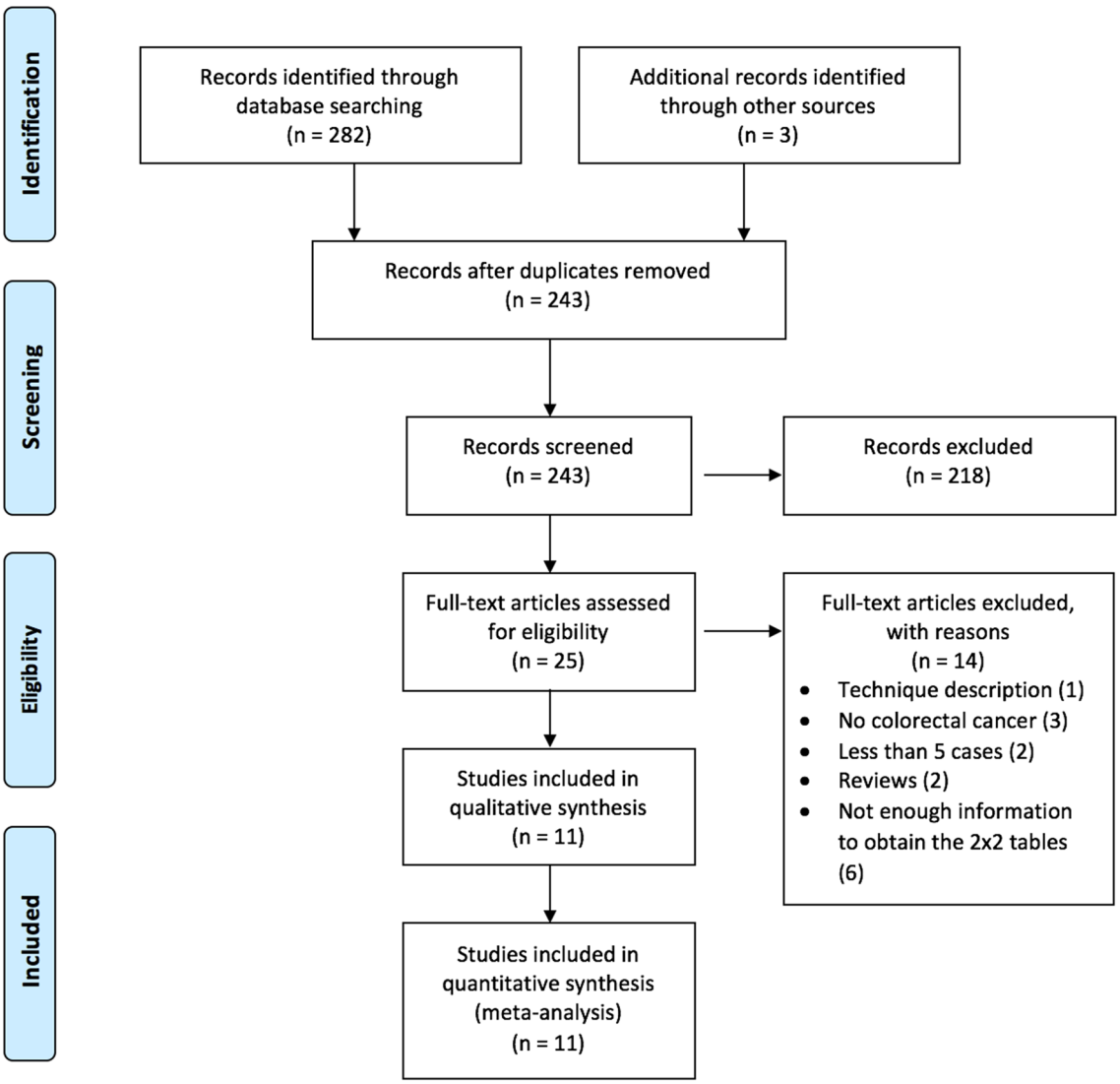

Fig. 1 PRISMA flow diagram for selected studies

review, 11 studies were retained for analysis [28–38], while 14 papers were excluded due to the following reasons: One of them because the technique used for surgery was not clear [39], three of them were about types of cancer other than colorectal cancer [40–42], two had less than five cases [43, 44] and two more were reviews [15, 45], and six of them because there was not enough information to obtain the 2 × 2 tables needed for analysis [3, 46–50]. The attributes of the included articles are portrayed in Table 1. Annex 1 details the full search strategy.

