

RESEARCH ARTICLE

Diagnostic Performance of Indocyanine Green-Guided Sentinel Lymph Node Biopsy in Breast Cancer: A Meta-Analysis

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Abstract

Background

The diagnostic performance of indocyanine green (ICG) fluorescence-guided sentinel lymph node biopsy (SLNB) for the presence of metastases in breast cancer remains unclear.

Objective

We performed a meta-analysis to investigate the diagnostic performance of ICG-guided SLNB.

Methods

Eligible studies were identified from searches of the databases PubMed and EMBASE up to September 2015. Studies that reported the detection rate of ICG fluorescence-guided SLNB with full axillary lymph node dissection and histological or immunohistochemical examinations were included. A meta-analysis was performed to generate pooled detection rate, sensitivity, specificity, false negative rate, diagnostic odds ratio (DOR) and a summary receiver operator characteristic curve (SROC).

Results

Nineteen published studies were included to generate a pooled detection rate, comprising 2594 patients. The pooled detection rate was 0.98 (95% confidence interval [CI], 0.96–0.99). Six studies finally met the criteria for meta-analysis, which yielded a pooled sensitivity of 0.92 (95% CI, 0.85–0.96), specificity 1 (95% CI, 0.97–1), and DOR 311.47 (95% CI, 84.11–1153.39). The area under the SROC was 0.9758. No publication bias was found.

Conclusion

ICG fluorescence-guided SLNB is viable for detection of lymph node metastases in breast cancer. Large-scale randomized multi-center trials are necessary to confirm our results.

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Citation: Zhang X, Li Y, Zhou Y, Mao F, Lin Y, Guan J, et al. (2016) Diagnostic Performance of Indocyanine Green-Guided Sentinel Lymph Node Biopsy in Breast Cancer: A Meta-Analysis. PLoS ONE 11(6): e0155597. doi:10.1371/journal.pone.0155597

Editor: Robert M. Hoffman, AntiCancer Inc., UNITED STATES

Received: February 2, 2016

Accepted: March 29, 2016

Published: June 9, 2016

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Data Availability Statement: All relevant data are within the paper.

Funding: The authors have no support or funding to report.

Competing Interests: The authors have declared that no competing interests exist.

Introduction

In developed countries, breast cancer is a leading cause of cancer-related deaths in women aged 40 years and younger[1]. Early detection of breast cancer has been associated with reduced morbidity and mortality, compared to late detection[2]. In the early phase of breast cancer, breast cancer cells are mainly spread through the lymphatic system. Axillary lymph node dissection (ALND) has been used to evaluate lymph node status and identify the presence of metastases. However, ALND appears correlated with increased morbidity of lymphedema, pain, stiffness and shoulder weakness, seroma formation, vascular and brachial plexus injuries, and other complications. In patients with low-risk breast carcinoma, sentinel lymph node biopsy (SLNB) reportedly avoids ALND and thus reduces the complications associated with ALND[3].

Sentinel lymph nodes (SLNs) are the first lymph nodes that receive lymphatic drainage from the primary tumor [4]. SLNB is considered the standard care for patients without clinical or radiological evidence of axillary lymph node metastases in early-stage breast cancer[5]. A periareolar or interstitial injection of isotope and blue dye into the breast tumor is traditional in SLNB, and the 2 materials together are better than either alone [6].

A recent meta-analysis compared the traditional isotope-and-blue dye combination with 3 methods that are relatively new: indocyanine green fluorescence (ICG), contrast-enhanced ultrasound using microbubbles, and superparamagnetic iron oxide nanoparticles [4]. The newer methods showed clinical potential, but the false-negative rate of the compared methods ranged from zero for ICG to 30% for blue dye [4]. There was no ALND confirmation in some of the included studies, which potentially increased bias. Additionally, a jumping metastasis, or an abnormality in the lymphatic drainage pathway, makes a false negative inevitable, and an extrapolation of comparisons among different techniques is more difficult. In our opinion, the gold standard to identify whether a technique is reliable should be followed, that is, ALND plus histological or immunohistochemical confirmation.

In this study, we performed a meta-analysis to investigate the diagnostic performance of indocyanine green (ICG) fluorescence-guided SLNB in the presence of metastases in breast cancer, with ALND plus histological or immunohistochemical results as the reference.

Methods

A systematic literature search was performed of the PubMed and EMBASE databases, for all relevant studies published until 24 September 2015. The study search was limited to patients and published in English. Keywords included “indocyanine green” and “breast cancer” and “sentinel lymph node”.

