Systematic Review and Meta-Analysis

Medicine

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# Sentinel lymph node mapping in early-stage cervical cancer

## Meta-analysis

Lijun Wang, MD[a], Shanshan Liu, PhD[b], Ting Xu, Master[a], Linnan Yuan, Bachelor[a], Xinyuan Yang, PhD[a,*]

**Abstract**

**Background:** The value of sentinel lymph node (SLN) mapping for early-stage cervical cancer remains controversial. Therefore, we collected data to investigate the feasibility and diagnostic accuracy of SLN in patients with early-stage (IA-IIA) cervical cancer.

**Methods:** We searched Embase, PubMed, and the Cochrane Library databases issued before June 1, 2020. The sample size of the selected study was at least 10 patients with early-stage (IA-IIA) cervical cancer, the pooled detection rates and the separate detection rate (overall detection rate, bilateral detection rate) using blue dye with Tc, technetium 99 (Tc) and indocyanine green (ICG) technique of early-stage cervical cancer was reported. R-3.6.1 software was used to evaluate pooled detection rate and sensitivity.

**Results:** Two thousand one hundred sixty-four patients included for analysis in 28 studies ranging from 12 to 405 patients. The combined overall detection rate of SLN mapping was 95% with a 72% pooled bilateral detection rate. The sensitivity of the combined overall detection rate of SLN mapping was 94.99% as well as a sensitivity of 72.43% bilateral detection rate. The overall detection rate of SLN was 96% for blue dye with Tc, 95% for Tc, 98% for ICG technique. The bilateral detection rate of SLN was 76% for blue dye with Tc, 63% for Tc, 85% for ICG technique. The sensitivity of the overall detection rate of SLN mapping was 97.76% as well as a sensitivity of 84.96% bilateral detection rate of ICG technique.

**Conclusion:** In early-stage cervical cancer, overall detection rate of SLN mapping is elevated while bilateral detection rate is lower. The overall detection rate (98%) as well as bilateral rate (85%) of ICG seems to be a better SLN mapping technique among the method of SLN mapping (using blue dye with Tc, Tc or ICG). We believe SLN mapping may be considered contemporary technique which could provide additional benefits over traditional pelvic lymphadenectomy. While promising results in SLN mapping has been found, larger patient samples, including randomized studies, are required at the same time.

**Abbreviations:** CI = confidence interval, FIGO = Federation of Gynecology and Obstetrics stage, ICG = indocyanine green, SLN = sentinel lymph node, Tc = technetium 99.

**Keywords:** bilateral detection rate, early-stage cervical cancer, meta-analysis, overall detection rate, sentinel lymph node

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*The studies we have included are all published documents and do not involve patients, so ethical approval is not required.*

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*The datasets generated during and/or analyzed during the current study are publicly available.*

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**Highlights**

- The combined overall detection rate of SLN mapping was 95% with a 72% pooled bilateral detection rate. The overall detection rate of SLN was 96% for blue dye with Tc, 95% for Tc, 98% for ICG technique.
- The overall detection rate (98%) as well as bilateral rate (85%) of ICG seems to be a better sentinel lymph node mapping technique among the method of SLN mapping (using blue dye with Tc, Tc or ICG).
- We believe sentinel lymph node mapping may be considered contemporary technique which could provide benefits over traditional pelvic lymphadenectomy.

## 1. Introduction

Cervical cancer is the leading cause of cancer-related mortality in women.[1] Lymph nodal status is used as the major predictor of survival. In addition, it guides postoperative treatment planning in early cervical cancer.[2] Pelvic lymphadenectomy procedure as well as radical hysterectomy procedure is routinely used as the treatment in order to avoid the under diagnosis of lymph node metastasis. From the past to the present, removal of pelvic lymph nodes has shown poor clinical effects, including nerve damage, lymphedema and lymphocyst formation, contributing to increased operative time, blood loss.[3] Lymph nodes status is the most significant indicator of cervical cancer surgery which can determine the prognosis of surgery. Moreover, studies show that the pelvic sentinel lymph node (SLN) can predict the state of the regional lymph nodes accurately.[4]

SLN is recognized as the first lymph node pass through when tumor cells metastasize in the primary lymphatic drainage area. SLN biopsy has been found to play the important role in 1977 by Cabanas and has been accepted in the treatment of human cancers such as melanoma, breast and vulvar cancers.[5] SLN can be indicated with lymphatic mapping, and a certain bioactive dye or radioactive tracer is injected around the primary malignant tumor, which can be drained to the regional lymph nodes with the lymph, and then recognized by visual inspection or special instruments. SLN biopsy can be considered as a novel method for staging of gynecological malignancy.[6] What is the most important is to identify major lymphatic pathways which drain the uterus as well as existing the primary identified node. The aim of SLN biopsy technique is to reduce the morbidity associated with lymphadenectomy while reducing negatively affecting of surgical staging and outcomes.

Despite numerous studies demonstrate that pelvic SLNs can predict the state of regional lymph nodes accurately in early-stage cervical cancer.[7] However, the use of the SLN technique in cervical cancer that to detect lymph node metastasis remains controversial. Meanwhile, the detection rate of this method requires validation. This study assessed the diagnostic performance of SLN mapping in early-stage cervical cancer through combined overall detection rate, bilateral detection rate and sensitivity. Since the SLNs can be identified during surgery by lymphoscintigraphy using technetium 99 ($^{99m}$Tc), blue dye, indocyanine green (ICG) and so on. To clear that each method has different sensitivity and detection rate, we assessed different tracer methods for the technique using a combined technique (blue dye with Tc), Tc or ICG.

## 2. Materials and methods

### 2.1. Literature search strategy

Two authors related to this current study have searched PubMed, Embase and the Cochrane Library from database inception to June 1, 2020 independently. Language of studies was restricted to official publication in English only. Details of identifying studies for this study are presented in Figure 1. The following medical subject heading terms was used: "cervical cancer", "sentinel lymph node", "sentinel lymph node biopsy", "early-stage cervical cancer". Furthermore, the combination of "cervical cancer", "sentinel lymph node", "sentinel lymph node biopsy" and "early-stage cervical cancer" were used as a free text term.

