



## PEER-REVIEW REPORT

**Name of journal:** *World Journal of Gastrointestinal Endoscopy*

**Manuscript NO:** 80187

**Title:** Endoscopic fluorescent lymphography for gastric cancer

**Provenance and peer review:** Invited Manuscript; Externally peer reviewed

**Peer-review model:** Single blind

**Reviewer's code:** 03768526

**Position:** Peer Reviewer

**Academic degree:** MD, PhD

**Professional title:** Professor

**Reviewer's Country/Territory:** Japan

**Author's Country/Territory:** Italy

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<b>Scientific quality</b>	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
<b>Language quality</b>	<input checked="" type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
<b>Conclusion</b>	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input checked="" type="checkbox"/> Major revision <input type="checkbox"/> Rejection
<b>Re-review</b>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<b>Peer-reviewer</b>	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous



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statements	Conflicts-of-Interest: [ ] Yes [ <b>Y</b> ] No
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### **SPECIFIC COMMENTS TO AUTHORS**

ICG fluorescent lymphatic mapping for gastric cancer is a recent topic. However, many of these studies are summarized from a one-sided point of view, and there is a fundamental problem. This paper summarizes these recent studies, and although it is of some value, it is, unfortunately, a one-sided review. First, the problems of ICG fluorescent lymphatic mapping for gastric cancer are listed. Fifty years ago, pioneers of gastric cancer surgery in Japan injected carbon nanoparticles and sky-blue ink into the stomach wall and regional lymph nodes during surgery to check the lymphatic flow and brush up the nodal dissection area. Thus, the range of D2 was established, the paraaortic lymph nodes were classified, and nodal dissection procedures were developed. The recently introduced ICG fluorescent navigation in lymph node dissection for gastric cancer is merely a revival of dye staining 50 years ago. Therefore, ICG fluorescent lymphatic mapping is unlikely to provide new insights except in sentinel node biopsy for early gastric cancer. ICG is just a dye. It has no tumor affinity. Since it is not a particle, it does not stay long in the lymph nodes. ICG can flow anywhere along with the lymphatic stream. In my experience (over hundreds of ICG fluorescent navigation surgeries), at your concentration and method of administration, the paraaortic lymph nodes must have fluorescence if you mobilize the duodenum. Is it necessary to dissect these nodes? When lymph node metastasis is advanced, the lymph vessels become obstructed, and the tracers cannot enter the metastatic nodes. This phenomenon is common in breast cancer sentinel node biopsy. Lymph nodes without fluorescence are not considered unnecessary for dissection. If the ICG fluorescence observations seem to increase the accuracy of the dissection, it is simply that the reporter's nodal dissection was less accurate. The increase in the number of dissected nodes with ICG fluorescence



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is simply due to inexperience in harvesting the nodes. ICG fluorescence facilitates lymph node pick-up at ease. If this improves survival outcomes, it is merely an observation bias of stage migration. Fluorescence observation varies considerably depending on the sensitivity of the equipment. In the latest device, the intensity of fluorescence can be adjusted. In other words, fluorescence observation is an analog element, and good results cannot be obtained unless the equipment and the observation method are strictly specified in the protocol. Next, I would like to address your misunderstanding of sentinel node mapping in your article. There are three methods of ICG mapping: naked eye observation under white light by Hiratsuka and Ichikura, Infrared light observation (IREE) by Nimura and Takahashi, and ICG fluorescent mapping (NIFI) by Kusano and Kinami. The three are entirely different methods and must be distinguished. Hiratsuka's method has poor contrast and is no longer used at all. Nimura's IREE is excellent, but this device is made by only Olympus and is no longer commercially available. Only ICG fluorescent mapping is currently performed. Your article should only deal with ICG fluorescent mapping. Sentinel node mapping for gastric cancer is a difficult technique that requires a learning phase of more than 30 cases, and good results cannot be obtained unless appropriate indications are followed. Therefore, meta-analysis is of little value. A multicenter prospective study in which only specialists participate and adhere to a strict protocol is essential. Only the SNNS study by Kitagawa and SENORITA in South Korea meet this criterion. The standard gastric cancer sentinel node biopsy method is a combination mapping with RI colloid and blue dye. ICG fluorescent mapping is only an alternative. The clinical application of sentinel node biopsy for gastric cancer must overcome the problem of rapid intraoperative diagnosis of micrometastasis in the sentinel node. The lymphatic basin dissection method has been proposed to overcome this problem and is regarded as the standard method. Without mentioning this, the consideration of sentinel node biopsy for gastric cancer is



