Sensitivity and specificity of indocyanine green near-infrared fluorescence imaging in detection of metastatic lymph nodes in colorectal cancer: Systematic review and meta-analysis

By

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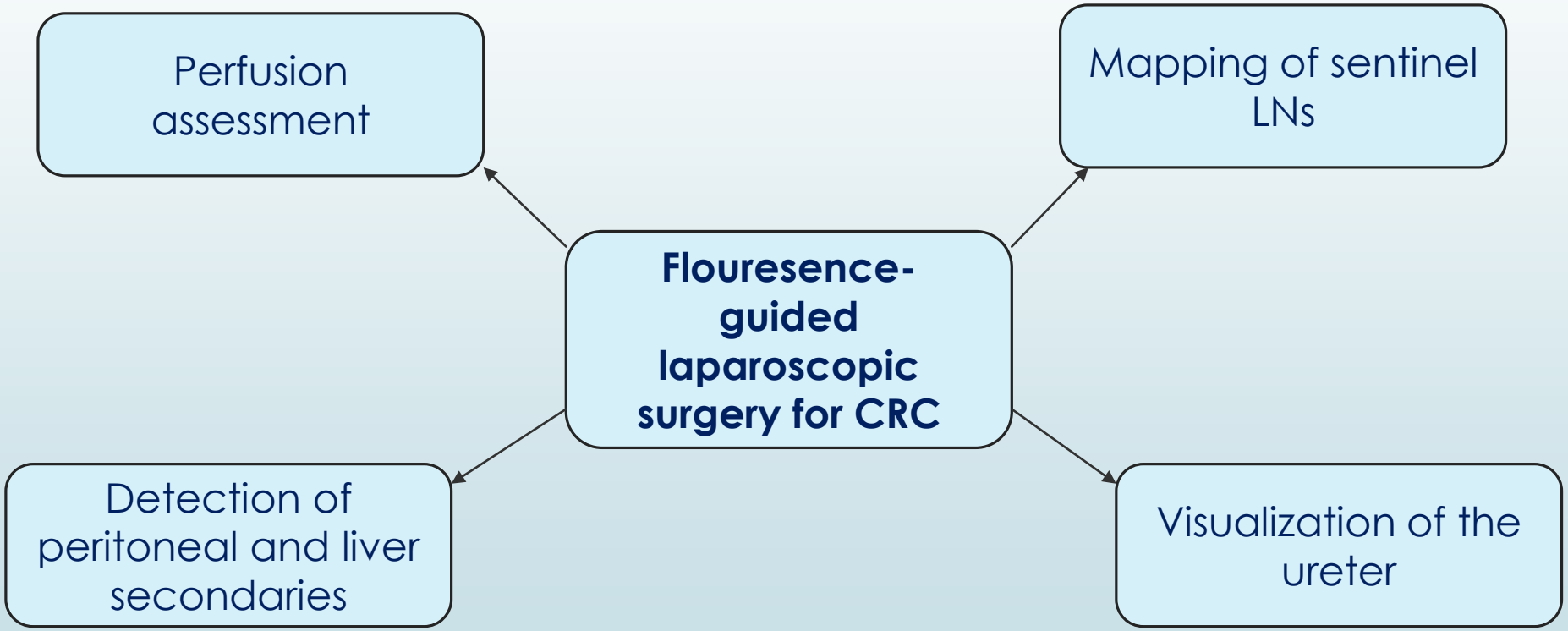
Background

- Fluorescence-guided surgery (FGS) is an imaging technique used to detect fluorescently labelled structures during surgery.
- Indocyanine green (ICG) a cyanine dye commonly used in FGS.
- It binds tightly to plasma proteins and has a half-life of 150-180 seconds.
- The fluorescence spectrum of ICG is in the near infrared (NIR) region, hence the flouresence system is called ICG-NIR fluorescence imaging