The selected studies conformed to 5 inclusion criteria: regional lymphadenectomy and pathological examination including hematoxylin-eosin staining or immunohistochemistry as the referenced standard; ICG fluorescence-guided SLNB and pathological examination as the diagnostic method; the sentinel lymph node (SLN) was the study’s major focus; pathological data of the reference standard and diagnostic method were both available; and included a defined subgroup of patients who underwent complete ALND after SLN dissection, regardless of the results of SLNB.

Studies were excluded for the following: reviews, meta-analyses and abstracts; animal studies; overlapping articles; lack of SLN identification rate of both SNL and patients’ statistical analysis; lack of pathological examination or unavailable pathological data; ICG combined with human serum albumin or other tracers (blue dye, radioisotope) while ICG data not separately reported; or the introduction of new technology.

Data extraction and quality evaluation

The following data were extracted from the selected studies: first author; year of publication; country of origin; sample size; participants' characteristics, tracers, concentrations, injected volumes, injected location, tumor characteristics; ICG-related adverse reactions, average number of detected SLNs, number of patients with successful fluorescence imaging, measures of test performance of ICG fluorescence-guided SLNB including true-positive, true-negative, and false-negative results. Six researchers were involved in data extraction.

The quality of each study was quantified using the quality assessment tool for diagnostic accuracy in systemic reviews (QUADAS, score from 0 to 14)[7]. QUADAS is a tool for assessing the evidence-based quality of studies for diagnostic accuracy.

Statistical analysis

The measures of interest for effect included detection rates, sensitivities, specificities, diagnostic odds ratios (DORs), the summary receiver operator characteristic (SROC) curve, the area under the curve (AUC), and the Q^* index. The closer the AUC is to 1.0, the better the diagnostic method. The Q^* index is a statistical value defined by the point on the SROC curve where sensitivity and specificity are equal.

The statistical heterogeneity among studies was evaluated using Cochran's Q statistic, P -values, and I^2 statistics. Heterogeneity was considered significant at $I^2 > 50\%$, or $P < 0.05$ (R GUI 3.0.1, R Project for Statistical Computing, USA). The sensitivity and specificity of each study was calculated by 2x2 contingency tables for correct diagnosis in the presence of lymph node metastasis.

The Mantel-Haenszel random-effects model was used to obtain the summarized detection rate, DOR, sensitivity, and specificity, considering the differences in patient characteristics, technical details, and operators' experiences. The Q^* index was subsequently produced from the SROC curve of all the included studies.

The publication bias for detection rate and diagnostic performance were explored by Harb or egger analysis, respectively, if sufficient studies were available[8]. $P < 0.05$ was considered statistically significant.

Results

We identified 38 studies from PubMed and 29 studies from EMBASE. After removal of overlapping studies, languages other than English, animal studies, technology introductions, and reviews, 55 studies remained for full review (Fig 1). Of these, 36 full-text articles were additionally excluded: 25 abstracts, letters, case reports, or other kinds of cancers; 6 studies without histological or immunohistological results; 3 studies in which there was no separate data regarding ICG alone (i.e., not in combination with other tracers); and 2 studies reported only the numbers of metastasized lymph nodes but not the number of patients.

Finally, we included 19 qualified studies for pooling the detection rate (Tables 1 and 2) [9–27]. The 19 studies were published from 2009 to 2015, and included a total of 2594 patients. The pooled detection rate was 0.98 (95% confidence interval [CI], 0.96–0.99). The heterogeneity of the pooled detection rate was low: I^2 value was 10.1%, $P = 0.33$ (Fig 2). Among 19 studies, there were only 6 studies [11–13, 15, 16, 18] in which after SLNB ALND was performed plus histology or immunohistochemistry as the reference, as required for our meta-analysis.

Altogether, 254 patients were included for the final analysis. The pooled sensitivity was 0.92 (95% CI, 0.85–0.96), and the specificity was 1 (95% CI 0.97–1). The heterogeneity of the pooled sensitivity analysis was low: I^2 value was 0.0% (Fig 3), and the heterogeneity of the pooled

