

# Indocyanine Green and Methylene Blue Dye Guided Sentinel Lymph Node Biopsy in Early Breast Cancer: A Single-Center Retrospective Survival Study in 1574 Patients

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## Abstract

**We collected 1574 breast cancer patients' clinicopathological and postoperative treatment follow-up data, who underwent sentinel lymph node biopsy using a dual-tracer method of indocyanine green combined with methylene blue. By analyzing the statistical indicators including the identification rate, the number of sentinel lymph nodes, regional lymph node recurrence, disease-free survival and overall survival, we conclude that indocyanine green combined with methylene blue dualtracer method is safe and effective in sentinel lymph node biopsy in early breast cancer patients.**

**Background:** Currently, the standard tracing method is to use blue dyes and radioisotope as the tracer for sentinel lymph node biopsy (SLNB). However, there are variations in the choice of tracer in different countries and regions. Some new tracers are also gradually applied in clinical practice, but there is still a lack of long-term follow-up data to confirm their clinical application value. **Patients and Methods:** Clinicopathological and postoperative treatment follow-up data were collected from patients with early-stage cTis-2N0M0 breast cancer who underwent SLNB using a dual-tracer method of ICG combined with MB. Statistical indicators including the identification rate, the number of sentinel lymph nodes (SLNs), regional lymph node recurrence, disease-free survival (DFS) and overall survival (OS) were analyzed. **Results:** Among the 1574 patients, SLNs were successfully detected during surgery in 1569 patients, with a detection rate of 99.7%; the median number of SLNs removed was 3. A total of 1531 patients were included in the survival analysis, with a median follow-up of 4.7 (0.5-7.9) years. In total, patients with positive SLNs had a 5-year DFS and OS of 90.6% and 94.7%, respectively. The 5-year DFS and OS of patients with negative SLNs were 95.6% and 97.3%, respectively. The postoperative regional lymph node recurrence rate was 0.7% in patients with negative SLNs. **Conclusion:** Indocyanine green combined with methylene blue dual-tracer method is safe and effective in sentinel lymph node biopsy in patients with early breast cancer.

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**Keywords:** Breast cancer, Indocyanine green, Methylene blue, Regional lymph node recurrence, Sentinel lymph node biopsy

## Introduction

Blue dyes and radioisotope (RI) are currently the standard tracers for sentinel lymph node biopsy (SLNB) in breast cancer. However,

there are differences in the choice of tracer in different countries and regions. In recent years, new tracers such as fluorescent tracers indocyanine green (ICG) and nanocarbons have gradually replaced or in combination with traditional tracers in breast cancer SLNB. Since 2014, our center has been using ICG and methylene blue (MB) in combination for breast cancer SLNB, aiming to explore the efficacy and safety of these two tracers.

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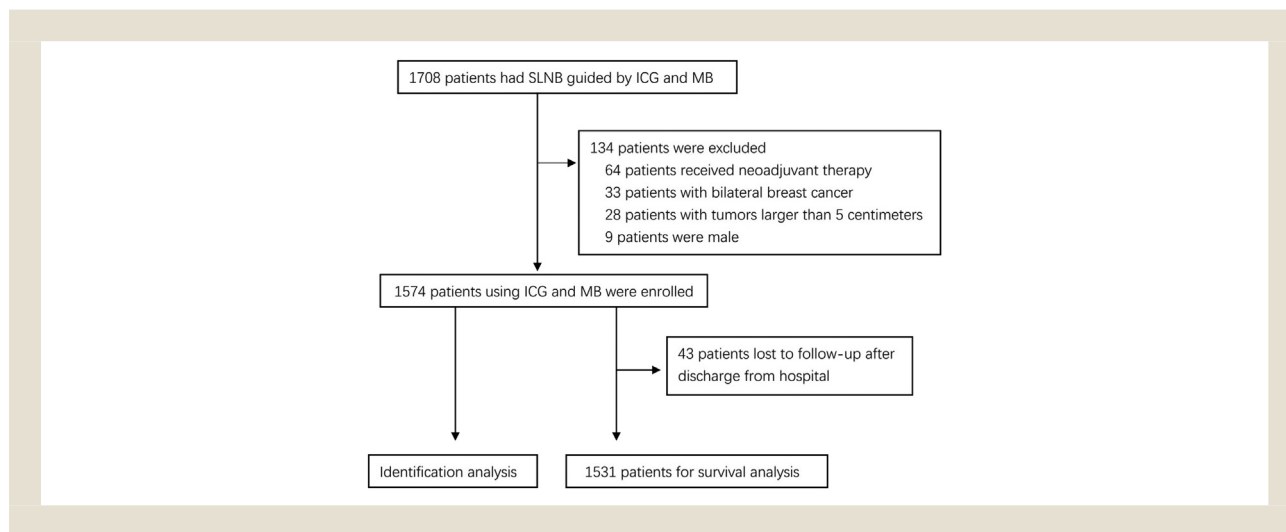
## Patient and Methods