Flouresence-guided laparoscopic surgery for CRC



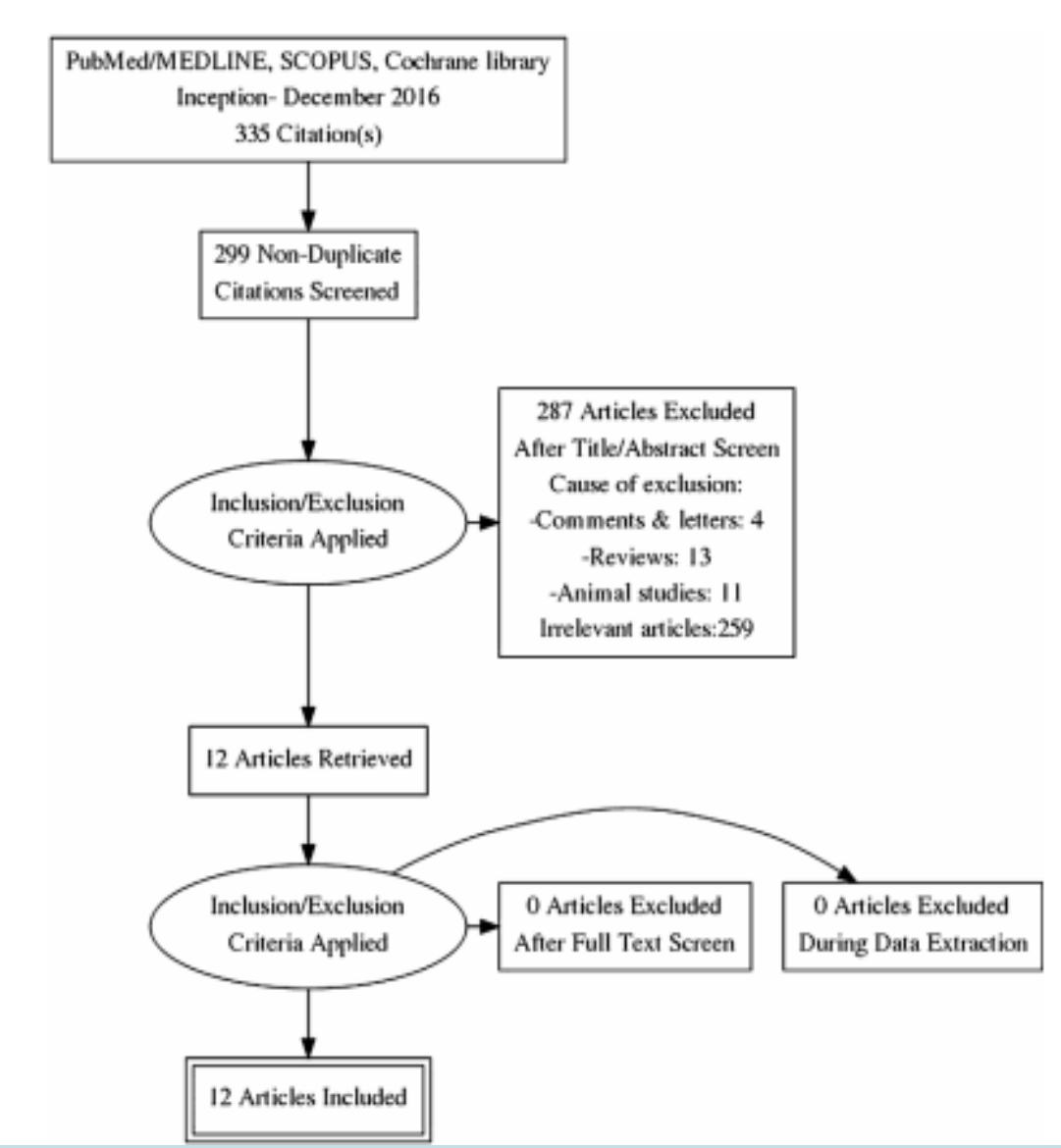
Mapping of sentinel LNs

- Detection and removal of metastatic LNs is an integral part of the radical treatment of CRC.
- Mapping of SLN can be achieved preoperatively via various imaging modalities or intraoperatively.
- SLN detection can lead to better staging of CRC and warrant the indication for adjuvant chemotherapy in some cases.
- Furthermore, SLN mapping helps recognize aberrant lymphatic patterns which may change the extent of radical lymphadenectomy

Methods

- Systematic literature search in PubMed/MEDLINE, Scopus, and Cochrane library according to PRISMA guidelines.
- Original articles in the English language that assessed the efficacy of ICG NIR fluorescence in the detection of SLN in CRC were included.
- We excluded animal studies, irrelevant articles, editorials, comments, reviews, and meta-analyses.
- Studies that did not report the technical details of ICG injection and/or NIR fluorescence technique were excluded

