Received: 23 January 2020 | Accepted: 8 February 2020

DOI: 10.1002/jso.25874

HOW I DO IT

Journal of SURGICAL ONCOLOGY WILEY

Real-time near-infrared fluorescence imaging mediated by blue dye in breast cancer patients

Lili Jiang MM | Taiyuan Liu MM | Xuan Wang MM | Jun Li MD | Haidong Zhao MD, PhD

Department of Breast Surgery, Second Affiliated Hospital of Dalian Medical University, Dalian, Liaoning, China

Correspondence
Jun Li, MD and Haidong Zhao, MD, PhD, Department of Breast Surgery, Second Affiliated Hospital of Dalian Medical University, 467, Zhongshan Road, Shahekou District, Dalian, Liaoning 116023, China.
Email: dyeylj@hotmail.com and z.hddl@hotmail.com

Abstract

Background: Near-infrared (NIR) fluorescence imaging has recently been introduced to the sentinel lymph node (SLN) mapping because of the benefits of the SLN biopsy, such as providing real-time and high-resolution optical guidance. Methylene blue is available and less expensive as an SLN mapping tracer. Our study aims to identify SLN through the NIR fluorescence imaging system mediated by blue dye.

Methods: Early-stage breast cancer patients were prospectively enrolled. All participants received a subareolar or peritumoral injection of 1 mL methylene blue (MB) before surgery. The MB fluorescence system was set immediately after injection. SLNs were searched and removed under the guidance of fluorescence and blue dye.

Results: We identified SLN adequately with the help of real-time lymphography and blue dye. Symbolic lymphatic drainage patterns were also observed.

Conclusion: NIR fluorescence imaging mediated by blue dye has benefits on the identification of lymph vessels, the location of SLN, and the patterns of breast lymphatic flow.

KEYWORDS

breast cancer, methylene blue, near-infrared fluorescence, sentinel lymph node

Near-infrared (NIR) fluorescence imaging has gathered significant interest in sentinel lymph node (SLN) detection of various cancer types.[1,2] It has several characteristics to the benefit of the SLN biopsy, including noninvasive, hypotoxicity, as well as real-time, high-resolution optical guidance. Moreover, those real-time, high-resolution images provide clear identification of lymphatic channels, which has shown to be conducive to the visualization of the lymphatic drainage pathway and position of the SLN.[3,4] There have been several studies investigating NIR fluorescence imaging in SLN biopsy of breast cancer patients and receiving reasonable expectations.[5,6]

Indocyanine green (ICG) is currently being validated clinically as a NIR dye and provides potential benefits and drawbacks associated with low molecular weight contrast agents.[7] Methylene blue (MB), which is a lower molecular weight contrast agent, can be taken up and transported quickly throughout the lymphatic vessels, usually is used as a blue dye. Research has indicated MB is also a fluorophore, as same as ICG.[8] It emits light in the NIR range (~700 nm) after being excited. It is worthy of being mentioned that the fluorescence from MB has a relatively higher penetration into living tissue (up to 10 mm) because MB does not bind to albumin, compared with fluorescence from ICG (up to 5 mm). Therefore, it can be seen across the skin and fatty tissue clearly (Video S1). Due to higher absorption, MB causes less fluorescent contamination than ICG, which is suitable for observation.

As a result of the above, the NIR fluorescence imaging system mediated by blue dye was evaluated (Figure 1). NIR fluorescence imaging system utilizes a light spectrum with wavelengths between 650 and 850 nm. Fluorophores are excited and fluorescence in the NIR spectrum is captured by hand-held NIR probe. The dynamic video of NIR fluorescence is acquired and displayed simultaneously in real-time on the monitor.

In our study, we intend to use this system to discriminate SLN in breast cancer patients. In this letter, we describe our early experience of using this novel technique.

FIGURE 1 Near-infrared fluorescence imaging system mediated by blue dye, which is composed of a computer, a monitor screen, and a hand-held probe for exciting near-infrared light [Color figure can be viewed at wileyonlinelibrary.com]

This study was approved by the Ethical Committee of the Second Affiliated Hospital of Dalian Medical University and was registered as the Chinese Clinical Trials Registry No. 1900022745. All participants were diagnosed with early-stage breast cancer and signed informed consent. All procedures strictly followed the Helsinki Declaration guidelines. Before surgery, a total of 1 mL MB (Jiangsu, China) was injected at four sites around the areola or tumor after anesthesia administration. MB fluorescence was detected by a hand-held fluorescence detector and was projected to a screen for visualization. Real-time and percutaneous lymphatic drainage was observed. Draw the lymphatic drainage pathway by following the fluorescent signal on the surface. Remove the fluorescent and/or blue-dyed lymph nodes. The specific steps were showed in Video S1.

NIR fluorescence imaging mediated by MB could provide both preoperative guidance with fluorescence and intraoperative direction with blue-dyed lymphatics (Figure 2). Surgeons could identify SLN easily guided by a real-time lymphography visible across the skin. Besides, we found two remarkable points. First, we noticed that the MB could flow to axilla smoothly from injection sites without massage, but massage will accelerate lymphatic drainage. Second, as a result of efficient migration in lymphatic vessels, MB could reach SLNs within 5 minutes. The above points were entirely different from the Chinese guidelines of SLN biopsy with the dye method. To solve existing problems, our extensive clinical trial is in progress.