Risk of bias of the included studies

Among the 11 included studies [28–38], author's judgement for risk of bias depicted high risk of bias in six studies according to patient selection [29, 32–36], while two more had high risk of bias according to the index test [33, 38] and one more in the reference standard [38]. Only four studies showed an unclear risk of bias according to the reference standard [28, 32, 33, 35]. Supplementary Figs. 1 and 2 tabulates the risk of bias of the studies included in the meta-analysis according to the QUADAS-2 tool for diagnostic test accuracy reviews [51].

Synthesis of results

Eleven studies [28–38] were selected for this systematic review and meta-analysis adding up to 281 patients that underwent surgery because of colorectal cancer. Participant's age at surgery was 66.5 (SD 4.3) years. The mean number of retrieved lymph nodes per patient was 11, ranging from 2 to 23, while the number of metastatic lymph nodes detected by HE staining during histological examination was 4.6 (SD 4.2). The mean latency period from Indocyanine green injection to the node mapping was 39.4 min, ranging from 6 to 152 min. From the 281 patients that were included, 36% (102/281) underwent open colorectal cancer surgery (laparotomy), 39% had laparoscopic surgery, and 25% of the patients had no specification on which technique was used for surgery.

Indocyanine green for sentinel lymph node mapping

Detection rates were obtained from the 11 eligible studies [28–38]. The weighted detection rate by random effects model using Indocyanine green staining for sentinel lymph node mapping was 91% (95% CI 80–98%). Figure 2 shows the forest plot for the individual and overall detection rates. There was a high between-study heterogeneity ($I^2 = 87\%$; $T^2 = 0.06$; $p < 0.01$). Bias quantification by Egger method showed significant publication bias among studies (−3.77; −6.04 to 1.51; $p = 0.003$). Nonetheless, the sensitivity analysis showed that studies rated as high quality by the QUADAS-2 scale had 0% heterogeneity and 94% detection rate (87–98%) (Fig. 3).

Meta-regressions for sentinel lymph node mapping

A meta-regression was performed to assess the influence of different variables to the pooled detection rate. The only significant variable influencing the pooled detection rate was the type of cancer, patients with colon cancer had significantly higher detection rates (estimate: 1.3001; 95% CI 1.114–1.486; $p < 0.001$) and those with rectal cancer had the lowest detection of sentinel lymph nodes at surgery (estimate: −0.3793; 95% CI −0.7534 to 0.0052; $p < 0.046$). Also, a significant positive influence was found when surgery was performed using a laparoscopic approach rather than by laparotomy (estimate: 1.3495; 95% CI 1.1029–1.5961; $p < 0.001$). Table 2 shows the calculated estimates for all variables.

Performance of Indocyanine green for the detection of metastatic lymph nodes

A total of 11 studies [28–38] had information on the total number of metastatic nodes stained by indocyanine green. The constructed hSROC curve (Fig. 4) showed an area under the curve of 66.5% with pooled sensitivity of 64.3% (95% CI 51–76%) and specificity of 65% (95% CI 36–85%). The mean positive and negative likelihood ratios were 2.0 (95% CI 1.1–3.6), and 0.59 (95% CI 0.40–0.86), respectively, resulting in a Diagnostic Odds Ratio of 3.81 (95% CI 1.3–8.2). Visual assessment of heterogeneity by Galbraith's plot depicted a low heterogeneity among studies, while Deeks' test found no significant publication bias ($p = 0.11$; Supplemental Fig. 3). Individual estimates of diagnostic performance for each study are shown in Fig. 5.