PRISMA flow chart



Results

- Twelve prospective case series were included in the review
- The study population comprised 248 patients of a mean age of 66.3 years.
- There were 129 (52%) males and 119 (48%) females with a mean BMI of 25.8 Kg/m2.
- 58% of patients had an early stage (TNM I/II) CRC and 42% had stage III/IV CRC.
- The percentage of patients with early stage CRC varied among the studies from 30 to 100% (median = 41%)

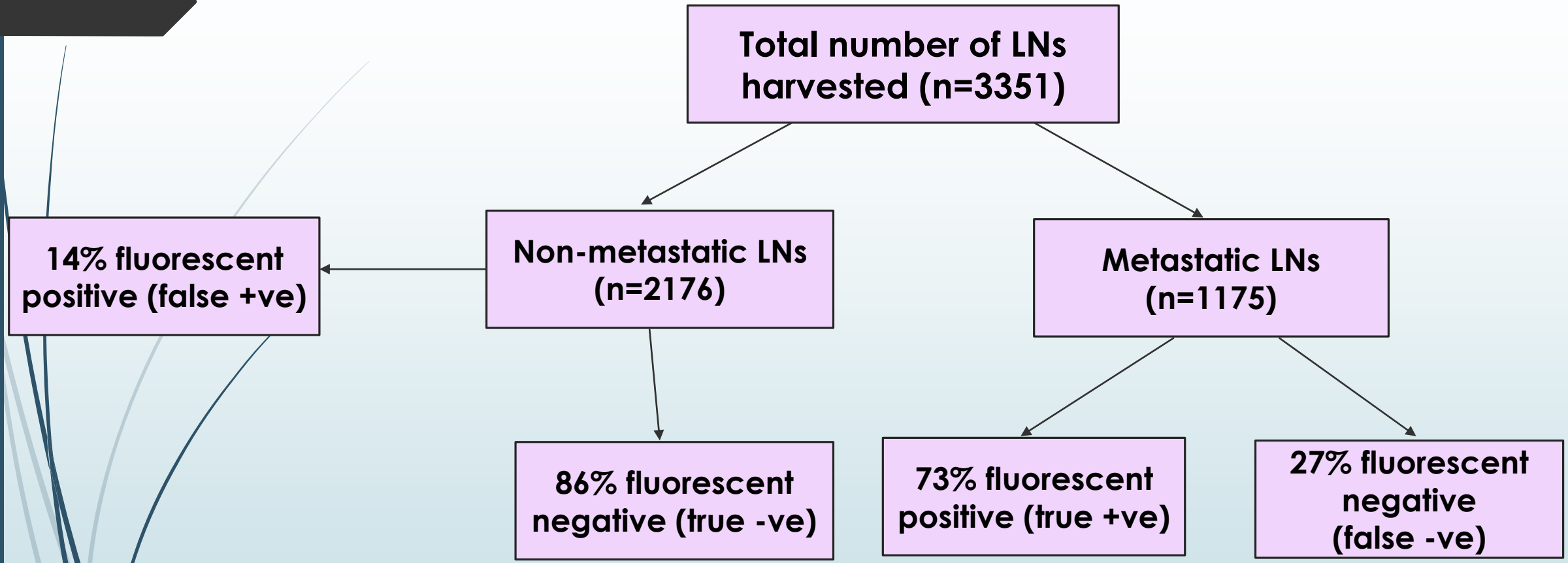
Study Characteristics

Study	Period of the study	Country	No.	Age	BMI	Early stage (I/II) tumors	Location of the tumor
Watanabe et al[21]	July 2013-Jan 2016	Japan	31	67.5	23.6	31 (100%)	Splenic flexure
Liberale et al[34]	NA	Belgium	12	62.8	Na	Na	Right & left colon, rectum
Liberale et al[34]	Sept 2013-Nov 2015	Belgium	20	70.5	26.3	6 (30%)	NA
Liberale et al[24]	NA	Belgium	2	59.5	Na	0	Right & left colon
Handgraaf et al[25]	NA	The Netherlands	5	69	Na	2 (40%)	Rectum
Nishigori et al[26]	March 2013-June 2014	Japan	21	65.2	Na	8 (38%)	Right & left colon, rectum, appendix
Noura et al[27]	Jan 2007-Dec 2007	Japan	25	58.4	Na	9 (36%)	Rectum
Van der pas et al[28]	NA	The Netherlands	14	75.5	25.1	Na	Na
Hirche et al[29]	N/A	Germany	26	67	28.4	11 (42.3%)	Right & left colon, rectum
Cahill et al[30]	NA	UK	18	66.4	29.1	10 (55.5%)	Right & left colon, rectum
Kusano et al[31]	2004-2006	Japan	26	70	Na	Na	Right & left colon, rectum
Nagata et al[32]	July 2002-Dec 2004	Japan	48	63.9	22.5	37 (77%)	Right & left colon, rectum

Technical aspects

- The studies used ICG of different commercial names, with different concentrations (0.5, 2.5, 5 mg/mL) and doses (0.2-5 mL).
- Additionally, there were variations in the site of ICG injection (submucosal, subserosal, both submucosal and subserosal, and intravenous) and the timing of the injection (preoperative, intraoperative, or both pre- and intraoperative).
- Time elapsed between ICG injection and detection of fluorescent LNs by NIR light ranged between 5 min in one study, 10 min in two studies, 15 min in two studies, and 30 min in three studies .