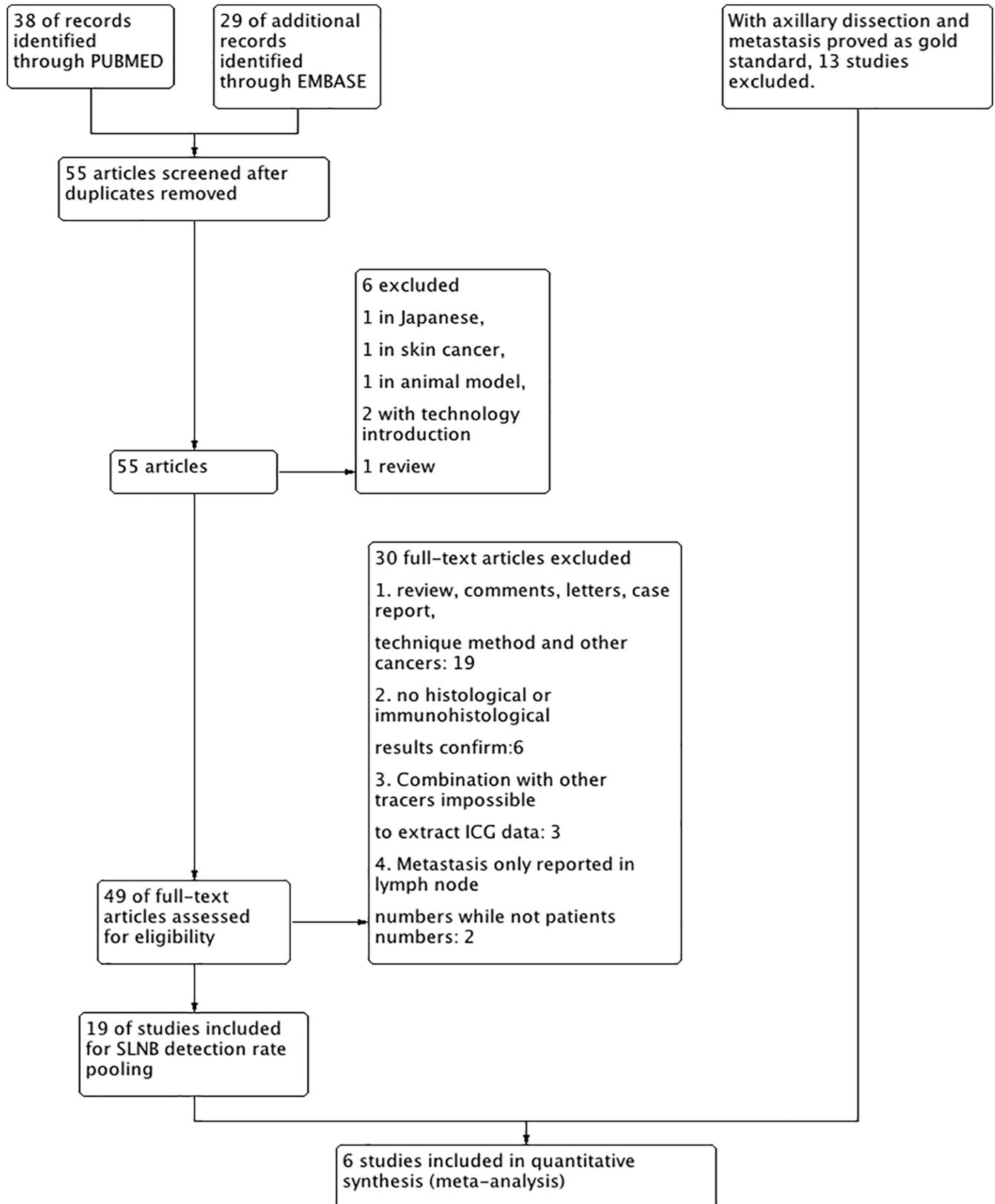


Fig 1. Flow chart for the selection of the included studies.

doi:10.1371/journal.pone.0155597.g001

Table 1. Nineteen studies for the pooled detection rate analysis.