### Patients' Selection

From June 2014 to December 2018, a total of 1708 patients with early cN0 breast cancer underwent sentinel lymph node biopsy using ICG combined with MB dual-tracer method (Figure 1). Clini-

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Figure 1 Study flowchart.



copathological data and postoperative follow-up data were obtained from the Bethune-Laval Oncology Unit Database. Inclusion criteria: female, primary breast cancer confirmed by pathological diagnosis, cTis-2N0M0, no history of axillary surgery; Exclusion criteria: male, preoperative neoadjuvant therapy, and bilateral breast cancer patients. A total of 1574 patients met the inclusion criteria of this study, with a median age of 52 (25-86) years. The procedures followed in this study have been approved by the Medical Ethics Committee of the Bethune First Hospital of Jilin University.

### SLNB Procedure

After general anesthesia, 0.5 mL of 1% MB (Jichuan Pharmaceutical, Jiangsu, China) was intradermally injected at 9 o'clock and 12 o'clock on the areola border 5 to 10 minutes before surgery. At the same time, 1 mL of 0.5 mg/mL ICG (Dandong Pharmaceutical, Liaoning, China) was intradermally injected at the site adjacent to the MB injection to form skin mounds. Massage the breast for 1 to 3 minutes after all the tracer has been injected. Before surgery, the location of the lymphatic vessels can be known according to the in vitro imaging of the fluorescence detector (MingDe Medicine, China). During the operation, the blue-stained or fluorescent lymph nodes were found along the blue-stained or fluorescent lymphatic vessels in the surgical field area, and then resected. All resected sentinel lymph nodes were sent for quick frozen pathological examination during surgery. After surgery, routine paraffin section pathological examination of sentinel lymph nodes is required again. If the frozen pathological result is negative and paraffin section pathology confirms the presence of metastasis in sentinel lymph nodes, axillary surgery or radiotherapy is decided according to the results of metastasis (isolated cells, micrometastasis, or macrometastasis). The whole group of patients received standardized postoperative adjuvant therapy after multidisciplinary treatment.

### Follow-up

The patients were followed up every 1 year through the outpatient electronic medical record system and telephone, and the cases

lost to follow-up after discharge were excluded, and the follow-up deadline was March 30, 2022. Local recurrence was defined as recurrence in the ipsilateral breast or chest wall; new contralateral breast cancer was defined as unilateral breast cancer at initial diagnosis, and breast cancer was re-diagnosed on the contralateral side after surgery; regional lymph node recurrence was defined as axillary, supraclavicular, and inferior lymph nodes, and recurrence of internal mammary lymph nodes; distant metastases were defined as metastases to distant tissues and organs. Disease-free survival (DFS) was defined as the time from a patient's diagnosis of breast cancer to disease recurrence (local recurrence and regional recurrence), distant metastasis, the occurrence of contralateral breast cancer, or death from any cause. Overall survival (OS) was defined as the time from the diagnosis of breast cancer to the occurrence of death from any cause.