Fluorescent Vs Pathologic Examination of LNs

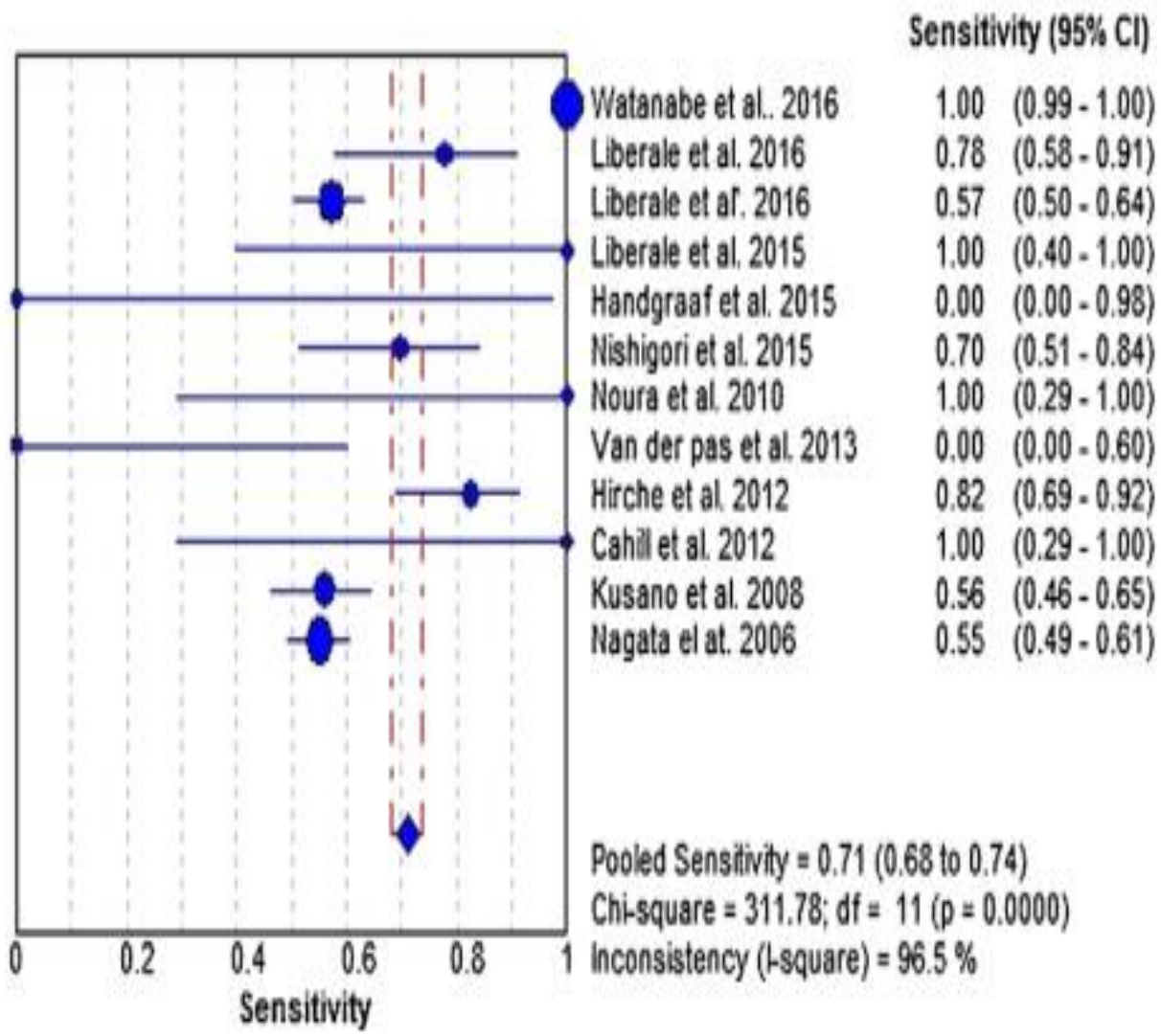


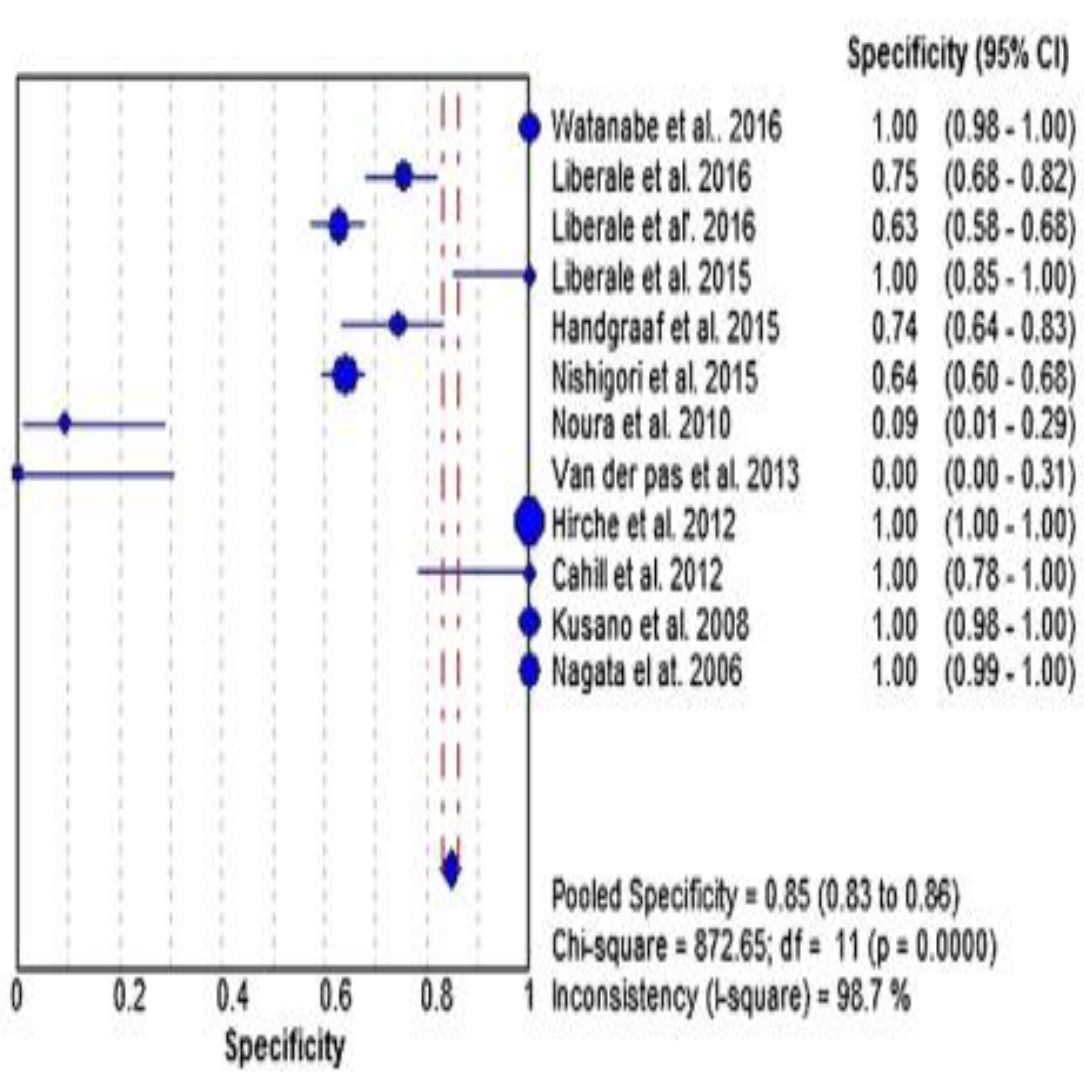
Sensitivity and Specificity of ICG NIR