Meta-regression for the detection of lymph node metastasis

To establish the influence of all possible determinants influencing the overall sensitivity for lymph node metastasis, several meta-regressions were performed. The only two variables that influenced the pooled sensitivity were the type of cancer, where colon cancer was found to have significantly higher sensitivity compared to colorectal and rectal cancer (estimate: 0.655; 95% CI 0.548–0.762; $p < 0.001$), and the surgical approach, where the use of laparoscopy yielded higher sensitivity when compared to open surgery (estimate: 0.677; 95% CI 0.543–0.812; $p < 0.001$). Table 2 shows all calculated estimates.

Table 1 Characteristics of the included studies

Author	Year	Country	Study design	Inclusion criteria	Exclusion criteria	Patients included	Mean age at surgery	Mean Lymph nodes per patient	ICG SLNM assessment	Lymph node metastasis at histological analysis	Camera for near-infrared light	Latency time from ICG injection to node mapping	Surgical technique performed
Kusano	2008	Japan	Case series	Patients with standard colonic resection	N/S	26	70	2.4	In vivo	6	Photodynamic Eye, PDE; Hamamatsu Photonics	N/S	Laparotomy
Noura	2008	Japan	Prospective cohort	Patients with rectal cancer stage II or III	N/S	25	59.9	1.9	In vivo	7	N/S	60 min	Laparotomy
Noura	2010	Japan	Prospective cohort	Patients with rectal cancer stage II or III	N/S	25	58.4	2.1	In vivo	3	Photodynamic Eye, PDE; Hamamatsu Photonics	30 min	Laparotomy
Cahill	2012	UK	Prospective cohort	N/S	N/S	18	66.4	3.6	In vivo	14	CE approved prototype device by Olympus	N/S	Laparoscopy
Hirche	2012	Germany	Prospective cohort	N/S	N/S	26	67	1.7	In vivo	11	IC-View, Pulsion Medical Systems	3–10 min	Laparotomy
Liberale	2016	Belgium	Prospective cohort	Patients with primary Colorectal cancer undergoing cytoreductive surgery	N/S	20	70.5	6.5	In vivo	7	Photodynamic Eye, PDE; Hamamatsu Photonics	N/S	Laparoscopy/laparotomy
Liberale (2)	2016	Belgium	Prospective cohort	Patients with primary colorectal cancer	N/S	12	62.8	15.2	Ex vivo	6	Photodynamic Eye, PDE; Hamamatsu Photonics	152 min ex vivo	Laparoscopy

Table 1 (continued)

Author	Year	Country	Study design	Inclusion criteria	Exclusion criteria	Patients included	Mean age at surgery	Mean Lymph nodes per patient	ICG SLNM assessment	Lymph node metastasis at histological analysis	Camera for near-infrared light	Latency time from ICG injection to node mapping	Surgical technique performed
Watanabe	2016	Japan	Cohort	Patients with a preoperative diagnosis of colon cancer at the hepatic flexure or splenic flexure	Past history of colonic surgery, extended colorectal resection, allergic hypersensitivity to ICG, or allergic hypersensitivity to iodine	20	70.2	N/S	In vivo	4	D-Light P by Karl Storz	30 min	Laparoscopy
Andersen	2017	Denmark	Prospective cohort	Patients above 18 years old with colon cancer	Iodine allergy, poor kidney function, liver cirrhosis, pregnancy and lactation and previous major abdominal surgery	29	69	24	In vivo/ex vivo	10	SPIES ICG camera Karl Storz.	In vivo 20 min Ex vivo	Laparoscopy

Table 1 (continued)