### Statistical Analysis

Statistical software (SPSS, version, 26.0; GraphPad Prism, version 8.4) was used for data analysis. The count data were expressed by frequency and composition ratio. The Kaplan-Meier method was applied to draw the survival analysis curve, and the Log-Rank method was used to compare the differences. All tests were 2-sided, and  $P < 0.05$  was considered statistically significant.

## Results

### General Results

There were 1564 patients stained by both tracers. While 10 patients were not stained clear by different tracers as 5 of them were stained fluorescent-only and others weren't dyed. SLNs were successfully found in 1569 of 1574 patients, with an identification rate of 99.7%. The median number of SLNs excised was 3. Five patients underwent cALND for failed tracing. The detailed clinicopathological data of the enrolled patients are shown in Table 1. All the patients had intraoperative frozen pathology during the operation. According to the results of the intraoperative rapid freezing pathological examination, the appropriate axillary treatment

**Table 1** Patient and Tumor Characteristics

Characteristics	Patients, n	Value (%)
Total	1574	
Age, (years)		
<40	147	9.3
40-60	1033	65.6
>60	394	25.0
Menstrual status		
Premenopausal	739	47.0
Menopause	835	53.0
Family history		
Yes	1466	93.1
No	108	6.9
Histological subtype		
Invasive ductal carcinoma	1152	73.2
Others	422	26.8
pT		
pTis	162	10.3
pT1	901	57.2
pT2	511	32.5
Estrogen receptor		
Positive	1250	79.4
Negative	316	20.1
Unknown	8	0.5
Progesterone receptor		
Positive	1128	71.7
Negative	438	27.8
Unknown	8	0.5
Her-2		
Positive	334	76.0
Negative	1196	21.2
Unknown	44	2.8
Ki-67		
≤14	444	28.2
>14	1112	70.6
Unknown	18	1.1
Tumor subtype		
Luminal A	343	21.8
Luminal B	871	55.3
Her-2 enriched	153	9.7
Triple negative	151	9.6
Unknown	56	3.6
Type of breast surgery		
Mastectomy	1310	83.2
Breast-conserving surgery	251	15.9
Breast reconstruction surgery	13	0.8
Type of axillary surgery		
SLNB	1320	83.9
ALND	254	16.1
Adjuvant therapy		
Chemotherapy	925	58.8
Radiotherapy	460	29.2
Endocrine	1198	76.1

Abbreviations: ALND = axillary lymph node dissection; Her-2 = human epidermal growth factor receptor-2; SLNB = sentinel lymph node biopsy.

**Table 2** Adverse Events

Events	SLN (-) (n = 1221)	SLN (+) (n = 310)
Breast cancer-related events		
Local recurrences		
Ipsilateral breast	3	0
Chest wall	3	0
Regional lymph node recurrences		
Axillary	7	1
Supraclavian	1	1
Axillary and supraclavian	1	0
Contralateral breast cancer	3	1
Distant metastases	26	20
Total events	38	23
Death		
Breast cancer-specific mortality	20	12
Death for other cause	8	2
Total death	28	14