- The median **sensitivity** rate for ICG fluorescence in the detection of malignant lymph nodes was 73.7, the median **specificity** rate was 100% and the median **accuracy** rate was 75.7%.

- The pooled **sensitivity** was 71% (95%CI: 68.3-73.3) with I2 = 96.8%, P < 0.0001.

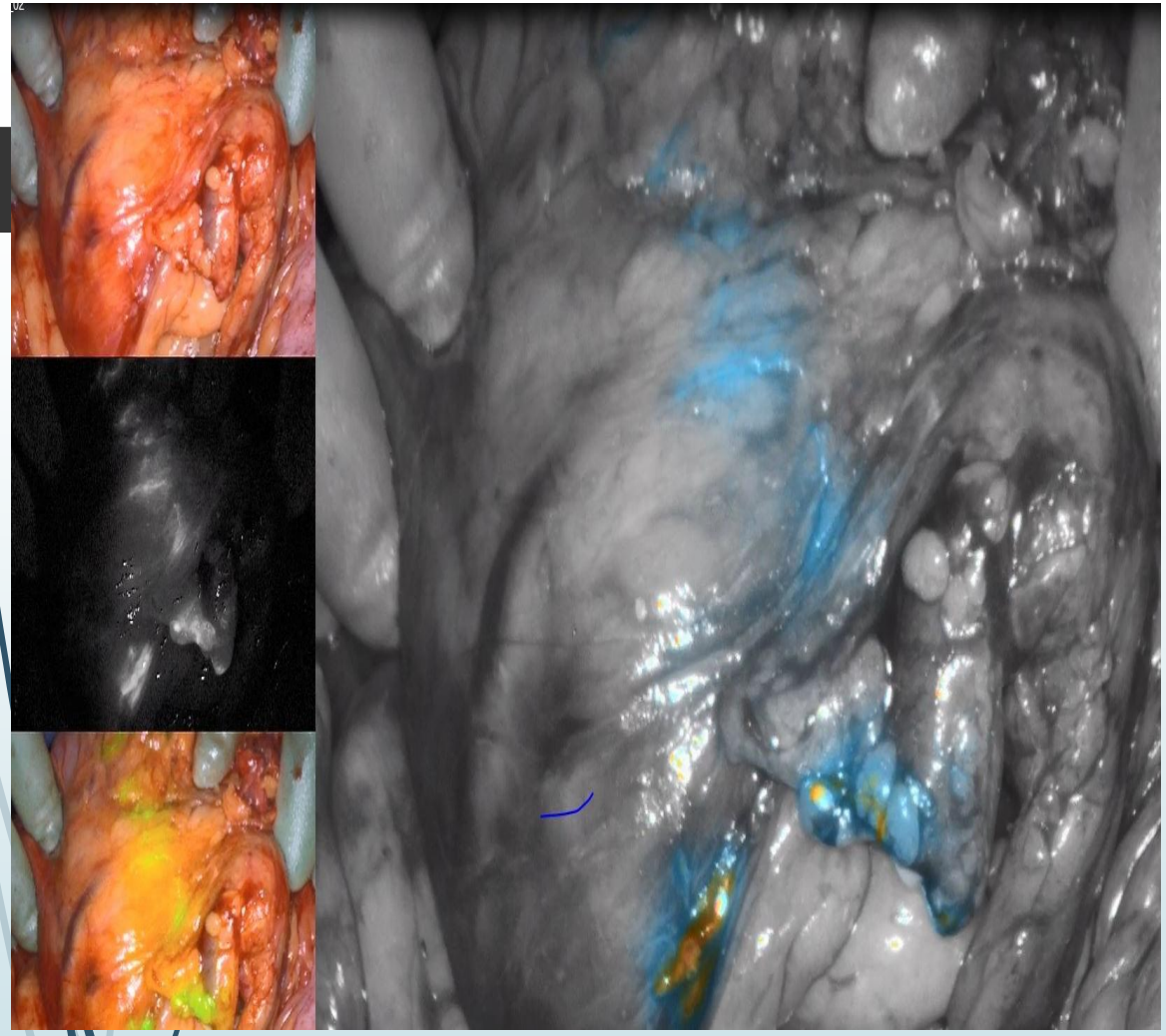
- The pooled **specificity** was 84.6% (95%CI: 83.2-86) with I2 = 96.5%, P < 0.0001.