| First author | Year | Country | Pnt/Cnt, n | Tumor stage | Other RI tracers used | Injection location | Dose (mL; mg/mL) |
|---------------|------|-------------------|------------|-------------|---------------------------|--|------------------|
| Abe | 2011 | Japan | 128/1 | T1-2, cN0 | ICG+BD | Intradermal areola | 0.15; 5 |
| Aoyama | 2011 | Japan | 312/1 | cN0 | ICG only | Subareolar & periareolar | 5; 0.125 |
| Chi | 2013 | China | 22/1 | T1-2N0M0 | ICG only | Areola | 0.5–2; 5 |
| Guo [12] | 2014 | China | 86/1 | Tis-T2 | ICG+BD | Subareolar | 1; (1/20) |
| Guo [13] | 2014 | China | 36/1 | Tis-T2 | ICG only | Subareolar | 1; (1/20) |
| Hirano | 2012 | Japan | 108/1 | Tis-T4, cN0 | ICG+BD cf. BD(along) | Subareolar | 2.5; 2 |
| Hirche | 2012 | Germany | 47/1 | N0-N3 | ICG only | Subareolar | 2.2; 5 |
| Hirche | 2010 | Germany | 43/1 | N0-N3 | ICG only | Subareolar | 2.2; 5 |
| Hojo | 2010 | Japan | 141/1 | Tis-T2, cN0 | ICG+BD cf. ICG+RI | Tumor & sub-areolar | 2; NA |
| Murawa | 2009 | Germany | 30/1 | T1-4 | ICG for all, part with RC | Periareolar | 1, 2, 3; 5 |
| Polom | 2012 | Poland | 28/1 | N0-N1 | ICG+RC cf. ICG+RC +HSA | Tumor or periareolar | 1; 10 |
| Samorani | 2015 | Italy | 301/1 | NA | ICG+radioactive | Periareolar | 0.4–1.2; 5 |
| Schaafsma | 2013 | Netherlands | 32/1 | NA | ICG+BD+RC | Tumor or periareolar | 0.25–0.5 mg; NA |
| Sugie | 2013 | Japan | 99/6 | Tis-TX | ICG cf. BD | Subareolar | 0.5–1; 5 |
| Sugie | 2015 | Japan | 821/12 | T1-2 | ICG +RC | Subareolar | 1; 5 |
| Takeuchi | 2012 | Japan | 145/1 | Tis-T2, cN0 | ICG+BD for each | Subcutaneously into the periareolar area | 1; 5 |
| Tong | 2014 | China | 96/1 | Tis-T4, cN0 | ICG+BD cf. BD | Subareolar | 2; 5 |
| van der Vorst | 2012 | Netherlands | 24/1 | cN0 | (ICG+RC)+BD cf. no BD | Intradermal & periareolar | 1.4; 500 µmol |
| Verbeek | 2014 | USA & Netherlands | 95/2 | T1-4 | ICG+RC | Periareolar& peritumor | 1.6; 0.39 |

BD, blue dye; Cnt, medical centers; HSA, human serum albumin; NA, not available or not reported; Pnt, patient; RI, radioisotope

doi:10.1371/journal.pone.0155597.t001

specificity also had a I^2 value of 0.0%. The pooled DOR was 311.47 (95% CI, 84.11–1153.39). The heterogeneity of the pooled studies was low: $I = 0.0%$, $P = 0.97$ (Fig 4).

The AUC of the SROC was 0.9758 (Fig 5), and the Q^* index = 0.93. Publication bias was not shown in any of the 19 studies analyzed early (Fig 6A), or the 6 studies in the meta-analysis (Fig 6B).

Discussion

The 3 main findings of our study are, that ICG fluorescence-guided SLNB in breast cancer has a 98% detection rate for SLN; the pooled sensitivity and specificity were relatively high and the false-negative rate was relatively low; and in the presence of metastases, the diagnostic performance of this method is good, with relatively high sensitivity and very high specificity.

SLNB has been the first choice for axillary staging of patients with early breast cancer with clinically negative axillary lymph nodes. The good diagnostic performance of SLNB is essential for cancer staging, surgical treatment, and therefore substantially influences the prognosis. Currently, blue dye and radiocolloid are the two most common methods for SLNB. Blue dye is relative simple and inexpensive. However, the detection rate of blue dye is low[28]. Isotope has a relatively high detection rate, but its challenges include the handling and disposal of isotopes, high expense of storage, transport and even legislative issues which limit its wide use[29].

The use of ICG in SLNB has some advantages compared to isotope: lower cost, fewer adverse effects, and quick transcutaneous real-time visualization (within several minutes),

Table 2. Nineteen studies of the pooled detection rate analysis.