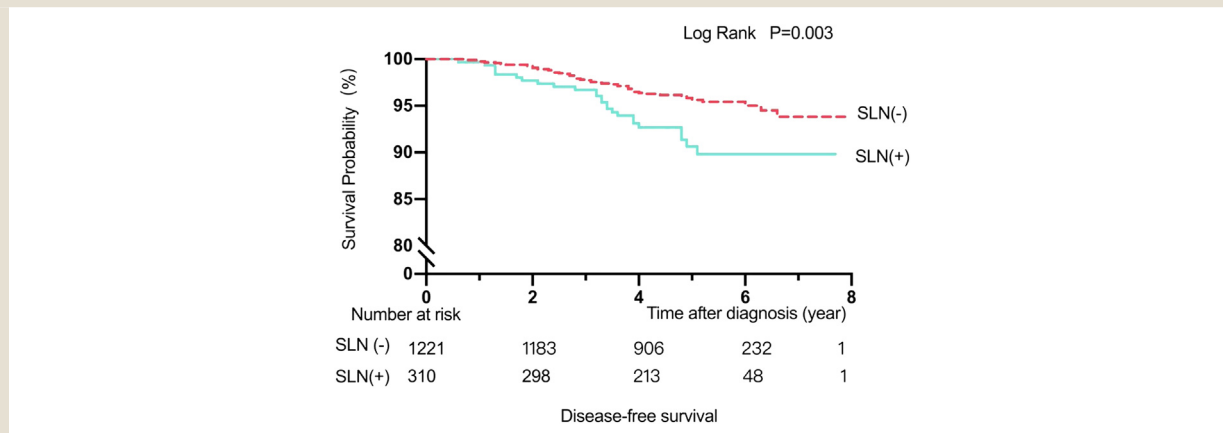
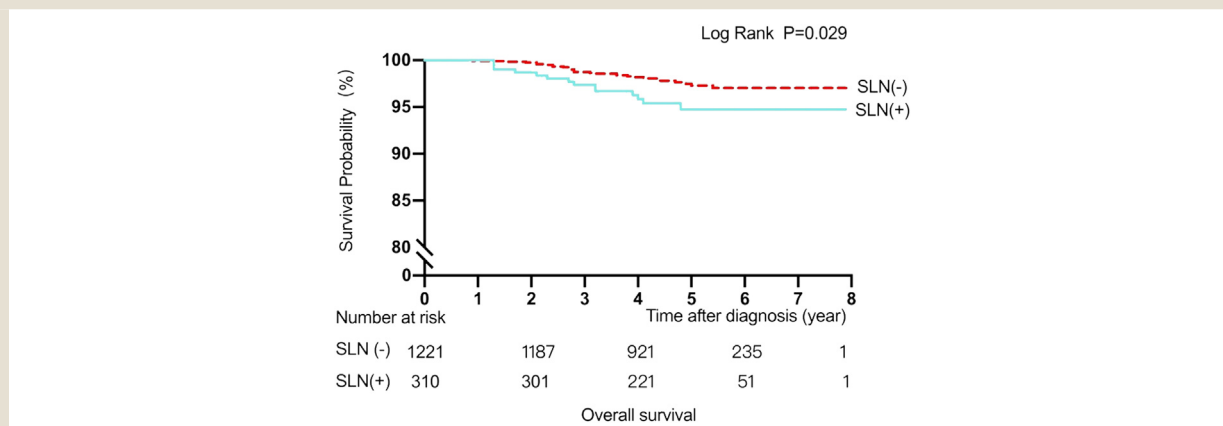
Two patients had ipsilateral breast and axillary recurrences; Abbreviation: SLN = sentinel lymph node.

method was selected for the patient. Breast-conserving patients who met the criteria of the American College of Surgeons Oncology Group's (ACOSOG) Z0011 trial avoided ALND. Forty-two patients who underwent breast-conserving surgery had intraoperative frozen pathology confirmed metastasis, and 21 of them underwent completion ALND (cALND). Final paraffin pathology confirmed SLNs negative in 1258 (79.9%) patients and positive in 316 (20.1%) patients. Eighty of 316 patients' frozen pathological results were negative but paraffin section pathology confirmed the presence of metastasis in sentinel lymph nodes, including 14 isolated cells, 58 micrometastases and 8 macrometastases.

### Survival Analysis

Forty-three patients who were lost to follow-up after discharge were excluded and long-term follow-up data were obtained for the remaining 1574 patients. A total of 1531 patients were included in the survival analysis, with a median follow-up of 4.7 (0.5-7.9) years, including 310 (20.2%) SLNs positive and 1221 (79.8%) negative patients. During the follow-up period, a total of 75 (4.9%) had recurrence, metastases, contralateral new breast cancer, and death events (Table 2). Among them, 10 (0.7%) had local recurrence after surgery, 11 (0.7%) had regional recurrence, 2 (0.1%) had ipsilateral breast and axillary lymph node recurrence after breast-conserving surgery, 4 (0.3%) had contralateral breast cancer, and 46 (3.0%) distant metastases; a total of 42 (2.7%) deaths occurred, 32 breast cancer-specific deaths and 10 patients died of other causes. Patients with negative and positive SLNs had 5-year DFS of 95.6% and 90.6%, respectively (Figure 2), and 5-year OS of 97.3% and 94.7%, respectively (Figure 3). Nine of the 1221 patients (0.7%) with negative SLNs had postoperative regional lymph node recurrence, and the median time from the diagnosis of breast cancer to the occurrence of regional lymph node recurrence was 3.6 years. The