Author	Year	Country	Study design	Inclusion criteria	Exclusion criteria	Patients included	Mean age at surgery	Mean Lymph nodes per patient	ICG SLNM assessment	Lymph node metastasis at histological analysis	Camera for near-infrared light	Latency time from ICG injection to node mapping	Surgical technique performed
Currie	2017	UK	Prospective cohort	T1 or T2 colonic cancer	T3 or T4 colon cancer, pregnant, lactating, allergy to any of the compounds being used for lymphatic mapping, hyperthyroidism, or renal insufficiency.	30	69	34	In vivo	9	CE approved prototype device by Olympus	7 min	Laparoscopy
Weixler	2017	Switzerland	Prospective cohort	N/S	Colon cancer stage IV, age < 18 years, extraperitoneal rectal cancer, prior abdominal cancer surgery, history of other malignancies, allergy to indocyanine green, pregnancy, and breast feeding	50	68.7	23.4	Ex vivo	25	Mini-FLARE	10 min	Laparoscopy/laparotomy

N/S not stated, *ICG* indocyanine green, *SLNM* sentinel lymph node mapping

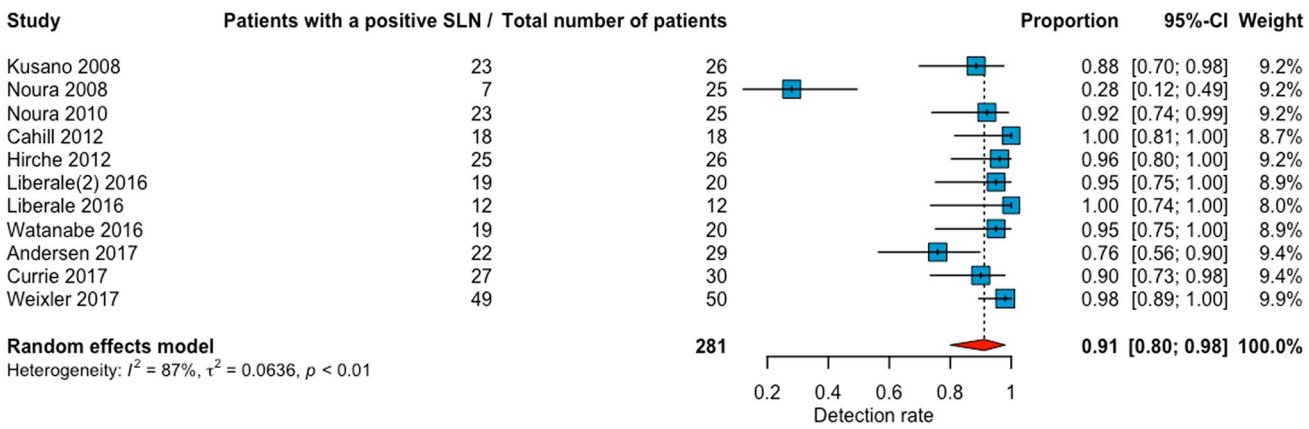

Fig. 2 Forest plot on the pooled and individual detection rates for sentinel lymph node mapping

