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 fluorescence system is called ICG-NIR fluorescence imaging.
Fluorescence-guided laparoscopic surgery for CRC

- Perfusion assessment
- Mapping of sentinel LNs
- Detection of peritoneal and liver secondaries
- Visualization of the ureter
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

PubMed/MEDLINE, SCOPUS, Cochrane library
Inception: December 2016
335 Citation(s)

299 Non-Duplicate Citations Screened

Inclusion/Exclusion Criteria Applied

287 Articles Excluded
- After Title/Abstract Screen
- Cause of exclusion:
  - Comments & letters: 4
  - Reviews: 13
  - Animal studies: 11
  - Irrelevant articles: 259

12 Articles Retrieved

Inclusion/Exclusion Criteria Applied

0 Articles Excluded
- After Full Text Screen

12 Articles Included
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%)
<table>
<thead>
<tr>
<th>Study</th>
<th>Period of the study</th>
<th>Country</th>
<th>No.</th>
<th>Age</th>
<th>BMI</th>
<th>Early stage (I/II) tumors</th>
<th>Location of the tumor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Watanabe et al²¹</td>
<td>July 2013-Jan 2016</td>
<td>Japan</td>
<td>31</td>
<td>67.5</td>
<td>23.6</td>
<td>31 (100%)</td>
<td>Splenic flexure</td>
</tr>
<tr>
<td>Liberale et al³⁴</td>
<td>NA</td>
<td>Belgium</td>
<td>12</td>
<td>62.8</td>
<td>Na</td>
<td>Na</td>
<td>Right &amp; left colon, rectum</td>
</tr>
<tr>
<td>Liberale et al³⁴</td>
<td>Sept 2013-Nov 2015</td>
<td>Belgium</td>
<td>20</td>
<td>70.5</td>
<td>26.3</td>
<td>6 (30%)</td>
<td>NA</td>
</tr>
<tr>
<td>Liberale et al³⁴</td>
<td>NA</td>
<td>Belgium</td>
<td>2</td>
<td>59.5</td>
<td>Na</td>
<td>0</td>
<td>Right &amp; left colon</td>
</tr>
<tr>
<td>Handgraaf et al²⁵</td>
<td>NA</td>
<td>The Netherlands</td>
<td>5</td>
<td>69</td>
<td>Na</td>
<td>2 (40%)</td>
<td>Rectum</td>
</tr>
<tr>
<td>Nishigori et al²⁶</td>
<td>March 2013-June 2014</td>
<td>Japan</td>
<td>21</td>
<td>65.2</td>
<td>Na</td>
<td>8 (38%)</td>
<td>Right &amp; left colon, rectum, appendix</td>
</tr>
<tr>
<td>Noura et al²⁷</td>
<td>Jan 2007-Dec 2007</td>
<td>Japan</td>
<td>25</td>
<td>58.4</td>
<td>Na</td>
<td>9 (36%)</td>
<td>Rectum</td>
</tr>
<tr>
<td>Van der pas et al²⁸</td>
<td>NA</td>
<td>The Netherlands</td>
<td>14</td>
<td>75.5</td>
<td>25.1</td>
<td>Na</td>
<td>Na</td>
</tr>
<tr>
<td>Hirche et al²⁹</td>
<td>N/A</td>
<td>Germany</td>
<td>26</td>
<td>67</td>
<td>28.4</td>
<td>11 (42.3%)</td>
<td>Right &amp; left colon, rectum</td>
</tr>
<tr>
<td>Cahill et al³⁰</td>
<td>NA</td>
<td>UK</td>
<td>18</td>
<td>66.4</td>
<td>29.1</td>
<td>10 (55.5%)</td>
<td>Right &amp; left colon, rectum</td>
</tr>
<tr>
<td>Kusano et al³¹</td>
<td>2004-2006</td>
<td>Japan</td>
<td>26</td>
<td>70</td>
<td>Na</td>
<td>Na</td>
<td>Right &amp; left colon, rectum</td>
</tr>
<tr>
<td>Nagata et al³²</td>
<td>July 2002-Dec 2004</td>
<td>Japan</td>
<td>48</td>
<td>63.9</td>
<td>22.5</td>
<td>37 (77%)</td>
<td>Right &amp; left colon, rectum</td>
</tr>
</tbody>
</table>
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.
Total number of LNs harvested (n=3351)

- Non-metastatic LNs (n=2176)
  - 86% fluorescent negative (true -ve)
  - 14% fluorescent positive (false +ve)

- Metastatic LNs (n=1175)
  - 73% fluorescent positive (true +ve)
  - 27% fluorescent negative (false -ve)
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 $I^2 = 96.8\%$, $P < 0.0001$.

- The pooled specificity was 84.6% (95%CI: 83.2-86) with $I^2 = 96.5\%$, $P < 0.0001$. 
Sensitivity, specificity, and accuracy of ICG NIR fluorescence according to dose, site, and time of injection of ICG

<table>
<thead>
<tr>
<th>Variable</th>
<th>Number of studies</th>
<th>Median sensitivity (%) (range)</th>
<th>Median specificity (%) (range)</th>
<th>Median Accuracy (%) (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.5 mg/mL</td>
<td>1</td>
<td>57 (0-100)</td>
<td>100 (0-100)</td>
<td>60.5 (0-100)</td>
</tr>
<tr>
<td>2.5 mg/mL</td>
<td>4</td>
<td>84.8 (0-100)</td>
<td>72.5 (0-100)</td>
<td>82.1 (0-100)</td>
</tr>
<tr>
<td>5 mg/mL</td>
<td>5</td>
<td>55.7 (0-100)</td>
<td>100 (9.1-100)</td>
<td>75.7 (20-99)</td>
</tr>
<tr>
<td>0.25 mg/kg</td>
<td>2</td>
<td>89 (77.8-100)</td>
<td>87.7 (75.5-100)</td>
<td>88 (75.8-100)</td>
</tr>
<tr>
<td>Site of injection</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subserosal</td>
<td>5</td>
<td>55.7 (0-82.3)</td>
<td>100 (0-100)</td>
<td>75.7 (0-99)</td>
</tr>
<tr>
<td>Submucosal</td>
<td>4</td>
<td>84.8 (0-100)</td>
<td>59.7 (9.1-100)</td>
<td>68.8 (20-100)</td>
</tr>
<tr>
<td>Combined subserosal &amp; submucosal</td>
<td>1</td>
<td>100 (0-100)</td>
<td>100 (0-100)</td>
<td>100 (0-100)</td>
</tr>
<tr>
<td>Intravenous</td>
<td>2</td>
<td>89 (77.8-100)</td>
<td>87.7 (75.5-100)</td>
<td>88 (75.8-100)</td>
</tr>
<tr>
<td>Time of injection</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative</td>
<td>3</td>
<td>100 (0-100)</td>
<td>74.4 (9.1-100)</td>
<td>73.5 (20-100)</td>
</tr>
<tr>
<td>Intraoperative</td>
<td>8</td>
<td>67.4 (0-100)</td>
<td>100 (0-100)</td>
<td>80.2 (0-100)</td>
</tr>
<tr>
<td>Preoperative and intraoperative</td>
<td>1</td>
<td>69.7 (0-100)</td>
<td>45 (0-100)</td>
<td>64.2 (0-100)</td>
</tr>
</tbody>
</table>
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 fluorescence SLN mapping requires further large, well-designed randomized trials comparing different techniques of ICG injection to reach valid conclusions about its ultimate clinical utility.
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