### 2.2. Inclusion and exclusion criteria

Studies were included if they had the following criteria: (1) including a sample size at least 10 patients diagnosed with International Federation of Gynecology and Obstetrics stage (FIGO) IA-IIA cervical cancer; (2) studies mainly focus on SLN mapping; (3) studies reported outcomes measures including the detection rate of the SLN biopsy (overall SLN detection rate: the percentage of patients in which at least 1 SLN was identified;

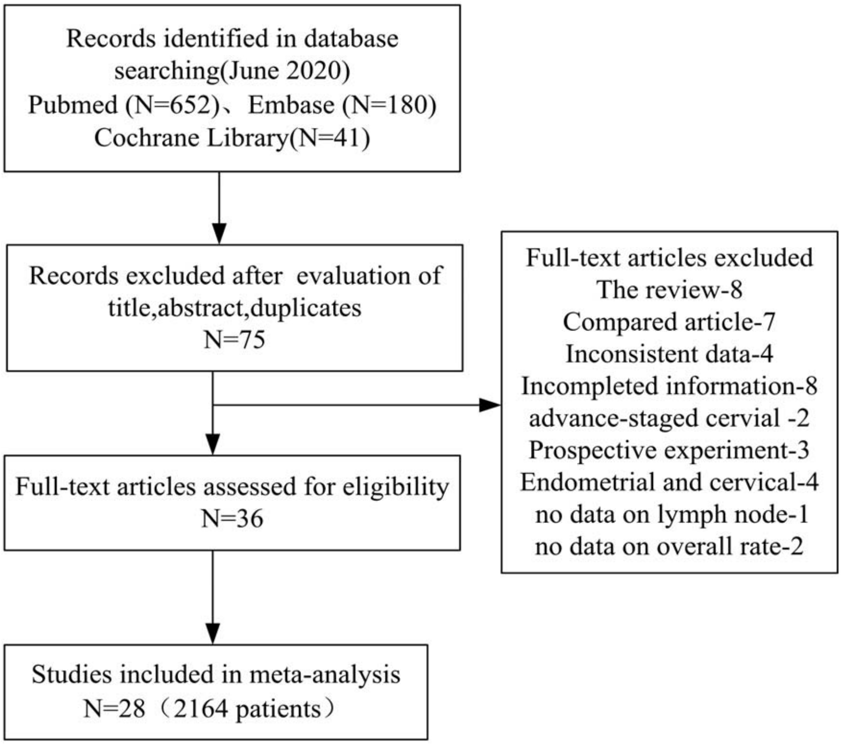


**Figure 1.** Flow diagram of study selection.

**Table 1**

**Characteristics published on sentinel lymph node biopsy in early-stage cervical cancer.**

| Author, year | Study size | Time period | Stage (FIGO) | Median Age (yr) | Histology | Overall DR (per patient) (%) | Bilateral DR (per patient) (%) | Median number of SLN / patient | Sensitivity* (%) | Specificity* (%) | Negative predictive value* (%) (by patient) | Tracer |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Andrea Papadia, 2015[8] | 62 | Between April 2008 and July 2015 | IA-IIA | 44 (25–72) | SCC43; 'AC17; Other2 | 95.1 | 87 | 3 (0–15) | NR | NR | 100 | ICG+blue dye+Tc |
| Berta Diaz-Feijoo, 2019[9] | 128 | Between September 2000 to October 2016 | 1A2,IB1,IIA1 | 48.4±12.2 | SCC79; AC49 | 98.4 | 76 | 2.0 | 79.2 | 100 | 95.4 | Blue dye+Tc |
| V. Balaya, 2019[10] | 405 | Between 2005 and 2012 | IA-IIA | 45.4 (22–85) | SCC250; AC95; other:60 | 94.1 | 80.5 | 3 (1–11) | 91.2 | NR | 97.2 | Blue+isotopic |
| Gloria Salvo, 2017[11] | 188 | From August 1997 to October 2015 | IA1-IIA1 | 38 (21–68) | SCC95; AC65; AS15; other:13 | 90 | 62 | 3 (1–18) | 96.4 | NR | 99.3 | ICG+blue dye+Tc |
| Anna L. Beavis, 2016[12] | 30 | From10/2012 to 02/2016 | ≤IA2,IB1,IB2 | 42.5 (28–77) | SCC20; AC7; AS:3 | 100 | 86.7 | 2 (0–11) | NR | NR | NR | ICG |
| Marrije R. Buist, 2002[13] | 25 | Between December 2000 and May 2002 | IB1,IB2,IIA | 41 (22–55) | SCC18; AC7 | 100 | 88 | NR | 96 | NR | NR | Blue dye+Tc |
| Andrea B. DiStefano, 2005[14] | 50 | Between January 2003 and January 2005 | IA2-IIA | 45.9 (28–65) | SCC42; AC2; AS:6 | 90 | 60 | 1.9 (1–4) 45 patients | NR | NR | 97.2 | Blue dye |
| Hitoshi Niikura, 2004[15] | 20 | Between January 2001 and May 2003 | IB1,IB2,and IIA | 47.5 (31–65) | SCC12; AC:6; AS:2 | 90 | 75 | 2.3 (1–5) | 100 | 100 | 100 | Blue dye+Tc |
| T Lantzsch, 2001[16] | 14 | Between January 1999 and September 2000 | IBI | 46 (28–67) | SCC12; AC2 | 93 | 36 | 1.86 | NR | NR | NR | Tc |
| John D. O'Boyle, 2000[17] | 20 | NR | IB -IIA | 40 (23–65) | SCC13; AC1; AS:4; other:2 | 60 | 25 | 1.15 | NR | NR | NR | Isosulfan blue dye |
| Eric Lambaudie, 2002[18] | 12 | Between April 2001 and March 2002 | IB1,IA2 IB1 | 45.3±11.6 | SCC10; AC2 | 91.7 | 83 | 2.92 | 66 | 100 | 90 | Blue dye+Tc |
| Marie Plante, 2003[19] | 70 | From October 2000 to September 2002 | IA,IB,IIA | 42 (21–63) | SCC48; AC22 | 87 | 60 | 1.93 | 93 | NR | 100 | Blue dye |