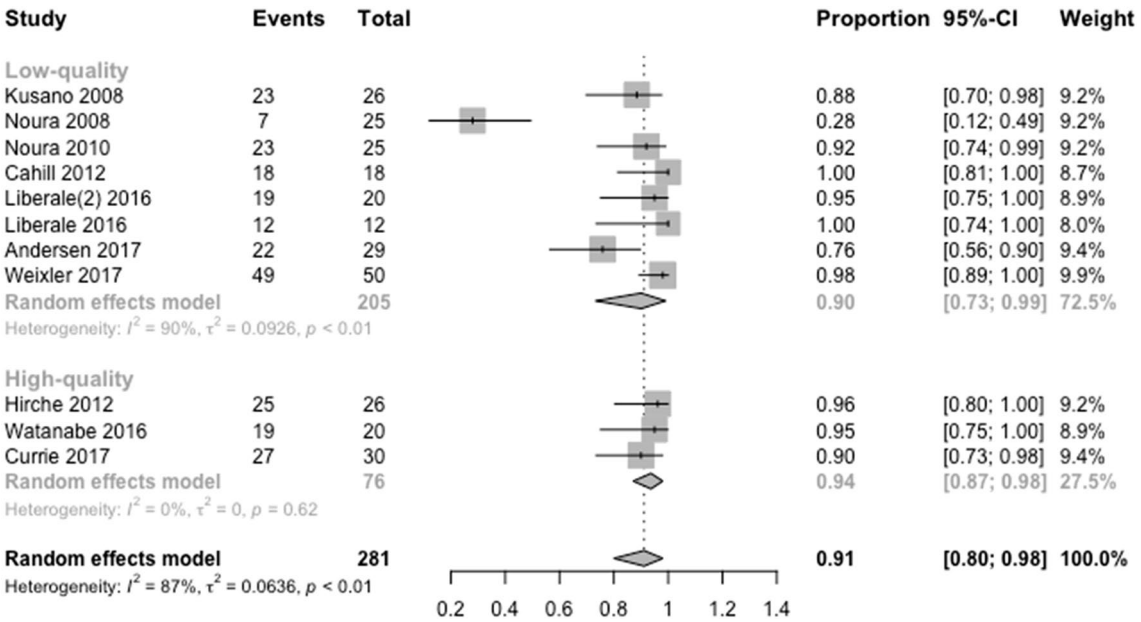

Fig. 3 Sensitivity analysis on the pooled and individual detection rates for sentinel lymph node mapping

Discussion

Main findings

There are three main findings in our analysis: Firstly, there is a 91% (95% CI 80–98%) detection rate when using Indocyanine green for the lymph node mapping. Although this yields a significant heterogeneity among studies, the sensitivity analysis showed that this would be reduced to 0% for high quality studies as evaluated by the QUADAS-2 scale, resulting in higher overall detection of lymph nodes (94% detection rate; 95% CI 87–98%). Secondly, the meta-regression analysis showed that the main cofactors influencing the detection of lymph nodes and the performance of Indocyanine green for lymph node metastasis were the type of cancer being assessed, where colon cancer yielded higher detection rates and higher sensitivity, and also, the usage of a laparoscopic approach, with higher detection rates and sensitivity compared to open surgery. And finally, an AUC of 66.5%, a pooled sensitivity of 64.3% (95% CI 51–76%), and specificity of 65% (95% CI 36–85%) showed that the overall performance of Indocyanine green for the detection of metastatic nodes is poor.

Comparison with existing literature

A previous meta-analysis conducted by Xiong et al. in 2014, found Indocyanine green to be a promising and safe technique for lymph node mapping and the detection of

Table 2 Influence of several cofactors to the overall detection rate of lymph node mapping and node metastasis

Co-factor	Estimate	95% Confidence interval		*p* val
Detection of lymph node mapping				
Mean age at surgery	0.0213	−0.0172	0.0597	0.278
Mean number of lymph nodes retrieved	0.0026	−0.0138	0.0189	0.758
Latency time	0.0007	−0.0042	0.0056	0.778
Cancer type				
Colon cancer	**1.3001**	**1.114**	**1.4863**	**<0.001**
Colorectal cancer	0.1449	−0.1875	0.4774	0.392
Rectal cancer	**−0.3793**	**−0.7534**	**−0.0052**	**0.046**
In-vivo vs. Ex vivo node mapping	−0.2725	−0.6885	0.1435	0.199
Surgical method				
Laparoscopy	1.3495	1.1029	1.5961	<0.001
Laparotomy	−0.2392	−0.6055	0.127	0.201
Sensitivity for lymph node metastasis				
Mean age at surgery	0.0109	−0.0116	0.0335	0.342
Mean number of lymph nodes retrieved	0.003	−0.0055	0.0115	0.489
Latency time	0.0005	−0.0023	0.0033	0.741
Cancer type				
Colon cancer	**0.6555**	**0.5485**	**0.7624**	**<0.001**
Colorectal cancer	0.0774	−0.1213	0.2762	0.445
Rectal cancer	−0.1998	−0.4168	0.0173	0.071
In-vivo vs. Ex vivo node mapping	−0.1827	−0.4028	0.0374	0.103
Surgical method				
Laparoscopy	**0.6777**	**0.5431**	**0.8123**	**<0.001**
Laparotomy	−0.138	−0.3356	0.0596	0.171

