Comparison between the indocyanine green fluorescence and blue dye methods for sentinel lymph node biopsy using novel fluorescence image-guided resection equipment in different types of hospitals

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Sentinel lymph node biopsy (SLNB) has become a standard of care to detect axillary lymph metastasis in early-stage breast cancer patients with clinically negative axillary lymph nodes. Current SLNB detection modalities comprising a blue dye, a radioactive tracer, or a combination of both have advantages as well as disadvantages. Thus, near-infrared fluorescence imaging using indocyanine green (ICG) has recently been regarded as a novel method that has generated interest for SLNB around the world. However, the lack of appropriate fluorescence imaging systems has hindered further research and wide application of this method. Therefore, we developed novel fluorescence image-guided resection equipment (FIRE) to detect sentinel lymph nodes (SLNs). Moreover, to compare the ICG fluorescence imaging method with the blue dye method and to explore the universal feasibility of the former, a different type of hospital study was conducted. Ninety-nine eligible patients participated in the study at 3 different types of hospitals. After subcutaneous ICG allergy testing, all the patients were subcutaneously injected with methylene blue and ICG into the subareolar area. Consequently, 276 SLNs (range 1–7) were identified in 98 subjects (detection rate: 99%) by using the ICG fluorescence imaging method. In contrast, the blue dye method only identified 202 SLNs (range 1–7) in 91 subjects (detection rate: 91.92%). Besides, the results of the fluorescence imaging method were similar in the 3 hospitals. Our findings indicate the universal feasibility of the ICG fluorescence imaging method for SLNB using the fluorescence image-guided resection equipment in early breast cancer detection. (Translational Research 2016;178:74–80)

Abbreviations: ALN = axillary lymph node; ALND = axillary lymph node dissection; ASCO = American Society of Clinical Oncology; BMI = body mass index; FDA = Food and Drug Administration; FIRE = fluorescence image-guided resection equipment; HE = Hematoxylin-Eosin; ICG = indocyanine green; MB = methylene blue; NIR = near-infrared; SBR = signal-to-background ratio; SLN = sentinel lymph node; SLNB = sentinel lymph node biopsy

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Submitted for publication March 15, 2016; revision submitted July 8, 2016; accepted for publication July 11, 2016.

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1931-5244/$ - see front matter

http://dx.doi.org/10.1016/j.trsl.2016.07.010

AT A GLANCE COMMENTARY

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Background

Sentinel lymph node biopsy has become a standard of care to detect axillary lymph metastasis in early-stage breast cancer patients with clinically negative axillary lymph nodes. To facilitate intraoperative identification of the sentinel lymph node and transcutaneous lymphatic drainage visualization, real-time image-guided resection is essential during surgery. The novel fluorescence image-guided resection equipment (FIRE) developed for this study is capable to meet these needs by simultaneously displaying color, fluorescence, and merged images of tissues.

Translational Significance

Our novel FIRE is robust, reliable, and applicable in different types (general, district and specialized) of hospitals. Using a fluorescent contrast agent, it can achieve a high sentinel lymph node identification rate and minimal incision. Our results also indicate this method is noninferiority to the blue dye method.

INTRODUCTION

Traditionally, axillary lymph node dissection (ALND) has been frequently used to stage the axilla and to guide relevant treatment options during early breast conserving surgery. However, ALND may cause many side effects such as axillary subcutaneous effusion, upper limb lymphedema, and limitation of upper limb mobility and function and can thus seriously affect the quality of life of the patients.[1-3] In 2005 in the American Society of Clinical Oncology (ASCO) meeting, surgeons were recommended to use sentinel lymph node biopsy (SLNB) for most clinical axillary lymph node (ALN) negative breast cancer patients with axillary staging to alleviate the patients' pain and to improve treatment outcomes. In 2010, the National Comprehensive Cancer Network guidelines suggested that breast cancer patients clinically negative for ALN I, II should receive SLNB rather than ALND. Thus, SLNB now plays an important role in early breast conserving surgery.[4-6]

Currently, SLNB can be performed using a blue dye, a radionuclide tracer, or a combination of both.[7-9] The combination method is generally regarded as the best practice for SLNB.[10] However, each of these methods has some shortcomings. For example, the detection rate using the blue dye is relatively low at about 65%–93%.[11] Moreover, the subcutaneous injection of blue dyes may cause tissue necrosis in patients receiving breast-conserving therapy and may thus affect the cosmetic results.[12] An important limitation of the radionuclide tracer method is that it is not extensively accessible due to the lack of nuclear medicine in many hospitals. These limitations have increased international research on near-infrared (NIR) fluorescence imaging methods for cancer therapy.[13-16] Many intraoperative fluorescence imaging navigation systems[17-20] have been developed. However, only a few have an adjustable field of view and can simultaneously display color, fluorescence, and merged images of tissues. To meet these challenges and to provide better surgical conditions, we developed novel fluorescence image-guided resection equipment (FIRE) for SLNB.