| Ju-Hyun Kim, 2018[20] | 103 | From August 2015 to January 2017 | IA1-IIA | 45 (29–77) | SCC72; AC23; AS:4; other:4 | 100 | 85.44 | 2.34 | 71.43 | 100 | 93.98 | ICG |
| Andrea Papadia, 2017[21] | 60 | between December 2008 and November 2016 | IA1-IIA | 47 (27–72) | SCC45; AC1; AS11; other:3 | 91.7 | 83.4 | 3 (0–15) | 93 | 100 | 97 | ICG |
| Naoto Furukawa, 2010[22] | 12 | From August 2007 through December 2008 | IA1,IB1,IIA,IIB | 58 (36–68) | SCC9; AC3 | 83 | 83 | 7 (3–10) | NR | NR | NR | ICG |
| D. WYDRA, 2006[23] | 100 | Between January 2002 and May 2004 | IB1,IB2, IIA | 51.2 (26–82) | SCC94; AC5; AS:1 | 84 | 66 | 1.5 | 86.4 | 100 | 95.5 | Blue dye+Tc |
| J. Hauspy, 2007[24] | 39 | From April 2004 to April 2006 | IA1,IA2,IB1 | 38 (20–67) | SCC18; AC19; AS:2 | 98 | 72 | 2 (0–8) | 100 | 100 | 100 | Tc and/or lymphazurin |
| Shinji Ogawa, 2009[25] | 82 | Between May 2003 and December 2007 | IA1,IA2,IB1, IB2,IIA,IIB | 39 (20–79) | SCC58; AC22; other:2 | 88 | 66 | 1.92 (0–6) | 100 | NR | 100 | Tc |
| Michel Roy, 2011[26] | 211 | From October 2000 to December 2006 | IA1,IA2,IB1 , IB2,IIA | 39 (21–76) | SCC132; AC69; AS:10 | 99.1 | 85.8 | NR | 87.9# | NR | 100 | Tc+ISB |
| Michel Roy, 2011[26] | 166 | From October 2000 to December 2006 | IA1,IA2,IB1,IB2, IIA,IIB | NR | NR | 96.9 (161) | 86.7 (144) | NR | NR | NR | 100 | Tc |
| Pierangelo Marchiole, 2004[27] | 29 | Between January 2001 and May 2002 | IA1,IA2,IB1 | 41 (25–60) | SCC18; AC+AS:11 | 100 | 89.6 | NR | NR | NR | 87.5 | Blue dye |
| Lotten Darlin, 2010[28] | 105 | From March 2005 to April 2009 | IA1–IIA | 40 (24–76) | SCC60; AC44; other:1 | 90 | 59 | 2 (0–4) | 94 metastatic SLN | NR | 100 cancers ≤2 cm | Tc |
| P. Pelin Kara, 2008[29] | 32 | NR | IA2–IIA | 46 (38–80) | SCC24; AC3; AS1; other:4 | 100 | 50 | 2.09 (1–5) | NR | NR | NR | Tc |
| Omer Devaja, 2012[30] | 86 | From January 2005 to September 2011 | IA1–IIA | 37 (23–66) | SCC57; AC23; AS:5; other:1 | 97.7 | 73.3 | 3 (1–7) | NR | NR | 100 | Blue dye+Tc |
| A. Nickles Fader, 2008[31] | 38 | NR | IA1–IIA, IIB (1) | NR | SCC26; AC10; AS:2 | 92.1 | 47.4 | 2.1† | NR | NR | NR | Blue dye+Tc |
| Michael Frumovitz, 2012[32] | 20 | From March 2009 to June 2011 | IA1–IIA | 35 (21–68) | SCC14; AC2; AS:3; other:1 | 85 | 60 | 3 (0–8) | NR | NR | NR | Blue dye+Tc+India ink |
| David M. Kushner, 2007[33] | 20 | Between December 2003 and February 2006 | IA2-IIA | 39.3 (22–66) | SCC11; AC8; other:1 | 100 | 100 | 1.6 (1–4) | NR | NR | 100 | Blue dye+Tc |
| Beatrice Cormier, 2011[34] | 122 | Between March 2003 and September 2010 | IA1 withLVI to IIA | 35 (15–68) | SCC40; AC80; other:2 | 93 | 75 | 3 (0–13) | 87.5 | NR | 96.8 | Blue dye+Tc |
| John P. Diaz, 2010[35] | 81 | June 2003 to August 2009 | IA1–IIA | 36 (15–68) | SCC28; AC53 | 95 | 72 | 3 (0–10) | 88 | 100 | 95 | Blue dye+Tc |
| Total | 2164 | | | | | | | | | | | |