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**Figure 2** Kaplan-Meier curves of breast cancer disease-free survival by SLN status.  $P = .003$  (log-rank test).**Figure 3** Kaplan-Meier curves of breast cancer overall survival by SLN status.  $P = .029$  (log-rank test).

detailed pathological data and treatment methods of patients with recurrence are shown in Table 3.

## Discussion

RI is recommended by the American Society of Clinical Oncology (ASCO) guidelines as a stand-alone SLNB tracer while RI combined with blue dye dual-tracer method is the gold standard recommended by the current Chinese guidelines.<sup>1</sup> However, in China, only 0.91% of hospitals could use RI alone and 14.55% used RI and blue dye in combination for SLNB.<sup>2</sup> Due to the high requirements of RI on hospital nuclear storage facilities and waste disposal, many medical institutions are not qualified to use RI and cannot use it, only a single blue dye can be used for SLNB. Blue dye has the advantages of simplicity of operation, good visualization, no radiation hazard, and easy accessibility, including PB, IB, and MB. The molecular weight of MB is relatively small which is easy to diffuse to the surrounding tissue after injection to contaminate the surgical area, and the lymphatic vessels and lymph nodes

can be damaged. The color development of MB is lighter relative to PB and IB. However, as PB and IB are expensive relative to MB and not yet available in China, MB is the most used blue dye tracer in China due to its cheap price and easy availability. ICG is commonly used in angiography and liver clearance tests, where it binds to plasma proteins and absorbs light at a wavelength of about 800 nm to produce a fluorescent signal. Currently, ICG has been approved for imaging lymphatic drainage pathways in a variety of tumors, such as prostate cancer, cutaneous Cassipo sarcoma, and skin metastases from rectal cancer<sup>3</sup>. Although adverse effects of ICG are rare, it has not been included in the guidelines for breast cancer SLNB. Using the ICG fluorescence detector can detect the lymphoid tissue 1 cm below the surgical site. By moving the position of the fluorescence detector during the operation, a dynamic and clear lymphatic fluorescence image can be observed on the screen, which is more conducive to the operation of the operation. However, when using ICG for SLNB, severed lymphatic vessels may contaminate the surgical field, making it difficult to further identify SLN under

**Table 3** Characteristics of the 9 Patients Who Had Relapse at the Regional Lymph Nodes

Age	Tumor Size (cm)	Type of Breast Surgery	SLN Number	Tumor Subtype	Adjuvant Therapy	DFS (Year)	Relapse Site	OS (Year)
33	0.8	Bt	3	Luminal B	Chemotherapy, Letrozole	3.0	Axillary	6.5, alive
39	1.5	Bt	2	Triple negative	Chemotherapy	1.5	Axillary	6.6, alive
40	3.0	Bp	2	Triple negative	Chemotherapy, Radiotherapy	2.1	Ipsilateral breast and axillary	5.9, alive
61	2.0	Bt	3	Luminal B	Letrozole	6.1	Axillary	6.8, alive
48	1.9	Bt	1	Her-2 enriched	Chemotherapy, Trastuzumab	1.0	Axillary	1.5, dead
50	0.9	Bt	2	Luminal B	Tamoxifen	4.0	Axillary Supraclavian	4.7, alive
56	1.9	Bt	3	Luminal B	Chemotherapy, Letrozole	1.5	Axillary	4.1, alive
60	1.7	Bt	1	Her-2 enriched	Chemotherapy, Trastuzumab	0.8	Axillary	5.8, alive
41	1.0	Bp	3	Luminal B	Tamoxifen, Radiotherapy	5.3	Ipsilateral breast and axillary	6.9, alive

fluorescence. MB has good visibility to the naked eye, and it can be used in combination with ICG which may expedite the learning curve to complement each other. It not only avoids the phenomenon of ICG fluorescent agent spillage and interferes with surgery after the first sentinel lymph node is removed, but also compensates for the low recognition rate and high false negative rate of MB alone.<sup>4</sup>