Moreover, interesting lymphatic drainage patterns from the breast to SLN have been found with the visualization of lymph vessels and SLNs. To make this easier to follow, we labeled as type A, B, C, D. Type A (Video S2) represented a direct drainage from areola to axillary nodes without any branches; type B (Video S3) showed that lymph flowed to the internal mammary and/or infraclavicular regions as the first station, eventually reached axilla; type C (Video S4) indicated lymph around the tumor flowed to the axilla after integrating with subareolar lymph collecting vessels. Moreover, we found an entirely different drainage pathway from the areola or peritumor region to the axilla in type D (Video S5). Anatomically, type A corresponds with studies by Turner-Warwick, and type C could be interpreted by Sappey's theory of subareolar plexus of lymphatics.[9] As acknowledged, SLN was defined as the first node or nodes to which lymph drainage and metastasis from breast carcinoma occur.[10] It commonly locates at the axilla, also could be behind the pectoralis minor muscle or at infraclavicular, or maybe an intramammary node,

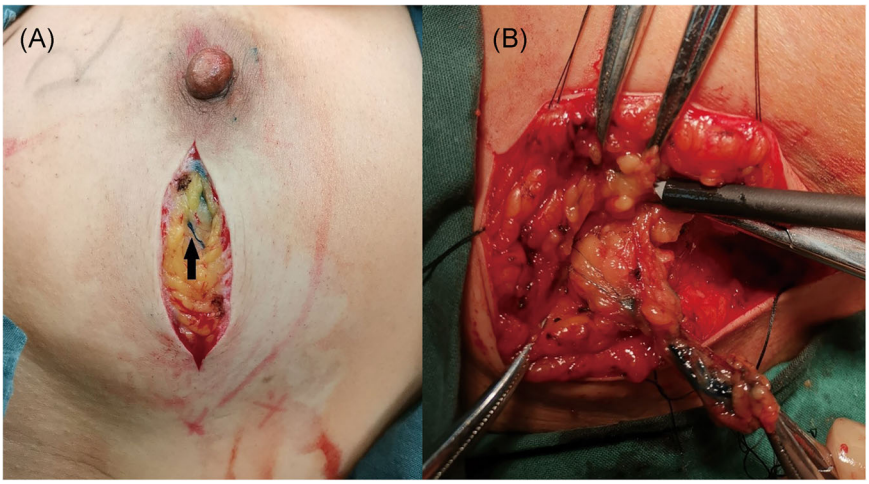

FIGURE 2 A, Blue-dyed subcutaneous superficial lymphatic vessel. B, The blue-dyed lymph nodes and vessels connecting to nodes [Color figure can be viewed at wileyonlinelibrary.com]

an interpectoral node, or an internal mammary node. As type B showed, we supposed these patients' SLN located outside the axilla. Based on this, it remained questionable that surgeons still did axillary lymph node biopsy and dissection for type B patients. Finally, type D was unexpected and suggested one sentinel node in the axilla could collect almost the entire breast's lymph, which corresponded with previous research.[9]

In conclusion, NIR fluorescence imaging mediated by blue dye has benefits on the identification of lymph vessels, the location of SLN and the patterns of breast lymphatic flow. To identify the best method using MB for SLN and investigate lymphatic drainage patterns, further studies are required.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ORCID

Haidong Zhao http://orcid.org/0000-0003-0761-3478

REFERENCES

1. van Manen L, Handgraaf HJM, Diana M, et al. A practical guide for the use of indocyanine green and methylene blue in fluorescence-guided abdominal surgery. *J Surg Oncol*. 2018;118:283-300.
2. Kinami S, Oonishi T, Fujita J, et al. Optimal settings and accuracy of indocyanine green fluorescence imaging for sentinel node biopsy in early gastric cancer. *Oncol Lett*. 2016;11:4055-4062.
3. Mieog JSD, Troyan SL, Hutteman M, et al. Toward optimization of imaging system and lymphatic tracer for near-infrared fluorescent sentinel lymph node mapping in breast cancer. *Ann Surg Oncol*. 2011; 18(9):2483-2491.
4. Tsukuura R, Sakai H, Fuse Y, Yamamoto T. Novel hands-free near-infrared fluorescence navigation and simultaneous combined imaging for elevation of vascularized lymph node flap. *J Surg Oncol*. 2018;118: 588-589.
5. Tagaya N, Aoyagi H, Nakagawa A, et al. A novel approach for sentinel lymph node identification using fluorescence imaging and image overlay navigation surgery in patients with breast cancer. *World J Surg*. 2011;35:154-158.
6. Kitai T, Kawashima M. Transcutaneous detection and direct approach to the sentinel node using axillary compression technique in ICG fluorescence-navigated sentinel node biopsy for breast cancer. *Breast Cancer*. 2012;19(4):343-348.
7. Verbeek FPR, Troyan SL, Mieog JSD, et al. Near-infrared fluorescence sentinel lymph node mapping in breast cancer: a multicenter experience. *Breast Cancer Res Treat*. 2014;143:333-342.
8. Hillary SL, Guillermet S, Brown NJ, Balasubramanian SP. Use of methylene blue and near-infrared fluorescence in thyroid and parathyroid surgery. *Langenbecks Arch Surg*. 2018;403(1): 111-118.
9. Suami H, Pan WR, Mann GB, Taylor GI. The lymphatic anatomy of the breast and its implications for sentinel lymph node biopsy: a human cadaver study. *Ann Surg Oncol*. 2008;15:863-871.
10. Manca G, Rubello D, Tardelli E, et al. Sentinel lymph node biopsy in breast cancer: indications, contraindications, and controversies. *Clin Nucl Med*. 2016;41:126-133.

How to cite this article: Jiang L, Liu T, Wang X, Li J, Zhao H. Real-time near-infrared fluorescence imaging mediated by blue dye in breast cancer patients. *J Surg Oncol*. 2020;121: 964–966. https://doi.org/10.1002/jso.25874