AC = adenocarcinoma; AS = adenosquamous carcinoma; CI = confidence interval; DR = detection rate; FIGO = International Federation of Gynecology and Obstetrics; ICG = indocyanine green; NR = not reported; SCC = squamous cell carcinoma; SLN = sentinel lymph nodes; Tc = technetium 99.

* Calculated on a per-patient basis.

\# Sensitivity of Tc99.

† A mean of 2.1 SLNs were detected per patient.

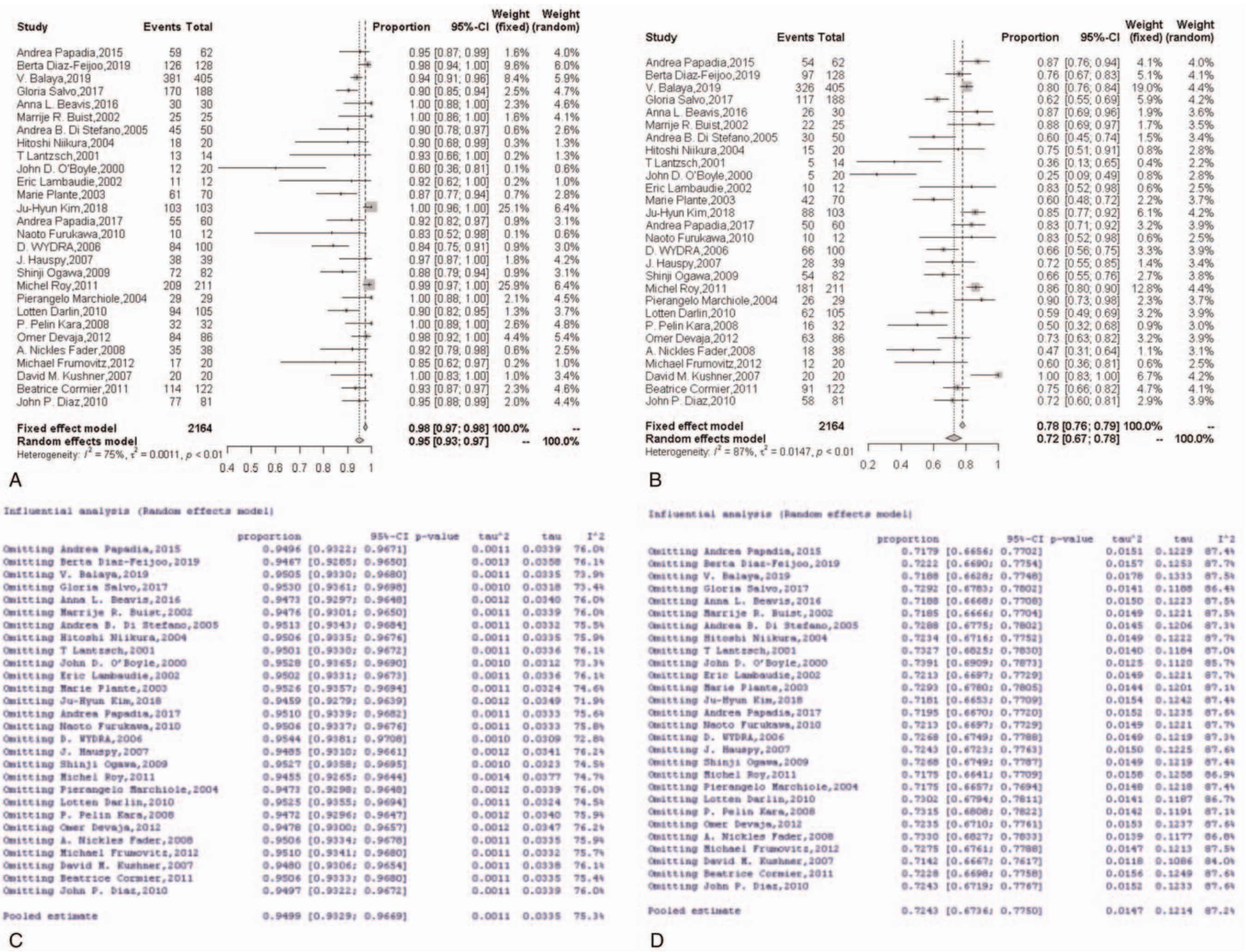

**Figure 2.** Forrest plot and sensitivity of the pooled overall and bilateral SLN detection rate. (A) Forrest plot of the pooled overall SLN detection rate [$I^2=75\%$, a random effects model was used to estimate the combined overall detection rate of SLN mapping, with a result of 95% (95% CI: 93%–97%)]. SLN = sentinel lymph node.). (B) Forrest plot of the combined bilateral SLN detection rate [$I^2=87\%$, a random effects model was used to estimate the pooled bilateral detection rate of SLN mapping, with a result of 72% (95% CI: 67%-78%)]. (C) Sensitivity of the pooled overall SLN detection rate; (D) Sensitivity of the combined bilateral SLN detection rate.

bilateral SLN detection rate: the percentage of patients with bilateral sentinel node identification).

The following information was exclusion criteria: sample size less than 10 patients, reviews, comments, case reports, editorials or meeting abstracts. The article lack of core data or incomplete information, advanced cervical cancer, articles included endometrial adenocarcinoma and cervical cancer. To avoid duplicating sample size of patient data in publications, we used articles with the largest sample size.

Working independently, 2 reviewers screened titles and abstracts, if necessary, reviewed full-text articles for inclusion exclusion, disagreements were settled by consensus.

### 2.3. Data extraction and quality assessment

Summary information includes first author, publication year, study size, stage (FIGO), number and median age of patients, tumor histology, median number of SLN. The sensitivity associated with SLN surgery is described as the true positive total number of histopathologically positive patients. Wherever possible, to evaluate the performance, the sensitivity, specificity, negative predictive value was extracted.

The QUADAS-2 tool was used by 2 reviewers independently to assess the risk of bias for included studies. When have disagreements in the process of study selection or data collection, problems were solved by review of the original articles.

### 2.4. Statistical analysis

R-3.6.1 software for Windows was using for statistical analysis. The heterogeneity of the studies was evaluated using the inconsistency statistic ($I^2$), results were considered homogenous when $I^2<50\%$ and the $P$ value $\geq$.10, in these conditions fixed-effect model was calculated. Otherwise ($I^2>50\%$ or $P$ value <.10), the studies were considered heterogeneous. At the same time, a random-effect model was employed. When heterogeneity exists, sensitivity analysis will be used to analyze the possible causes of heterogeneity. After checking for consistency, the