Indocyanine green (ICG) was used as the NIR fluorescent contrast agent because ICG is the only NIR fluorescent agent authorized by both American and Chinese Food and Drug Administrations for clinical usage. Generally, ICG is used as a fluorescent indicator for ophthalmic angiography, cardiac output identification, and determination of liver blood flow.[21-23] The use of ICG in the NIR fluorescence imaging method for SLNB has the following advantages: high signal-to-background ratio (SBR), nonphysical contact with patients, transcutaneous lymphatic vessel visualization, and real-time intraoperative imaging. Therefore, the NIR fluorescence imaging method is suitable for intraoperative SLNB.

To verify the universal feasibility of our ICG fluorescence imaging method for SLNB in early-stage breast cancer patients, a comparative trial between the NIR fluorescence imaging method and the blue dye method using methylene blue (MB) was conducted in 3 different types of hospitals. Further, we adopted the same standard operating procedure in the 3 hospitals: Chinese PLA General Hospital Breast Disease Center (general), Yijishan Hospital of Wannan Medical College (district), and Cancer Hospital of Shantou University Medical College (specialized).

MATERIALS AND METHODS

Fluorescence imaging system. The FIRE was developed by the Key Laboratory of Molecular Imaging of Chinese Academy of Sciences based on our previous studies.[24-26] The general design and intraoperative application of the system, which comprised 4 sections—the light source section, detector section, controller section, and display section—are illustrated in Fig 1. The light source section was mainly

Fig 1. General design and intraoperative application of the FIRE. (**A**) The structure of the FIRE. (**B**) The FIRE was used during surgery at the Chinese PLA General Hospital Breast Center. FIRE, fluorescence image-guided resection equipment.

composed of a visible light source (KL2500LCD, SCHOTT, Germany) and a NIR light source (center wavelength 760 nm, maximum power 200 mW).

The NIR light source consisting of 67 light-emitting diode bulbs was used to excite ICG, and the visible light source illuminated the surgical field. The detector section mainly contained a color camera (Pilot piA1400-17gc, Basler, Germany), NIR camera (ProEM 1024B eXcelon3, Princeton Instrument, USA), beam splitter (25 mm NIR, 47012, Edmund Optics, USA), and an F mount lens (Nikon Nikkor 24–120 mm, f/4G ED VR). The beam splitter installed on the front end of the lens was used to split the light into 2 beams (for color and fluorescence). The NIR fluorescence and visible light images were then captured separately by the 2 cameras. The controller section mainly included an application program, which was written by us for image acquisition, registration, fusion, enhancement, and reconstruction. Finally, the display section was composed of 2 high-definition monitors. Real-time intraoperative fluorescence, color, and merged images were displayed on the screen at a rate of 20 frames per second. The field of view of this system ranged from 25 cm × 25 cm to 60 cm × 60 cm at a work distance of 60 cm. The resolution was about 10 lp/mm, and the sensitivity was approximately 0.03125 mg/ml ex vivo. Data storage could be completed automatically.

Patients. Ninety-nine eligible female patients (age 31–72 years, median age 52 years), who were diagnosed for T1–3 primary breast cancer with clinically negative lymph node, participated in this multicenter study between January 2014 and September 2015. The characteristics of the study subjects are summarized in Table I. The average age of the patients was 51 years, and the average body mass index was 24.2 kg/m^2 (range 18.7–38.8). The inclusion criteria were female sex, preoperative diagnosis of clinical breast cancer, tumor diameter ≤3 cm, negativity for ALN, and absence of distant metastasis. The exclusion criteria included previous neoadjuvant chemotherapy or radiotherapy of the mammary area, previous surgery of the axillary area, ALN metastasis, inflammatory breast cancer, and pregnancy. This study was approved by the Institutional Review Board of the 3 hospitals. Every patient provided written informed consent before the surgery. SLNB was performed by experienced surgeons in accordance with the same standard operating procedure. This experiment strictly followed the Helsinki Declaration and Chinese relative clinical trial norms, laws, and regulations. The Clinical Trails number was NCT02084784.