Our purpose was to evaluate the feasibility of using ICG combined with MB double tracer method for breast cancer SLNB and to provide a certain basis for the improvement of SLNB. MB is currently the most widely used tracer in China. Only 10 of 1574 patients in our study were not stained by MB, which obtained a good tracer result. But the results of a meta-analysis of 18 studies using MB alone for SLNB showed that MB had a detection rate of only 91% and a false negative rate of 13%.<sup>4</sup> Kim et al reported a Meta-analysis with 34 studies and concluded that the detection rate for blue dye combined with RI was 91.9%, and the false negative rate was 7%.<sup>5</sup> The use of these tracer methods still has some weaknesses and needs to be improved. Therefore, considering the actual situation in China, it is necessary to find a simple and efficient tracer that can in combination with blue dye for SLNB.

Studies have shown that ICG is a very promising fluorescent tracer that can replace RI for SLNB.<sup>6</sup> The detection rate of breast cancer SLNB using ICG alone is 98%, the false negative rate is 8%, and its sensitivity and specificity are high.<sup>7</sup> The average number of SLNs removed by Aoyama et al using ICG was 3.4.<sup>8</sup> In addition, the effect of the combined method of ICG and MB is significantly better than the use of blue dye alone.<sup>9</sup> In our study by using the combined method of ICG and MB, a median of 3 SLNs were resected, and the detection rate was 99.7%, which met the guideline's requirement that the SLN recognition rate is higher than 97%.<sup>10</sup> In recent years, many studies have confirmed that the detection rate of MB combined with ICG dual-tracer method can reach more than 99%.<sup>11-13</sup> Previous studies have shown that the false negative rate decreases as the number of SLNs removed increases,

with false negative rates of 23.53%, 15.79%, 3.85% and 1.79% for 1, 2, 3, and 4 SLNs respectively when applying MB alone for SLNB.<sup>14</sup> Currently, the number of SLNs that should be removed for SLNB remains controversial, and Dumitru et al suggest that at least three SLNs should be removed for SLNB to reduce the false negative rate to less than 10%.<sup>15</sup> Using MB combined with ICG dual-tracer method can remove more SLNs, which would decrease the false negative rates. Several studies have reported that the median number of SLNs removed by ICG combined with MB is more than 3, and it is better than that of MB or ICG alone.<sup>11,16,17</sup> The ICG combined with MB dual-tracer method is an effective tracer with a high detection rate and identification of more SLNs, which is an effective tracing method.

In general, the incidence of adverse reactions to ICG is extremely low, with only 0.05% of patients experiencing an allergic reaction after ICG injection.<sup>18</sup> It should be noted that patients should be asked whether there is a history of iodine allergy before using ICG. Patients with iodine allergy are prone to anaphylactic shock after ICG injection. Side effects such as allergic reactions, skin necrosis and staining sometimes occur when using blue dyes.<sup>19</sup> In this study, no patients developed tracer-related allergic reactions and skin necrosis. Only a small number of patients had skin staining in the first 6 months after surgery.