Bold values mean statistical significant co-factors

metastatic lymph nodes. Xiong found an overall detection rate of 96% and high sensitivity (86%) and specificity (100%) for the detection of metastatic nodes. Nonetheless, the study conducted by Xiong was performed on different types of cancer, from breast cancer to colorectal cancer. In this analysis, we aimed to assess the detection rate and the performance of Indocyanine green only for colorectal cancer to avoid bias and to accurately assess the estimates for this disease.

In 2017, Currie et al. conducted a low-biased study on 30 patients with colon cancer [30]. In this study, the authors performed the procedure using a laparoscopic approach with the usage of Indocyanine green for the mapping of the lymph nodes. From the 30 patients enrolled, successful lymph node mapping was achieved in 27 of them, yielding a detection rate of 90%. From the 27 patients with successful lymph node mapping by indocyanine green, only nine patients had positive nodes containing malignancy resulting in a 33% sensitivity and 90% specificity. These results are comparable to the ones in this study, yielding a similar detection rate (90% vs. 91%) but not similar sensitivity (33% vs. 64%).

Another recent study by Weixler et al. enrolling 220 stage I–III colon cancer patients [38] using a similar methodology found Indocyanine green to have a 98% detection rate for lymph node mapping, and a pooled sensitivity of 64% and specificity of 93% for the detection of micro-metastasis.

Clinical implications

The primary purpose of colorectal cancer surgery is to perform the excision of the tumor, followed by the removal of the lymph nodes related to it. Thus, a method with proper detection of these tumor-related nodes would be the ideal