| First author | Year | Pnt SLN rate | SLN detection | | ALND confirm | Adverse effect |
|---------------|------|-----------------|---------------|------|--------------|--|
| | | | SLN No | mSLN | | |
| Abe | 2011 | 100% (128/128) | (1–6) | 3.1 | | NA |
| Aoyama | 2011 | 100% (312/312) | (1–12) | 3.41 | | Skin pigmentation for a certain period of time |
| Chi | 2013 | 100% (22/22) | (1–6) | 2.7 | Yes | No side effect |
| Guo [12] | 2014 | 93% (80/86) | NA | 2.4 | Yes | No adverse effect |
| Guo [13] | 2014 | 97.2% (35/36) | NA | 3.6 | Yes | Tattoo effect last for one week & disappear in two weeks |
| Hirano | 2012 | 99.1% (107/108) | (0–5) | 2.2 | | NA |
| Hirche | 2012 | 97.9% (46/47) | (1–3) | 2.0 | Yes | NA |
| Hirche | 2010 | 97.7% (42/43) | NA | 2.0 | Yes | NA |
| Hojo | 2010 | 99.3% (140/141) | NA | 3.8 | | NA |
| Murawa | 2009 | 97% (29/30) | NA | 1.75 | Yes | NA |
| Polom | 2012 | 96.4% (27/28) | (1–5) | 2 | | NA |
| Samorani | 2015 | 98.7% (297/301) | (1–5) | 1.94 | | No allergic reaction, (2.5%) developed paraesthesia.(3.2%) developed seromas |
| Schaafsma | 2013 | 100% (32/32) | NA | 1.5 | | NA |
| Sugie | 2013 | 99.0% (98/99) | NA | 3.4 | | NA |
| Sugie | 2015 | 97.2% (798/821) | NA | 2.3 | | No serious allergic reactions related to ICG injections reported in 833 consecutive patients. Grade 1 to 2 nausea or vomiting & pain observed in 8 (1.0%) & 6 (0.7%) patients, respectively. |
| Takeuchi | 2012 | 99.3% (144/145) | NA | | | NA |
| Tong | 2014 | 96.9% (93/96) | NA | | | NA |
| van der Vorst | 2012 | 95.8% (23/24) | NA | 1.5 | | NA |
| Verbeek | 2014 | 97.9% (93/95) | (1–5) | 1.9 | | NA |

Cnt, medical centers; mSLN, mean number of SLN; NA, not available or not reported; Pnt, patient

doi:10.1371/journal.pone.0155597.t002

facilitating the localization of the incision and the detection of SLNs during the surgery. In the clinical trial NSABP (National Surgical Adjuvant Breast and Bowel Project) trial B-32 that comprised 5611 patients, the combination of blue dye and radiocolloid showed a 97.1% detection rate for SLN, compared with 89.4% for radiocolloid alone and 70.2% for blue dye alone [30]. In another ALMANAC (Axillary Lymphatic Mapping Against Nodal Axillary Clearance) study including 842 clinically node-negative breast cancer patients, the combination of isotope and blue dye had a 96.1% detection rate, but that of either blue dye or isotope alone was 85.6%