Administration of contrast agents. MB was purchased from Jichuan Pharmaceutical LLC, Jiangsu, China. ICG (25-mg vials) was bought from Yichuang Pharmaceutical LLC, Dandong, China. After anesthesia administration, *1 ml of 1% MB* was subcutaneously injected in the 6, 9, and 12-o'clock directions of the breast near the areola. Immediately after 1–5 minutes of massage and sterilization of the injection sites, *1 ml of 0.5% ICG* was subcutaneously injected in the same directions. The area was then again massaged and sterilized.

Table I. Characteristics of the study subjects (n = 99)

Characteristics	Value	Percentage
Age		
30–40	14	14.14
41–50	35	35.35
51–60	28	28.28
61–70	21	21.21
71–80	1	1.01
BMI		
≥18.5, <22	27	27.27
≥22, <25	35	35.35
≥25, <30	30	30.30
≥30	7	7.07
Menstruation		
Ordinary	62	62.63
Disorderly	37	37.37
History of allergy		
Yes	5	5.05
No	94	94.95
Family medical history		
Yes	4	4.04
No	95	95.96
Tumor size		
Tis	3	3.03
T1	38	38.38
T2	47	47.47
T3	3	3.03
Tx	8	8.08
Type of surgery		
MRM + SLNB	75	75.76
BCS + ALND + SLNB	2	2.02
BCS + SLNB	15	15.15
MRM + ALND + SLNB	7	7.07

Abbreviations: BMI, body mass index; *ALN*, axillary lymph node; *ALND*, axillary lymph node dissection; *SLNB*, sentinel lymph node biopsy; *MRM*, modified radical mastectomy; *BCS*, breast-conserving surgery.

Imaging procedure. After routine injection of MB and ICG, the FIRE was used to perform fluorescence imaging at ~60 cm distance from the surgical field. Particularly, the operating astral lamp was turned down, and the visible light source of the FIRE was used to illuminate the surgical field. Before incision, percutaneous lymphatic drainage and potential SLNs were observed. Real-time color and fluorescence tissue images were simultaneously displayed on the upper screen. Meanwhile, the 2 kinds of images were merged into pseudo-colored (green) images displayed on the lower screen. After careful observation, the points of disappearance of the lymphatic pools and lymphatic vessels were marked. Notably, the special design of the FIRE enabled the surgeons to regulate the imaging angle and imaging field of view as required. Based on the SBR calculated using the ImageJ software, the fluorescence of a lymph node was determined. In this study, the SBR threshold value was defined at 1.2. After the standard MB guided SLNB procedure was completed, ICG-stained SLNs and palpated SLNs were also carefully removed in the incised region. The excised SLNs were then separately examined and classified into the following categories: simultaneously identified by ICG and MB (ICG+/MB+), only identified by ICG (ICG+/MB−), only identified by MB (ICG−/MB+), and merely identified by palpation (ICG−/MB−).

Histopathologic analysis. All the intraoperative dissected specimens were examined by pathologists following the standard pathological procedure with Hematoxylin-Eosin (HE) staining.

Statistical analysis. Statistical Product and Service Solutions was employed for the data analysis. First, the SBR of the lymph nodes identified using ICG was calculated using ImageJ. The number of SLNs identified using MB and those identified using ICG were compared. Second, the detection rate of ICG, which was defined by the percentage of patients carrying SLNs identified by this method and that of MB were separately calculated and compared. To prove the validity of the differences, Student's *t*-tests were conducted. A *P*-value < 0.05 was considered to indicate statistical significance.

RESULTS

Because the operation of the FIRE was easy and the equipment was robust and reliable, ICG fluorescence imaging was successfully completed and did not interfere with routine surgical procedures. The surgeons mastered the operation process with a short learning curve (about 10 cases). In addition, the display effect of the FIRE was fluent, and the equipment provided high-resolution and high-fidelity images. The process of ICG fluorescence image-guided SLNB using FIRE is illustrated in Fig 2. Before incision, percutaneous fluorescence identification of the lymphatic drainage and potential nodes was performed, and the SBR was high enough to guide the surgeons to locate the SLNs (Fig 2, *A–C*). Using the FIRE, minimal incision and precise resection were realized during the operation (Fig 2, *D–F*). The images of the excised SLN further confirmed the accuracy of this method (Fig 2, *G–I*).