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insufficient. Finally, I would like to address some points that could be improved in your review. As a general trend, the understanding of gastric cancer sentinel node biopsy is outdated, and there is a lack of critical verification of the significance of mapping for advanced gastric cancer. This makes the impression of the article one-sided and not up-to-date. The definition of the sentinel lymph node is incorrect. A sentinel node is defined as the node that receives lymphatic flow directly from a primary tumor. Feasibility studies of the sentinel node concept for gastric cancer have been conducted for a long time. Koichi Miwa was the first investigator for this in the world, with the first case in 1993 and the first paper in 1995. The multicenter prospective study is more important than meta-analysis in gastric cancer sentinel node biopsy. It is better to read the JCO paper by Kitagawa. RI mapping is a standard method and is still widely used today. ICG fluorescent mapping should be recognized as an alternative without large prospective studies. ICG fluorescence for lymph node detection and mapping in gastric cancer has been reported frequently, but it should be noted that more surgeons question its significance. Mapping is unnecessary if accurate lymph node dissection and careful harvesting are performed. On the other hand, the establishment of the sentinel node concept for gastric cancer, how to overcome the problems, and the safety of clinical application have already been sufficiently proven. Although the results of JCOG0302 are important, its shortcomings have been overwhelmed with the lymphatic basin dissection method, and this is only an old study. The superiority of function-preserving surgery guided by sentinel node biopsy has also been well demonstrated. See reports by Isozaki, Okubo, and Kinami, as well as the latest paper of SENORITA.



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<b>Language quality</b>	<input checked="" type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
<b>Conclusion</b>	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input checked="" type="checkbox"/> Major revision <input type="checkbox"/> Rejection
<b>Re-review</b>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<b>Peer-reviewer</b>	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous



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statements	Conflicts-of-Interest: [ ] Yes [ <b>Y</b> ] No
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### **SPECIFIC COMMENTS TO AUTHORS**

The manuscript entitled "Endoscopic fluorescent lymphography for gastric cancer" provides a profile of current progress of ICG guided gastric oncologic endoscopic surgery. It is a topic of interest to the researchers in the related areas but the paper needs improvement before acceptance for publication. my detailed comments as follows: 1. What's new in this manuscript? The ICG guided gastric oncologic surgery has been reviewed a lot. 2. The manuscript demonstrates the worry of cancer control because of false negative SLNs. Is there any methods to avoid the false negative SLNs or any factors related to it? Please provide evidences of related literatures. 3. The manuscript presents little clinical practice of endoscopic fluorescent lymphography for gastric cancer. More paragraphs should be added to elucidate the current practice of lymphography guided by ICG.



## RE-REVIEW REPORT OF REVISED MANUSCRIPT

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<b>Scientific quality</b>	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
<b>Language quality</b>	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
<b>Conclusion</b>	<input type="checkbox"/> Accept (High priority) <input checked="" type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
<b>Peer-reviewer statements</b>	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No



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#### **SPECIFIC COMMENTS TO AUTHORS**

I confirmed the revised content of the article. This revision includes favorable contents regarding the position of ICG fluorescent mapping in gastric cancer sentinel lymph node biopsy (SNB), recent advances in SNB, prospects, and some doubts about the significance of ICG mapping in advanced gastric cancer. This becomes now an impartial review, and it can be evaluated that the academic value has increased from Grade C to Grade B. Although the author's opinion differs from mine in some respects, their insights from the author's experience are important, and I have no further comments to add. I thank you for making the appropriate corrections. I think that this article is worthy of publication with this revision.