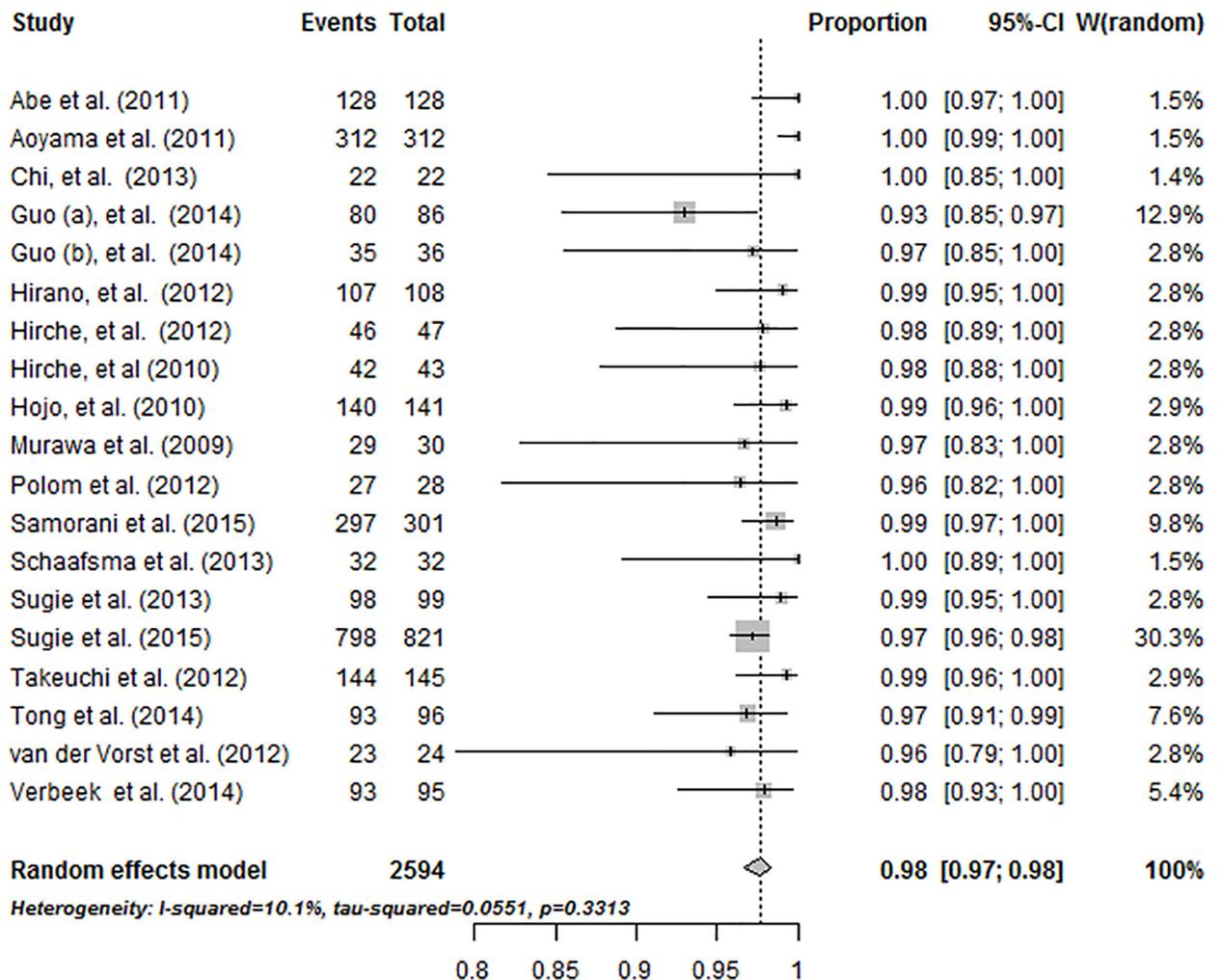


Fig 2. The pooled detection rates was 0.98 (95% confidence interval [CI], 0.96–0.99).

doi:10.1371/journal.pone.0155597.g002

[6]. Our present study showed that ICG fluorescence alone may reach a detection rate of 98%, which is even better than combined isotope and blue dye. Similarly, a recent meta-analysis comparing ICG with blue dye showed that ICG was significantly better than blue dye with regard to SLN identification (odds ratio, 18.37)[4].

In our present study, the pooled sensitivity was 92%, and the false-negative rate was 8%. This is comparable to the results of the NSABP B-32, in which the false-negative rate for combined blue dye and radioisotopes was 9.8%. Another study that pooled data based on 8000 patients showed that the false-negative rates were 10.9% for blue dye alone, and 8.8% for radiocolloid alone[3]. The accuracy of the ICG method was not superior to the combination of blue dye and radiocolloid. However, when ICG was combined with another technique, the accuracy seems to improve; a false-negative rate of 4% was observed when ICG was combined with blue dye[13]. This clearly showed another way to increase the sensitivity of ICG.

In the present study, high DOR and AUC suggested a good diagnostic performance for ICG fluorescence-guided SLNB. However, these results should be interpreted cautiously. For example, the pooled specificity of the present study was 100%, which is not surprising since it is impossible to have false-positive sentinel node results—if a sentinel node is pathologically

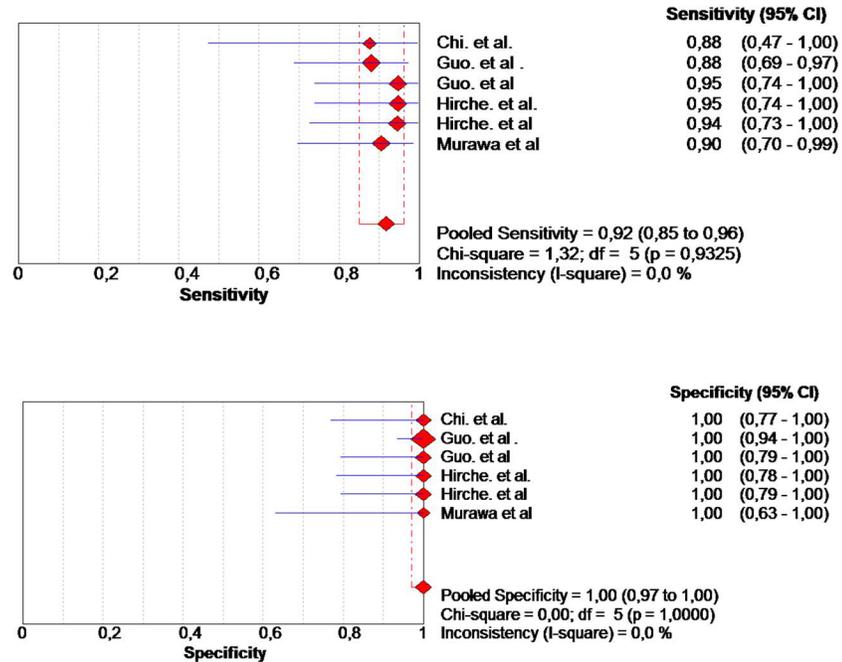


Fig 3. The pooled sensitivity was 0.92 (95% CI, 0.85–0.96), and the specificity was 1 (95% CI 0.97–1).

doi:10.1371/journal.pone.0155597.g003

involved, the axillary lymph node basin is also involved. The high specificity is clearly responsible for the high DOR, as the DOR shows the overall performance of a diagnostic test, considering both sensitivity and specificity together. The SROC and its derivatives (AUC and Q*) are also measures of overall accuracy.