A total of 194 SLNs were identified using ICG+/MB+ in 90 of the 99 patients (Table II). By calculation, 276 SLNs were identified in 98 of the subjects (detection rate 99%) using the ICG fluorescence imaging method. In contrast, only 202 SLNs were identified in 91 of the subjects (detection rate 91.92%) using the blue dye method, indicating that the number of SLNs detected by the former was more than that of the latter and the detection rate of the former was higher (*P* = 0.0094). Moreover, 5 palpated SLNs (ICG−/

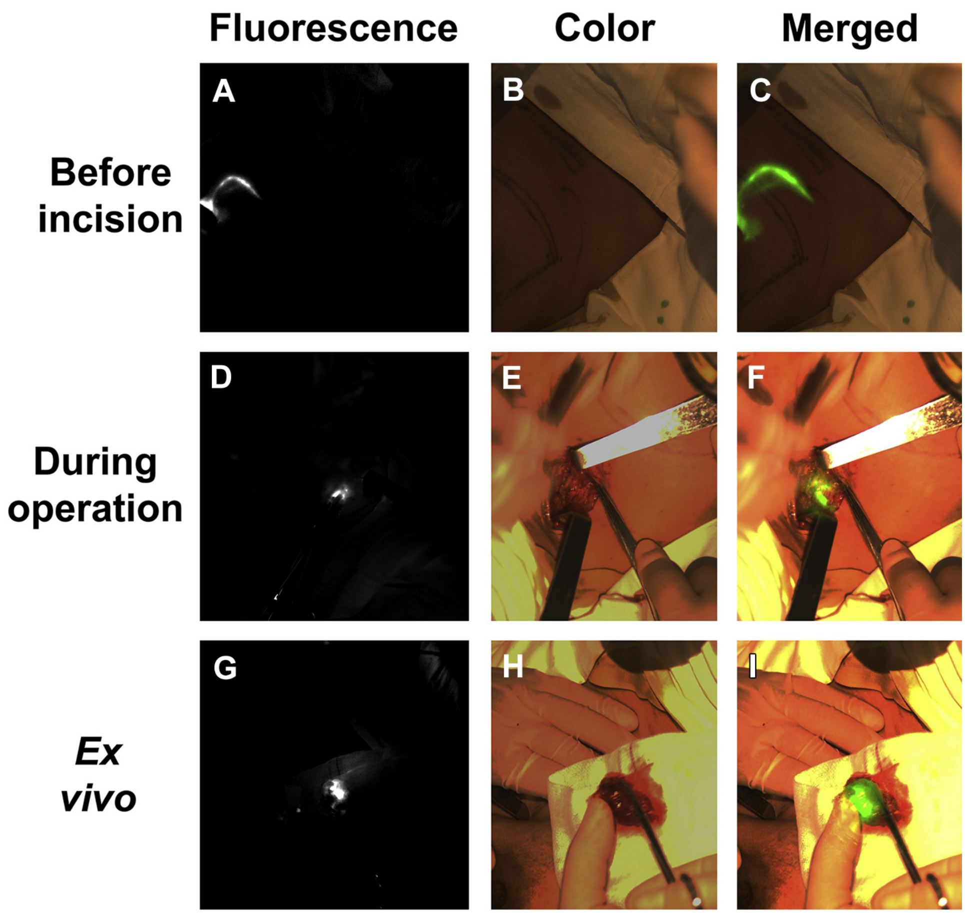

Fig 2. NIR fluorescence image-guided SLNB using the FIRE. (**A–C**) Percutaneous fluorescent identification of the lymphatic drainage before incision. (**D–F**) Precisely fluorescent image-guided SLN resection during surgery. (**G–I**) Images of the resected SLN ex vivo. SLNB, Sentinel lymph node biopsy; NIR, near-infrared; FIRE, fluorescence image-guided resection equipment; SLNs, sentinel lymph nodes.

MB−) were all pathologically confirmed as lymph nodes, but the histopathology indicated that they were all tumor negative. Therefore, we believe that they were probably never SLNs in the first place. Of note, 35 patients were diagnosed with tumor-positive SLNs, all of which were identified using ICG (false negative rate: 0%), whereas only 32 were detected using MB (false negative rate: 8.57%).

In addition, the SLNs identified using ICG or MB were separately classified according to the age of the patients, body mass index of the patients, and type of hospital (Table III). A preliminary analysis showed that the efficiency of SLN detection was independent of these factors, indicating that the NIR fluorescence imaging method for SLN detection was a robust one. However, whether SLN identification using the blue dye method correlates with these factors needs to be investigated in future studies. Moreover, no adverse reactions were observed during this multicenter experiment. In conclusion, the ICG fluorescence imaging method using the FIRE was not inferior to the blue dye method, which was also confirmed by histopathological analyses.