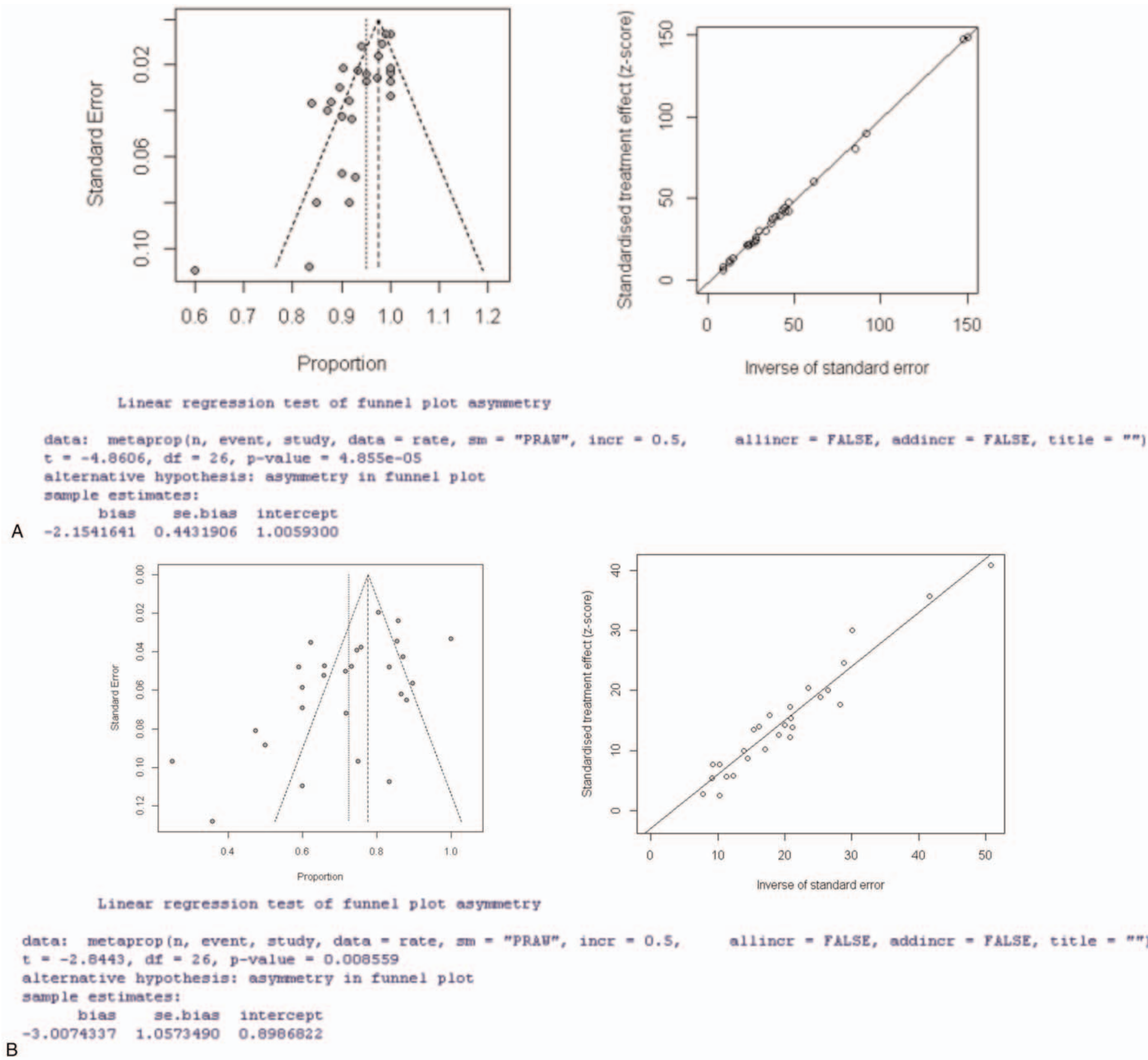


**Figure 3.** Publication bias of the pooled overall and bilateral SLN detection rate. (A) Funnel plots, inverse of standard error and Egger's regression of the pooled overall SLN detection rate; (B) Funnel plots, inverse of standard error and Egger's regression of the combined bilateral SLN detection rate.

Metaprop module in the R-3.6.1 statistical software package was used for the meta-analysis. The consequences were depicted graphically as forest plots. Publication bias was displayed graphically using funnel plots and Egger's regression.

## 3. Results

### 3.1. Characteristics of studies

A total of 2164 patients in 28 studies.[8–35] that met the inclusion criteria published between 2000 and 2019 were enrolled in our study. Figure 1 displays flow chart of the search process. 28 studies were included ranging from 12 to 405 patients with a median age between 35 and 58 years old. The characteristics of the 28 studies, including patient age, study size, clinical study time period, stage (FIGO), median age, tumor histology, overall detection rate, bilateral detection rate, sensitivity, specificity, negative predictive value are listed in Table 1. We calculate the SLN detection rate including blue dye with Tc, Tc, and ICG according to the different tracer methods.

### 3.2. Combined detection rate, sensitivity of SLNs

All 28 studies submitted data for the analysis of detection rate. $I^2$ value was 75% of the combined overall detection rate as well as 87% of the combined bilateral detection rate reflecting a high heterogeneity among the studies. Thence, a random effects model was used to estimate the combined overall detection rate of SLN

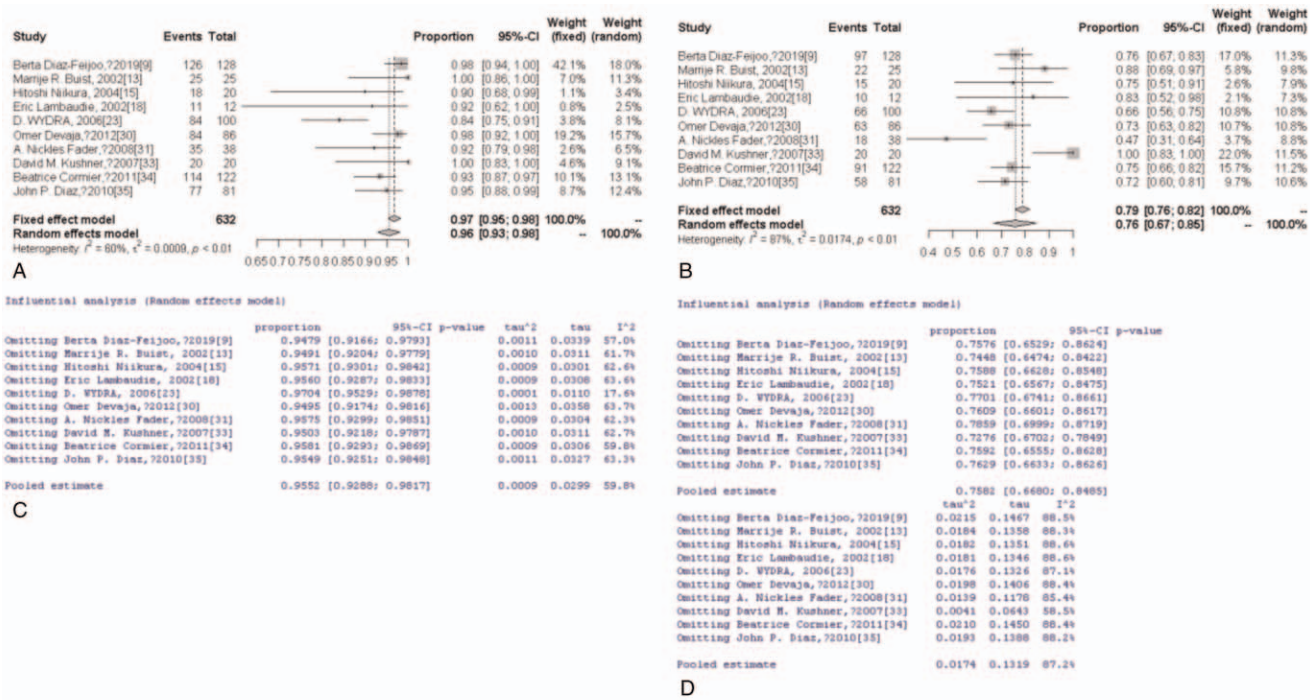


Figure 4. Forrest plot and sensitivity of the overall and bilateral SLN detection rate using blue dye with Tc technique. (A) Forrest plot of the overall SLN detection rate using blue dye with Tc technique. [$I^2$ = 60%, A random effects model was used to estimate the overall detection rate of SLN mapping, with a result of 96%]; (B) Forrest plot of the bilateral SLN detection rate using blue dye with Tc technique. [$I^2$ = 87%, A random effects model was used to estimate the bilateral detection rate of SLN mapping, with a result of 76%]; (C) Sensitivity of the overall SLN detection rate using blue dye with Tc technique; (D) Sensitivity of the bilateral SLN detection rate using blue dye with Tc technique.