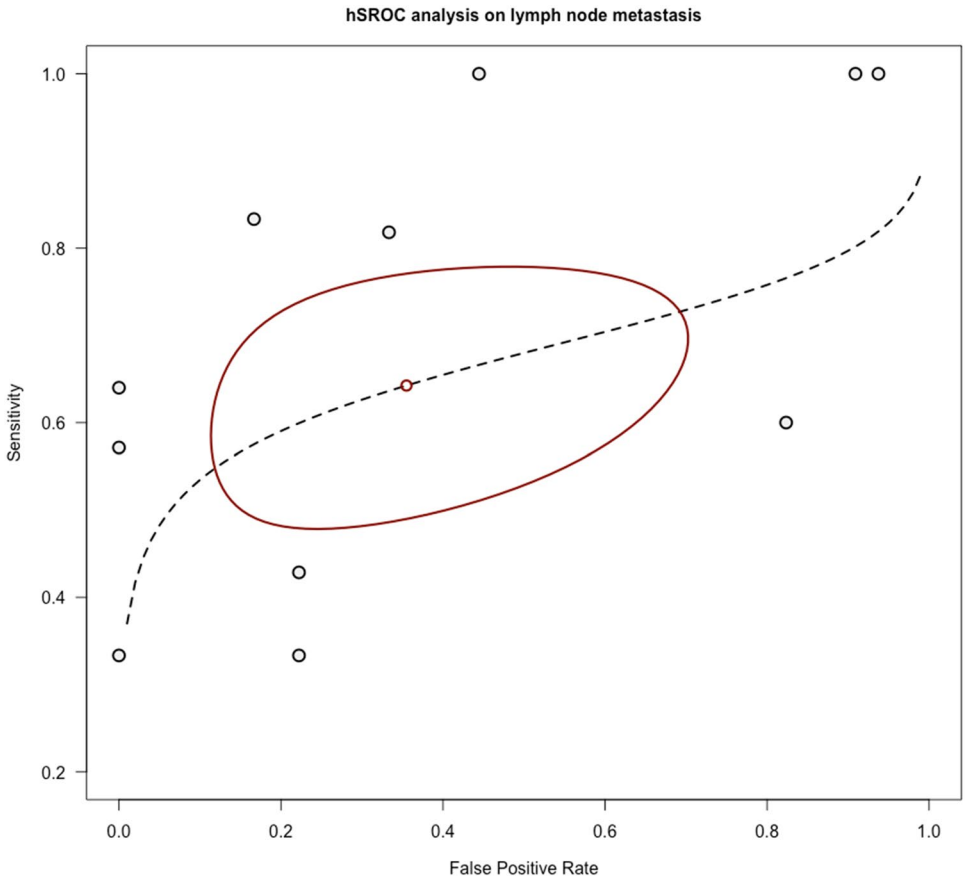

Fig. 4 Hierarchical summary roc curve analysis on the detection of lymph node metastasis

candidate for use in surgery. In this context, the results from this study suggest that the use of indocyanine green for sentinel lymph node mapping would yield good results, especially considering those higher quality studies (94%), supporting indocyanine green as a suitable method for node mapping as the primary focus of the test. This differs from the detection of node metastases, which are related not only to the sentinel lymph node itself but also to the extent of the tumor and clinical-histological classification. As for our clinical practice in Hospital Clinic of Barcelona, we have used this method for research purposes, and according to the results of this meta-analysis, we still need to gather higher quality information before incorporating this approach in our daily clinical practice.

Strengths and limitations

Our study has several strengths. Firstly, our systematic review was carried out by two independent investigators, who were blinded to authorship, hospital's name, and results, limiting the bias in selecting publications for the final analysis. Secondly, since there were no time restrictions for our search, a large number of papers were evaluated to ensure the best results for the systematic review and final analysis. We were able to analyze a total of 281 patients undergoing surgery for colorectal cancer. Finally, our statistical analysis allowed us to perform several tests to formally assess the high heterogeneity found between studies, including meta-regressions, and sensitivity analysis to show different results according to the influence of several cofactors.