There were no severe adverse effects reported in the trials included in this study. Only two trials [9, 12] reported pigmentation, which lasted for several weeks. This makes ICG fluorescence-guided SLNB all the more attractive, when compared with the complications observed in ALND.

One main shortcoming of ICG fluorescence-guided SLNB is that indocyanine does not specially label tumor cells. Tumor-specific fluorescent probes which can selectively glow tumors, which preferably be administered topically, could significantly improve cancer detection and

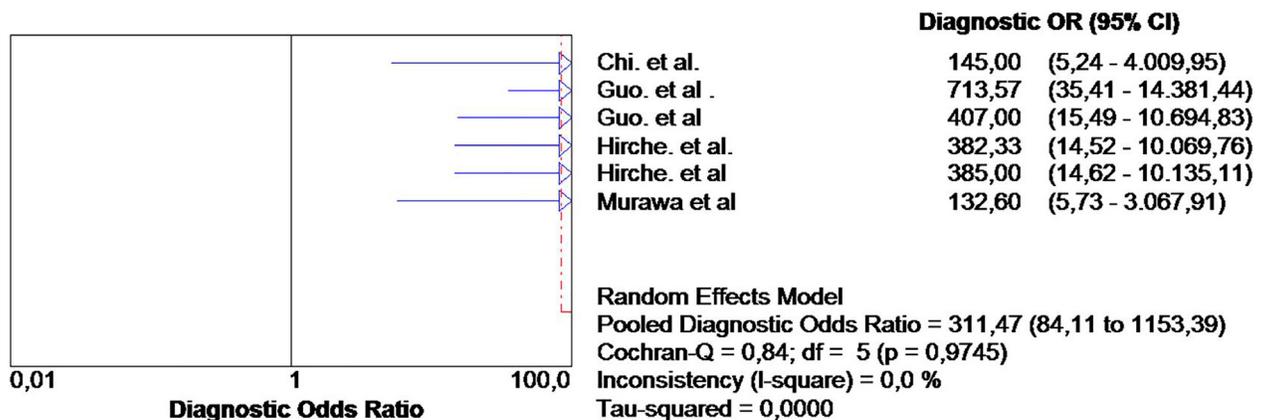


Fig 4. The pooled DOR was 311.47 (95% CI, 84.11–1153.39).

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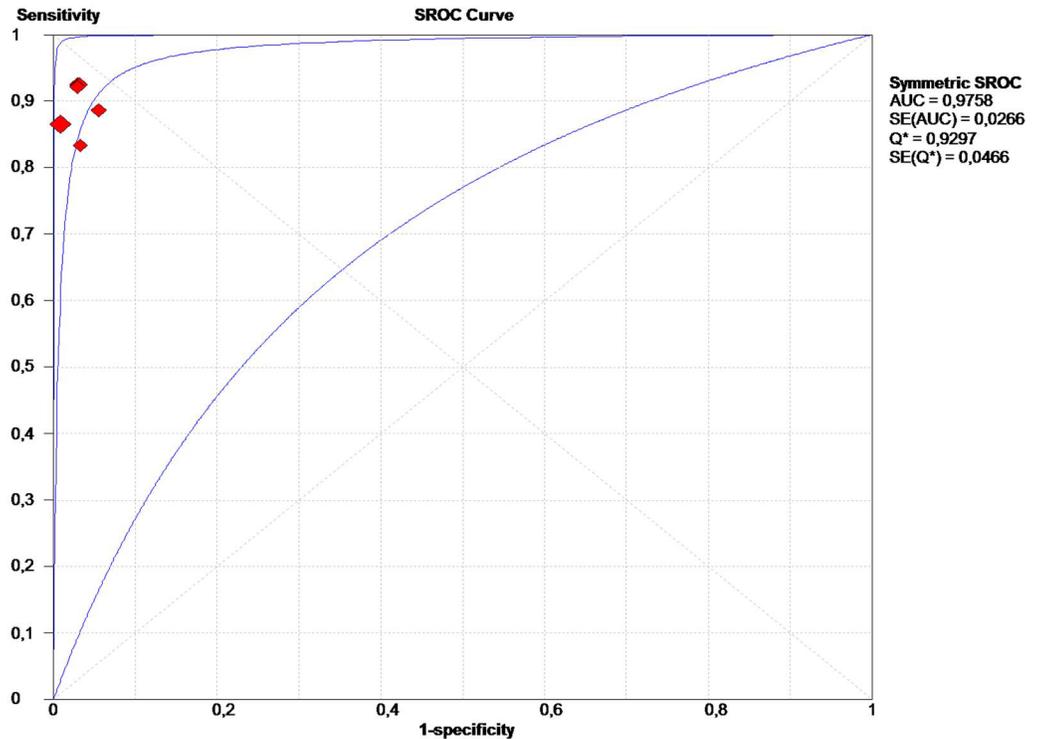