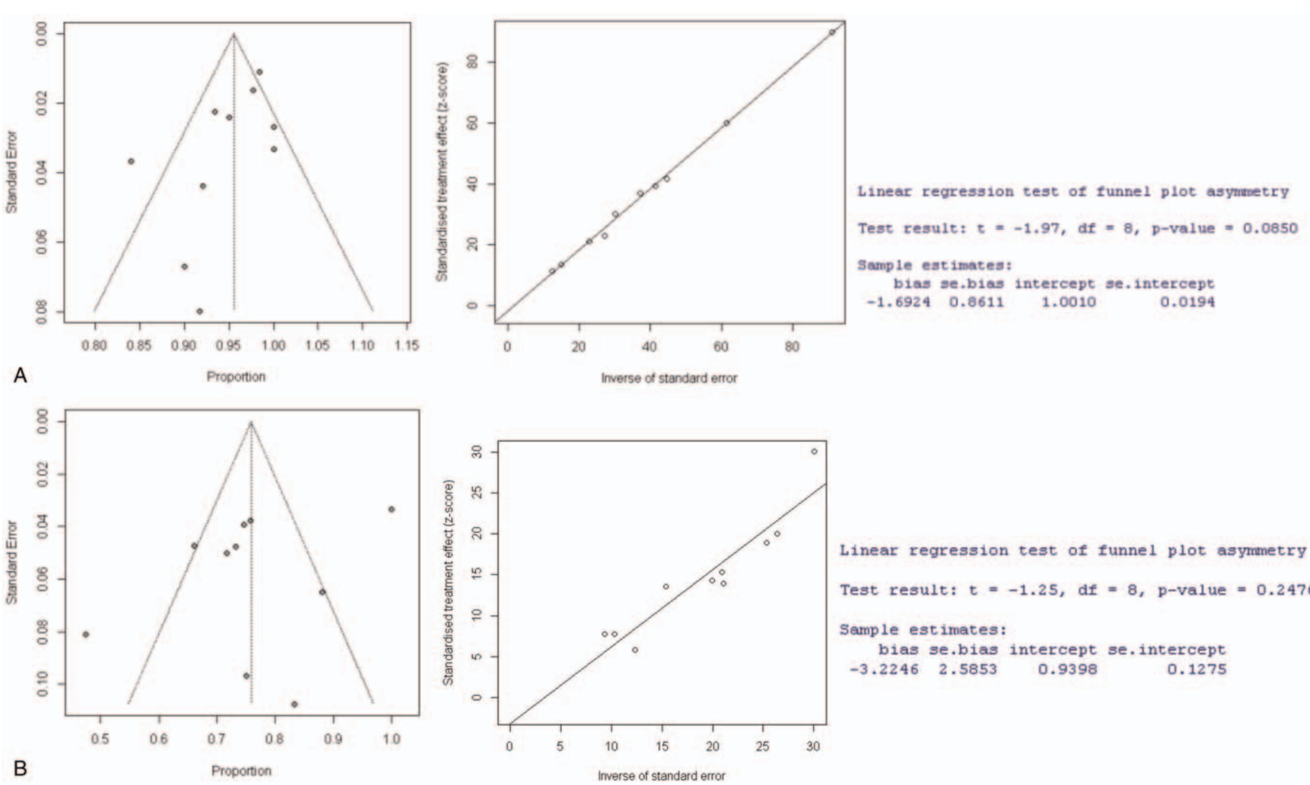


Figure 5. Publication bias of the overall and bilateral SLN detection rate using blue dye with Tc technique. (A) Funnel plots, inverse of standard error and Egger's regression of the overall SLN detection rate using blue dye with Tc technique; (B) Funnel plots, inverse of standard error and Egger's regression of the bilateral SLN detection rate using blue dye with Tc technique.