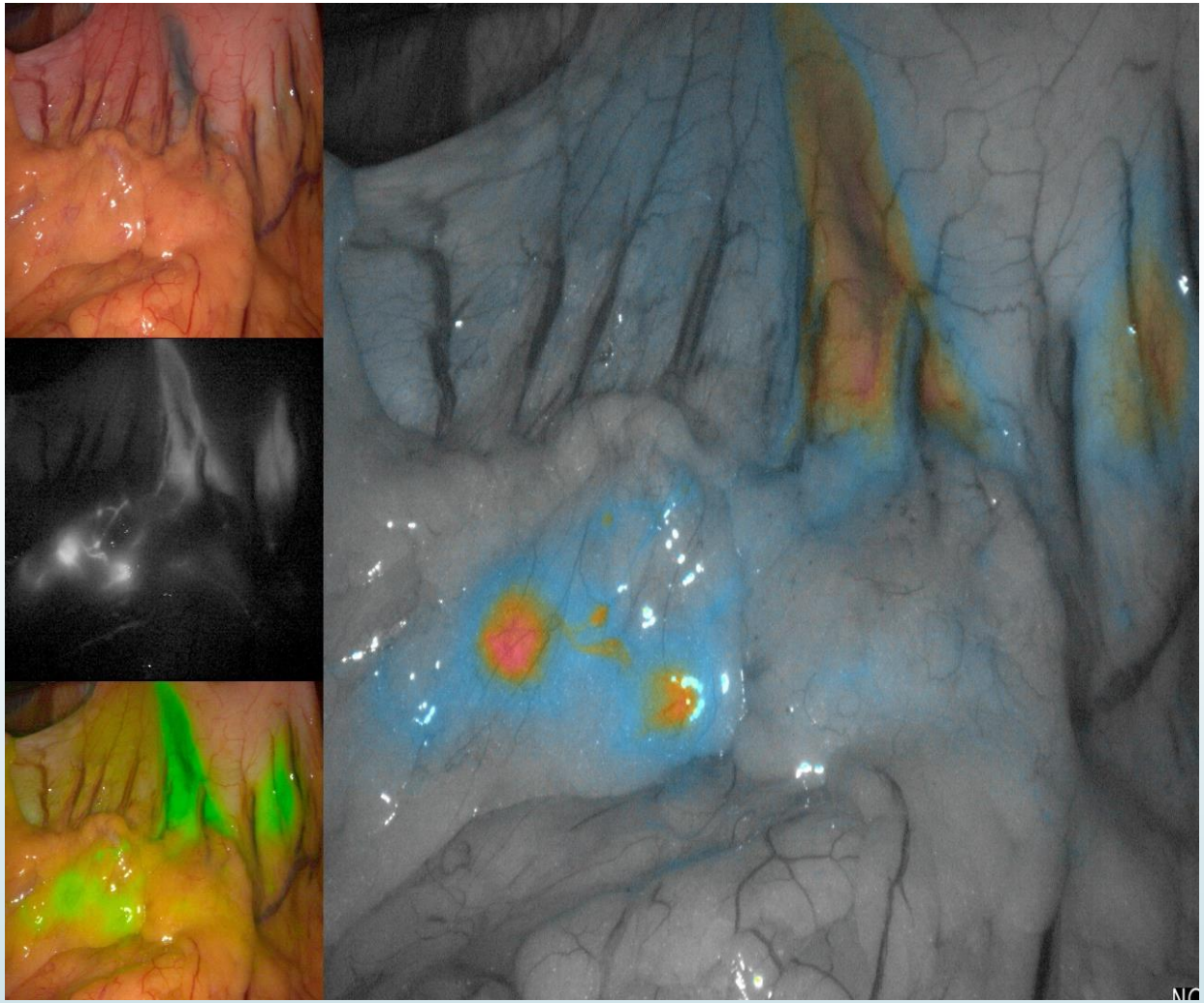

Sensitivity (95% CI)
Watanabe et al.. 2016 1.00 (0.99 - 1.00)
Liberale et al. 2016 0.78 (0.58 - 0.91)
Liberale et al'. 2016 0.57 (0.50 - 0.64)
Liberale et al. 2015 1.00 (0.40 - 1.00)
Handgraaf et al. 2015 0.00 (0.00 - 0.98)
Nishigori et al. 2015 0.70 (0.51 - 0.84)
Noura et al. 2010 1.00 (0.29 - 1.00)
Van der pas et al. 2013 0.00 (0.00 - 0.60)
Hirche et al. 2012 0.82 (0.69 - 0.92)
Cahill et al. 2012 1.00 (0.29 - 1.00)
Kusano et al. 2008 0.56 (0.46 - 0.65)
Nagata el at. 2006 0.55 (0.49 - 0.61)
Pooled Sensitivity = 0.71 (0.68 to 0.74)
Chi-square = 311.78; df = 11 (p = 0.0000)
Inconsistency (I-square) = 96.5 %
0 0.2 0.4 0.6 0.8 1
Sensitivity


Specificity (95% CI)
Watanabe et al.. 2016 1.00 (0.98 - 1.00)
Liberale et al. 2016 0.75 (0.68 - 0.82)
Liberale et al'. 2016 0.63 (0.58 - 0.68)
Liberale et al. 2015 1.00 (0.85 - 1.00)
Handgraaf et al. 2015 0.74 (0.64 - 0.83)
Nishigori et al. 2015 0.64 (0.60 - 0.68)
Noura et al. 2010 0.09 (0.01 - 0.29)
Van der pas et al. 2013 0.00 (0.00 - 0.31)
Hirche et al. 2012 1.00 (1.00 - 1.00)
Cahill et al. 2012 1.00 (0.78 - 1.00)
Kusano et al. 2008 1.00 (0.98 - 1.00)
Nagata el at. 2006 1.00 (0.99 - 1.00)
Pooled Specificity = 0.85 (0.83 to 0.86)
Chi-square = 872.65; df = 11 (p = 0.0000)
Inconsistency (I-square) = 98.7 %
0 0.2 0.4 0.6 0.8 1
Specificity

Sensitivity, specificity, and accuracy of ICG NIR fluorescence according to dose, site, and time of injection of ICG