The most reliable criterion for verifying the long-term safety of tracers is the recurrence of long-term regional lymph nodes. In previously reported studies, the recurrence rate of regional lymph nodes using RI combined with blue dye dual-tracer method was 0.5% to 3.2%,<sup>20-22</sup> and 0.5% to 1.9% using RI alone.<sup>23,24</sup> Hirche et al had no events of axillary lymph node recurrence after a median follow-up of 4.7 years in 43 patients who underwent SLNB using ICG alone.<sup>25</sup> Recently, Japanese scholars reported the survival data of 565 patients who used ICG combined with indigo carmine for SLNB. The regional lymph node recurrence rate after a median follow-up of 83 months was about 2.1%.<sup>26</sup> At present, there is no large

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Table 4 Recurrence After Negative SLN in Different Studies

Studies	Time period	Tracers	Patients With SLNB-Only	Median Follow-up Time (year)	Regional Lymph Node Recurrence (%)	Axillary Recurrence (%)
Galimberti et al <sup>23</sup>	1996-2006	RI	5262	7.0	101 (1.9)	91 (1.7)
Veronesi et al <sup>24</sup>	1996-2000	RI	953	3.2	5 (0.5)	3 (0.3)
Krag et al <sup>20</sup>	1999-2004	RI+ isosulfan blue	2011	8.0	14 (0.7)	8 (0.4)
Bomface et al <sup>21</sup>	2000-2004	RI+ patent blue	2216	10.5	71 (3.2)	57 (2.6)
Ogawa et al <sup>27</sup>	2002-2010	ICG or indigo carmine	500	5.0	13 (2.6)	13 (2.6)
Asaga et al <sup>26</sup>	2010-2013	ICG + indigo carmine	565	6.9	12 (2.1)	10 (1.8)
Our study	2014-2018	ICG + MB	1221	4.7	9 (0.7)	8 (0.7)
Wang et al <sup>11</sup>	2011-2015	ICG + MB	777	5.6	-	5 (0.6)
Inoue et al <sup>28</sup>	2007-2014	ICG + patent blue	464	3.2	-	2 (0.4)

Abbreviations: ICG = indocyanine green; MB = methylene blue; RI = radioisotope; SLN = sentinel lymph node; SLNB = sentinel lymph node biopsy.

sample study on the safety of long-term regional lymph node recurrence in patients using ICG combined with MB for SLNB. We deeply analyzed the survival data of the patients, and the results showed that the regional lymph node recurrence rate was 0.7% in the 1221 patients with negative SLNs. Compared with existing similar studies which used ICG combined with MB dual-tracer method as shown in Table 4, there is no significant difference in the reported results, but some studies have small sample sizes and lack long-term follow-up data, which clinical value needs further verification. In our study, the 5-year OS and DFS of SLN-negative patients were 97.3% and 95.6%, respectively, which were basically consistent with the survival data of previous studies.<sup>20</sup> This also shows that ICG combined with MB dual-tracer method is a reliable and safe method for axillary staging.

This study also has some shortcomings. First, this study is a single-center retrospective study with certain limitations. Secondly, the control experiment of RI combined with MB was not set up in the same period of this study. Finally, patients who were SLNB-negative in this study did not undergo cALND, and the false-negative rate of ICG combined with MB could not be obtained. Most of the studies on the use of ICG for breast cancer SLNB are from Asian countries, and there are fewer ICG applications in countries such as Europe and the Americas. Survival data on the use of ICG in breast cancer patients in large multicenter samples are lacking and the long-term safety has not been widely recognized.

## Conclusion

The ICG combined with MB dual-tracer method is an effective tracer with a high detection rate and identification of more SLNs, which is an effective tracing method. In addition, its side effects are rare and the long-term prognosis is safe. It has certain safety and effectivity, which can be used in SLNB of patients with early cN0 breast cancer.

## Clinical Practice points

- For areas deficient in radioisotope, the use of indocyanine green in combination with methylene blue is a reliable method for tracing sentinel lymph node biopsy.
- Patients undergoing sentinel lymph node biopsy using indocyanine green combined with methylene blue dual tracer method have a safe long-term prognosis.

## Consent for Publication

Not applicable.

## Ethics Approval

This study was approved by the Ethics Committee of The First Hospital of Jilin University (approval number:2022-365).

## Author Contributions

Ruming Yang: Data analysis, tables and figures, manuscript drafting and editing; Chengji Dong: Manuscript drafting; Tinghan Jiang, Xiaoxiao Zhang, Fan Zhang: Data collection; Zhimin Fan: Study design and supervision, manuscript review, revision. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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