Fig 5. Summary of receiver operator characteristic curves.

doi:10.1371/journal.pone.0155597.g005

even removal in the surgery [31]: indeed, selectively highlighting tumor cells either by gamma-glutamyl hydroxymethyl rhodamine green, an enzyme commonly found in cancer cells[32]; or genetically label tumors in situ with green fluorescent protein[33, 34]; Spray-painting tumors by using fluorescent tumor-specific antibodies[35]. All of these new methods could potentially strengthen ICG fluorescence-guided SLNB, which deserves more studies in the future.

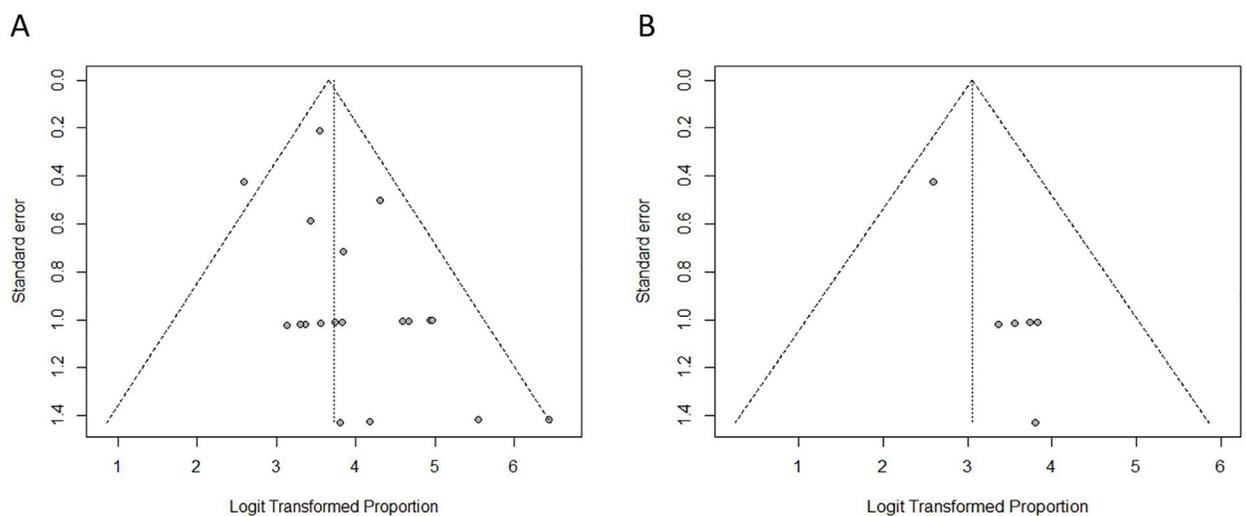


Fig 6. Funnel plots: (A) The 19 included studies for detection rate, (B) The 6 studies with ALND confirmation.

doi:10.1371/journal.pone.0155597.g006

However, this meta-analysis also has several limitations. First, we only included 6 studies for the meta-analysis, mainly due to the reference standard demanded by the study design. Secondly, the technical limitations of the pathophysiological method used as the reference might have influenced the results. Finally, a false-positive rate is not possible in ICG fluorescence-guided SLNB, and this decreased the statistical power of the study.

Conclusion

ICG fluorescence-guided SLNB is viable for detecting SLN in the presence of lymph node metastases in clinical node-negative breast cancer, and may allow the avoidance of ALND and its relatively greater complications. This study's results warrant large-scale randomized multi-center trials and long-term follow-up for confirmation.

Supporting Information

S1 PRISMA Checklist. PRISMA checklist.

(DOC)

S1 File. Included papers in the search of EMBASE.

(PDF)

Author Contributions

Conceived and designed the experiments: XZ QS. Performed the experiments: XZ. Analyzed the data: XZ Y. Li YZ FM Y. Lin JG. Contributed reagents/materials/analysis tools: XZ Y. Li. Wrote the paper: XZ.

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