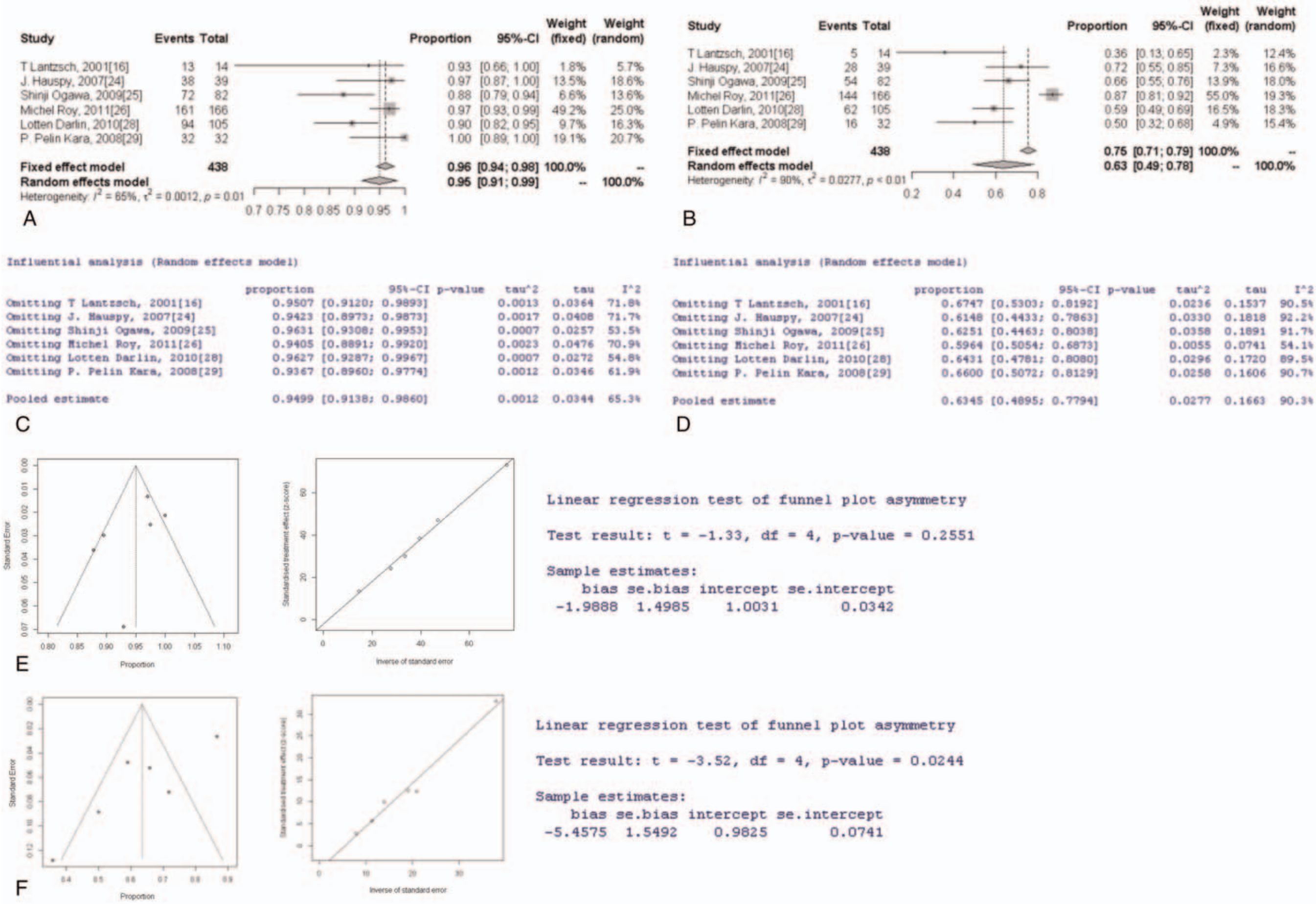


**Figure 6.** Forrest plot, sensitivity and publication bias of the overall and bilateral SLN detection rate using Tc technique. (A) Forrest plot of the overall SLN detection rate using Tc technique. [$I^2=65\%$, A random effects model was used to estimate the overall detection rate of SLN mapping, with a result of 95%]; (B) Forrest plot of the bilateral SLN detection rate using Tc technique. [$I^2=90\%$, A random effects model was used to estimate the bilateral detection rate of SLN mapping, with a result of 63%]; (C) Sensitivity of the overall SLN detection rate using Tc technique; (D) Sensitivity of the bilateral SLN detection rate using Tc technique; (E) Funnel plots, inverse of standard error and Egger's regression of the overall SLN detection rate using Tc technique; (F) Funnel plots, inverse of standard error and Egger's regression of the bilateral SLN detection rate using Tc technique.

mapping, with a result of 95% (95% confidence interval (CI): 93%–97%) (Fig. 2A). A random effects model was designed to estimate the pooled bilateral detection rate of SLN mapping, with a consequence of 72% (95% CI: 67%–78%) (Fig. 2B).

Figure 2C and D demonstrate the sensitivity of the detection rates in SLN mapping. The pooled sensitivity of SLN overall detection rate was 94.99% (95% CI, 93.29%–96.69%, $I^2=$ 75.3%) (Fig. 2C) with a sensitivity of 72.43% (95% CI, 67.36%–77.50%, $I^2=87.2\%$) bilateral sentinel node detection rate (Fig. 2D).

### 3.3. Detection rate, sensitivity of SLNs for different technologies

We evaluated the diagnostic accuracy SLN biopsy specimens collected from patients using blue dye with Tc (10 studies), Tc (6 studies), ICG (4 studies). $I^2$ value ($I^2>50\%$) reflecting a high heterogeneity among the studies, thence, a random effects model was used to estimate the detection rate of SLN mapping except ICG bilateral rate detection ($I^2=0\%$, $P=.97$). The SLN overall detection rates using blue dye with Tc, Tc, ICG were 96% (Fig. 3A), 95% (Fig. 4A) and 98% (Fig. 5A). The SLN bilateral detection rates using blue dye with Tc, Tc, ICG were 76% (Fig. 3B), 63% (Fig. 4B), and 85% (Fig. 5B), respectively.

The sensitivity of SLN overall detection rate using blue dye with Tc, Tc, ICG were 95.52% (Fig. 3C), 94.99% (Fig. 4C), and 97.76%% (Fig. 5C) while the bilateral detection rate were 75.82% (Fig. 3D), 63.45% (Fig. 4D), and 84.96% (Fig. 5D).

### 3.4. Publication bias of the included studies

We included 28 studies to analysis publication bias. Additionally, we generated funnel plots and Egger's regression intercepts for overall detection rate and bilateral detection rate for the SLN mapping in order to assess the publication bias of aggregated data. Every point is a separate study. Funnel plots and Egger's regression revealed noticeable evidence of publication bias (Fig. 6A, B). However, based on the plots, The results indicate that no significant different publication bias was emerged in the meta-analysis using blue dye with Tc, Tc, ICG (Figs. 7A, B, 4E, F, and 5E, F).