DISCUSSION

In this study, the universal feasibility of using the ICG fluorescence imaging method for SLNB in early-stage breast cancer patients was investigated. The combination of the FIRE and the NIR fluorescence imaging method showed a huge potential for clinical application. The particular design of the FIRE could simultaneously provide real-time intraoperative color, fluorescent, and merged images. Moreover, the field of vision was adjustable, and data storage was automatic. In addition, this method did not interfere with routine operations, and the surgeons managed to quickly learn the operation of this method, suggesting that the clinical application of the FIRE was very convenient.

The NIR fluorescence imaging method has several advantages over conventional methods. First, the high

Table II. SLN detection using ICG and/or MB

Characteristics	Patients (n = 99)	Percentage	SLNs (n = 289)	Percentage
ICG+/MB+	90	90.91	194	67.13
ICG+/MB−	8	8.08	82	28.37
ICG−/MB+	1	1.01	8	2.77
ICG−/MB−	0	0	5	1.73

Abbreviations: SLN, sentinel lymph node; *ICG*, indocyanine green; *MB*, methylene blue.

Table III. Classification of the identified SLNs by ICG or MB

Characteristics	Patients (ICG)	Percentage	Patients (MB)	Percentage
Age				
≤40	14	100 (14/14)	13	92.86 (13/14)
≥41, ≤50	35	100 (35/35)	34	97.14 (34/35)
≥51, ≤60	28	100 (28/28)	25	89.29 (25/28)
≥61	21	95.45 (21/22)	19	86.36 (19/22)
BMI				
≥18.5, <22	27	100 (27/27)	25	92.59 (25/27)
≥22, <25	35	100 (35/35)	33	94.29 (33/35)
≥25, <30	29	96.67 (29/30)	27	90.00 (27/30)
≥30	7	100 (7/7)	6	85.71 (6/7)
Hospital				
General	38	97.44 (38/39)	37	94.87 (37/39)
District	30	100 (30/30)	25	83.33 (25/30)
Specialized	30	100 (30/30)	29	96.67 (29/30)

Abbreviations: SLN, sentinel lymph node; *BMI*, body mass index; *ICG*, indocyanine green; *MB*, methylene blue.

sensitivity and real-time imaging helps surgeons realize accurate intraoperative SLNB and minimal incision. Second, the higher tissue penetration of ICG compared to that of blue dyes allowed observations of the percutaneous lymphatic drainage and potential SLNs before incision. Finally, the minor side effects and robust performance make the wide application of this method feasible.

Based on our preliminary analysis, we believe that the high detection rate of the fluorescence imaging method may be the result of the higher optical sensitivity of ICG compared to that of MB, and the low false negative rate of this method for SLNB can avoid the unnecessary need for ALND in patients with clinically negative SLNs.[27] Besides, obesity and age probably hinder the identification of SLNs.[28] However, SLNB can be stably achieved using fluorescence imaging possibly because of the higher tissue penetration of the fluorescent dye compared to that of blue dyes. Although the conditions in the different hospitals differed from one another, the ease with which the operation of the FIRE could be learnt and the common operating procedure contributed to realizing an optimal and steady detection of SLNs.

Based on our findings, we believe that the NIR fluorescence imaging method could be an alternative for SLNB to reduce patients' pain and to improve treatment outcomes in early breast cancer. In our future studies, we will conduct more research on the factors influencing the efficiency of the NIR fluorescence imaging method for SLNB, possibly by comparing breast peritumoral tracer injections and periareolar tracer injections, which are deemed to be equal in some studies.[29,30] To further study the effectiveness of the NIR fluorescence imaging method, we will compare it with the standard radiocolloid and blue dye method and try to combine the technology of Google glass[31] with the FIRE to develop a novel wireless wearable device that can facilitate voice control and real-time display on the screen of the glass.

CONCLUSIONS

In this multicenter experiment, we compared the ICG fluorescence imaging method using the FIRE with the blue dye method using MB to evaluate the clinical feasibility of the former. The results showed that a high SLN identification rate and minimal incision could be similarly achieved in different hospitals with the assistance of the FIRE. Our results also indicate this method to be not inferior to the blue dye method.

ACKNOWLEDGMENTS

Conflicts of Interest: All authors have read and understood the journal's policy on disclosure of potential conflicts of interest. There are no conflicts of interest to declare.

This article is supported by the National Natural Science Foundation of China under grant nos. 81227901, 81527805, 61231004, 61501462 and International Innovation Team, CAS, no. 20140491524.

All authors have read the journal's authorship agreement and the article has been reviewed by and approved by all named authors. The Clinical Trails was registered with the name of Application of Surgical Navigation System in Sentinel Lymph Node of Breast Cancer Research with no. NCT02084784.

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