Variable	Number of studies	Median sensitivity (%) (range)	Median specificity (%) (range)	Median Accuracy (%) (range)
Dose				
0.5 mg/mL	1	57	100	60.5
2.5 mg/mL	4	84.8 (0-100)	72.5 (0-100)	82.1 (0-100)
5 mg/mL	5	55.7 (0-100)	100 (9.1-100)	75.7 (20-99)
0.25 mg/kg	2	89 (77.8-100)	87.7 (75.5-100)	88 (75.8-100)
Site of injection				
Subserosal	5	55.7 (0-82.3)	100 (0-100)	75.7 (0-99)
Submucosal	4	84.8 (0-100)	59.7 (9.1-100)	68.8 (20-100)
Combined subserosal & submucosal	1	100	100	100
Intravenous	2	89 (77.8-100)	87.7 (75.5-100)	88 (75.8-100)
Time of injection				
Preoperative	3	100 (0-100)	74.4 (9.1-100)	73.5 (20-100)
Intraoperative	8	67.4 (0-100)	100 (0-100)	80.2 (0-100)
Preoperative and intraoperative	1	69.7	45	64.2





Courtesy of Manish Chand, Ph.D., UCL, UK

Conclusions

- ICG NIR fluorescence is a safe and promising technique for detecting metastatic LNs in CRC.
- The overall sensitivity, specificity, and accuracy of this technique vary according to a multitude of technical factors.
- Optimization of ICG flouresence SLN mapping requires further large, well-designed randomized trials comparing different techniques of ICG injection to reach valid conclusions about its ultimate clinical utility.

REVIEW ARTICLE

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Thank
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