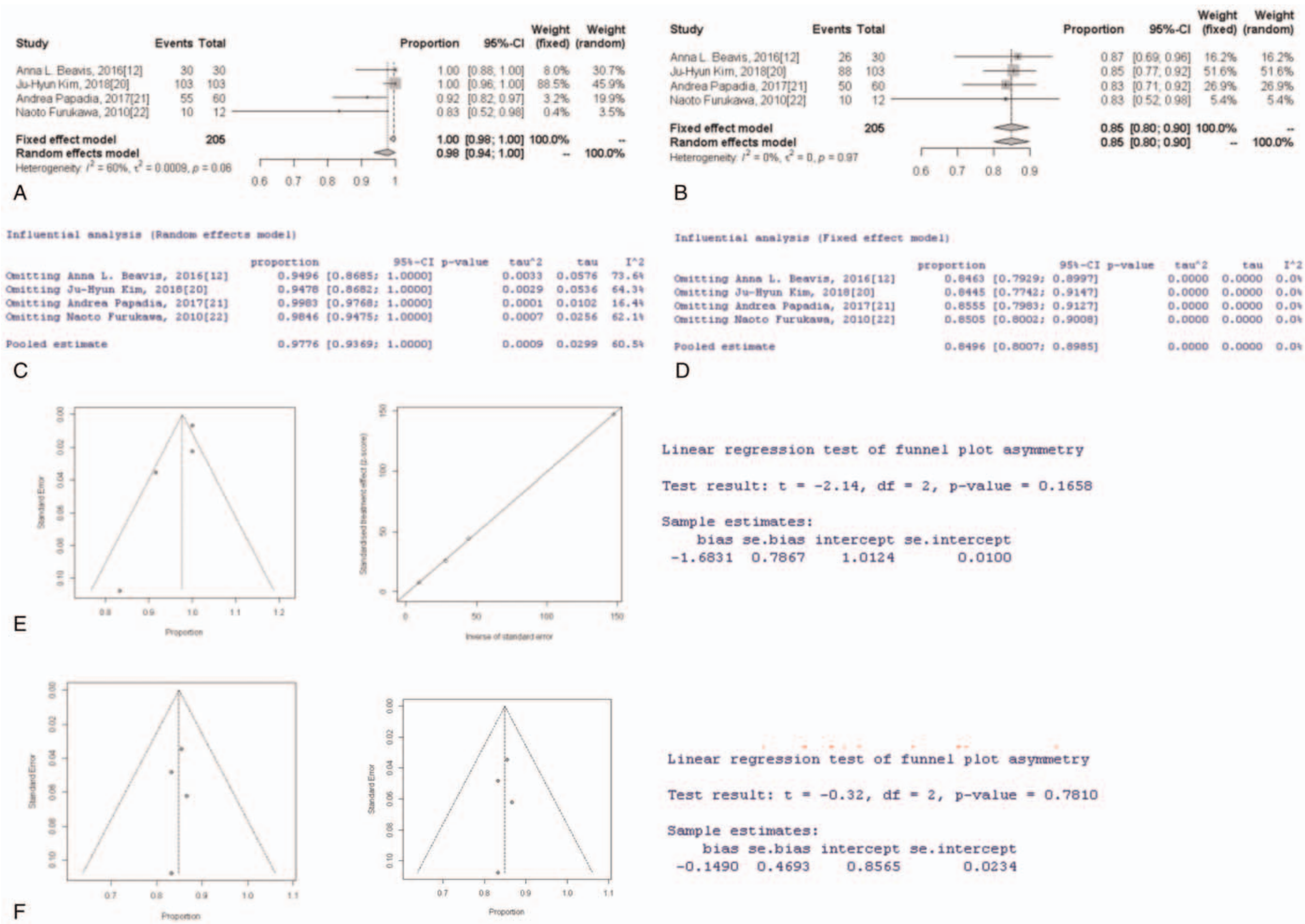


**Figure 7.** Forrest plot, sensitivity and publication bias of the overall and bilateral SLN detection rate using ICG technique. (A) Forrest plot of the overall SLN detection rate using ICG technique. [$I^2$=60%, A random effects model was used to estimate the overall detection rate of SLN mapping, with a result of 98%]; (B) Forrest plot of the bilateral SLN detection rate using ICG technique. [$I^2$=0%, $P$=.97, A fixed effects model was used to estimate the bilateral detection rate of SLN mapping, with a result of 85%]; (C) Sensitivity of the overall SLN detection rate using ICG technique; (D) Sensitivity of the bilateral SLN detection rate using ICG technique; (E) Funnel plots, inverse of standard error and Egger's regression of the overall SLN detection rate using ICG technique; (F) Funnel plots, inverse of standard error and Egger's regression of the bilateral SLN detection rate using ICG technique.

## 4. Discussion

### 4.1. Main findings

The pathologic status of lymph nodes is a major prognostic factor in patients with early-stage cervical cancer.[36] Therefore, pelvic lymphadenectomy and radical hysterectomy still remain the standard for women with early-stage cervical cancer. However, the incidence of lymph node metastases in early-stage cervical cancer is just 15% to 20%.[37] Patients undergo unnecessary pelvic lymph node dissection, which enhances complications of the procedure. To reduce the number of patients undergoing lymphadenectomy together with the occurrence of early and late complications after surgery. Clinical trials have established the procedure as an indispensable part of the treatment of patients with melanoma and breast cancer.[38] Lymphatic mapping together with SLN biopsy of early-stage cervical cancer has been assessed in numerous trials. There was no difference in the overall detection rates between mapping agents, surgical method, patients with and without conization or between patients with tumors <2 and ≥2 cm,[11] the sensitivity can be >99% in well-selected patients at the mean time.[39] In cervical cancer, the clinical research of SLN biopsy is also actively carried out and has achieved ideal clinical treatment results. It has been incorporated into the cervical cancer National Comprehensive Cancer Network (NCCN) treatment guidelines, which are a very prospective surgical approach. Despite a large number of women with early-stage cervical cancer in some regions and countries, such as China, the SLN mapping technique has not been promoted in the hospital. The reason largely due to the role of SLN evaluation and the detection rates together with techniques of SLN biopsy in early-stage cervical cancer remains unclear.

Therefore, our article summarizes an overview of the published literature of SLN including pooled detection rates of early-stage cervical cancer and analyzes the separate detection rate (overall detection rate, bilateral detection rate) using blue dye with Tc, Tc and ICG technique. Additionally, Jerry reports that the average detection rate ranges from 78% to 100%.[40] This is in agreement with the recent meta-analysis by Kadkhodayan which reported pooling detection rate of 89.2% and sensitivity was 90% when compiling data from 67 published studies of uterine cervix cancer SLN mapping.[41] The observed results of this meta-analysis compare favorably with those reported in previous studies. In our study, the combined overall detection rate of SLN mapping was 95% with a 72% bilateral SLN detection rate. The sensitivity of the combined overall detection rate was 94.99% together with 72.43% bilateral SLN detection rate. Moreover, based on the results of our study, the overall detection rate (98%) as well as bilateral rate (85%) of ICG seems to be a better SLN mapping technique among the method of SLN mapping (using blue dye with Tc, Tc or ICG). The latest detailed data shows that the pooled specific side detection rates were 85% in tumors up to 2 cm, 67% in tumors over 2 cm, 75.2% for blue dye, 74.7% for Tc, 84% for combined technique, and 85.5% for ICG.[42] These consequences consistent with the results of other authors. Despite caveats in current evidence and discrepancies in available data, there is growing evidence that SLN mapping is feasible and results in an excellent detection rate in patients with cervical cancer.

### 4.2. Limitations

There are certain limitations in this meta-analysis. First of all, although our study can detect the difference in the detection rate through cartographic technology among blue dye with Tc (632 patients included in 10 studies), Tc (438 patients included in 6 studies) and ICG technique (206 patients included in 4 studies). Based on the results of the current study, we believe that SLN biopsy using ICG is the most useful method of SLN detection in patients with uterine cervical cancer, many studies have shown that using ICG is associated with high detection rates in early-stage cervical cancer compared with other modalities, such as $^{99}$mTc with blue dye, blue dye alone.[43] Other studies showed[44] that the detection rates of SLN using $^{99}$m tech ($^{99}$mTc)-tincolloid, indigo carmine and ICG were 85.8%, 20.2% and 61.6%, respectively. Because of fewer articles and insufficient cases, the reliability of the results in our article needs further verification.

Secondly, publication bias is a major issue that could be taken into account in some systematic reviews. Therefore, we evaluated the publication bias through a funnel plots together with Egger's regression. Funnel plots of detection rate revealed some asymmetry of publication bias. Egger's regression intercept made the overall detection rate 2.15 ($P < .05$) while the bilateral detection rate was 3.007 ($P < .01$), which indicates that Egger's tests were also statistically significant. This indicates publication bias may be a fundamental limitation in this meta-analysis and deserves attention as well. However, after adjusting for possible publication bias or utilizing fixed models, the combined detection rate and sensitivity hardly changed. In a nutshell, publication bias may not be considered as a major limitation in our meta-analysis.

### 4.3. Significance

In conclusion, our research demonstrates SLN mapping has high detection rates of patients with early-stage cervical cancer and ICG has the highest detection rate of the 3 tracers. SLN mapping has been a sensitive method, which can be an alternative standard for staging and management of select patients with cervical cancer. Whether SLN mapping can replace a more complete lymphatic assessment has to be assessed in a larger, prospective, randomized, follow-up study of patient with early-stage cervical cancer.

## Author contributions

Lijun Wang: Data curation, Formal analysis, Investigation, Software, Writing – original draft.
Shanshan Liu: Formal analysis, Software.
Ting Xu: Investigation.
Linnan Yuan: Software.
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