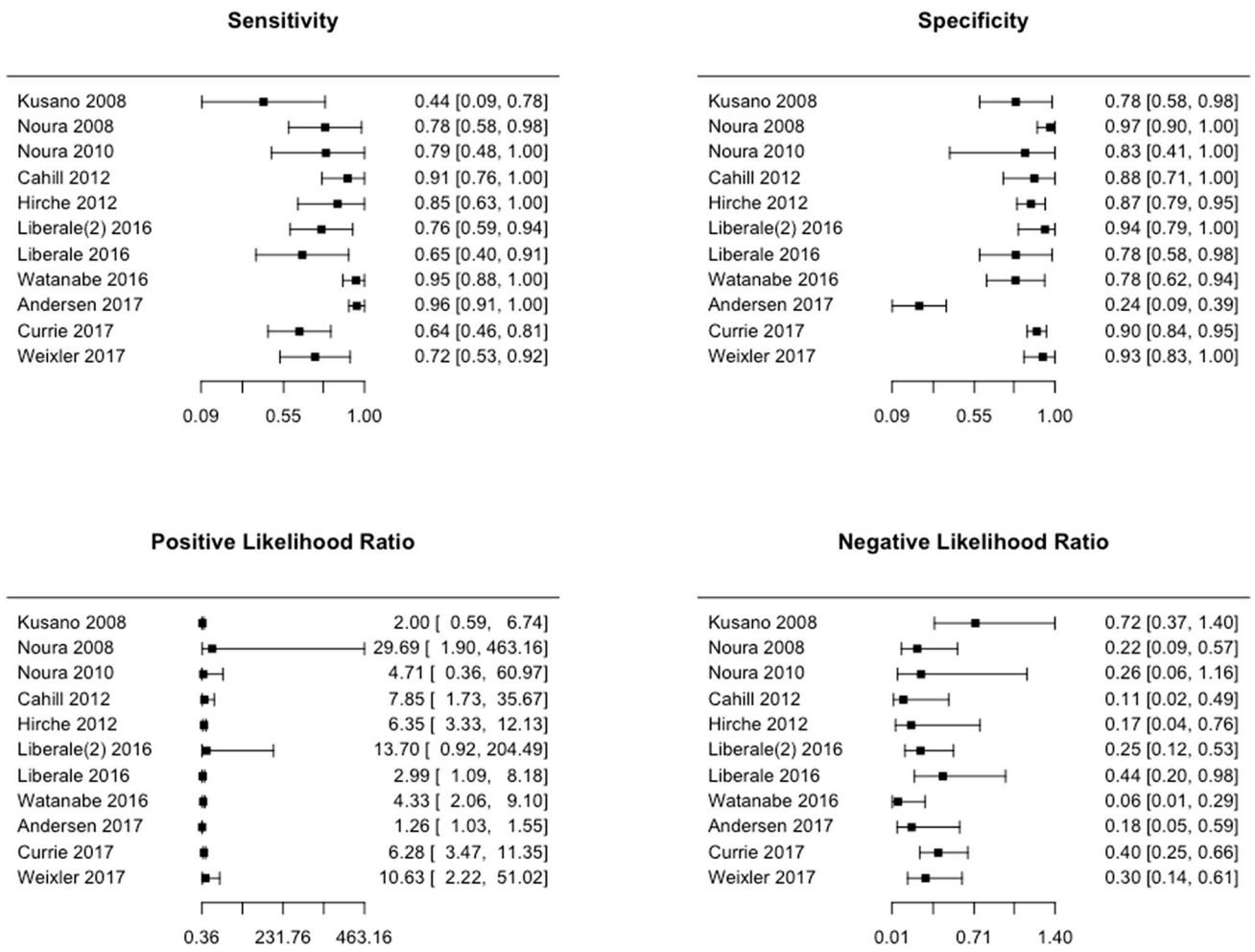

Fig. 5 Individual assessment for sensitivity, specificity, positive and negative likelihood ratios

Limitations of this study are the significant heterogeneity found between studies, which was later reduced in the case of high quality studies using the sensitivity analysis. And in the same scenario, the low number of high quality studies found in the literature could limit the interpretation of results; thus, no recommendations can be made at this stage until more information is gathered in higher quality studies.

Conclusion

Indocyanine green is a useful method for lymph node mapping when used in colorectal cancer surgery; this significantly improves in colon cancer and through a laparoscopic approach. Nonetheless, there is still a need for higher quality evidence evaluating the performance of indocyanine green in colorectal cancer; thus, no recommendations can be made from the existing literature regarding its performance and security.

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Authors' contribution All authors participated in the study. VTE, JLJ, and JVV performed the literature search and the acquisition of data. DGG and FPR performed the quality analysis for the selected studies. MPR and DLFB performed the data analysis. MPB, OPA, and LAM participated in the interpretation of data and revised the article. All authors approved the final version of the article.

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Compliance with ethical standards

Conflict of interest Antonio M. Lacy, PhD. reports grants from Medtronic, grants from Olympus Medical, personal fees from Applied Medical, personal fees from Conmed, outside the submitted work, but reports no conflicts of interests. Eduardo Villegas-Tovar, Julio Jimenez-Lillo, Valeria Jimenez-Valerio, Alejandro Diaz-Giron-Gidi, Regina Faes-Petersen, Ana Otero-Piñeiro, Beatriz Martin-Perez, Borja De Lacy, and Raigam J. Martinez-Portilla have no conflicts of interest or financial ties to disclose.

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