Japanese Journal of Clinical Oncology, 2025, 1–12
https://doi.org/10.1093/jjco/hyaf063
Original Article

JJCO Japanese Journal of Clinical Oncology
OXFORD

Sentinel lymph node biopsy mapped with carbon nanoparticle suspensions in patients with cervical cancer: a systematic review and meta-analysis

Ting Qu[1], Guangfu Zeng[1], Jinmei Yang[1], Kexin Tang[1,2], Ping Xie[1,3,*], Xiaohai Tang[1,*]

[1]Sichuan Enray Pharmaceutical Sciences Company, No. 1480 North Tianfu Avenue, High - tech Zone, Chengdu 610041, China
[2]Department of Biology, Emory University, 1510 Clifton Road NE, Atlanta, GA 30322, United States
[3]State Key Laboratory of Oral Diseases, West China, College of Stomatology, Sichuan University, No. 14, Section 3, Renmin South Road, Chengdu 610041, China

*Corresponding authors. Ping Xie, State Key Laboratory of Oral Diseases, Sichuan University, No. 14, Section 3, Renmin South Road, Chengdu 610000, China. E-mail: 1137528028@qq.com; Xiaohai Tang, Sichuan Enray Pharmaceutical Sciences Company, No. 1480 North Tianfu Avenue, High-tech Zone, Chengdu 610000, China. E-mail: pharmmateceo@enraypharm.com

Abstract

Background: The mapping technique significantly influences the detection rate of sentinel lymph nodes in cervical cancer. This study aims to evaluate the clinical efficacy of carbon nanoparticle suspensions (CNSs) in guiding sentinel lymph node biopsy (SLNB) for cervical cancer patients.

Methods: Systematic search of China National Knowledge Infrastructure, Cqvip, Wanfang, PubMed, EMBASE, Web of Science, and the Cochrane Library from inception until June 2024. Studies on cervical cancer patients receiving SLNB with CNSs are included. An individual participant data meta-analysis was conducted. The protocol was prospectively registered on the International Prospective Register of Systematic Reviews (PROSPERO: CRD42024569290).

Results: In total, 26 publications involving 1671 patients were analyzed. The overall detection rate of CNSs in SLNB for cervical cancer was 0.92, with bilateral and unilateral detection rates of 0.74 and 0.20, respectively. This detection rate exhibited a correlation with lesion size and the administration of neoadjuvant chemotherapy. The pooled sensitivity, specificity, positive likelihood ratio, and negative likelihood ratio were 0.93 (95% CI: 0.88–0.96, $I^2 = 35.89\%$), 1.00 (95% CI: 0.98–1.00, $I^2 = 90.01\%$), 216.84 (95% CI: 40.47–1161.85, $I^2 = 77.68\%$), and 0.07 (95% CI: 0.05–0.12, $I^2 = 54.96\%$), respectively. The area under the curve of the summary receiver operating characteristic curve was 0.97. No significant differences were found in subgroup analyses based on the method, time, and dose of CNS injection. However, significant publication bias was detected among the included studies based on Deeks' funnel plot [Slope (Bias) = −15.61, $P = .001$]. Nonetheless, sensitivity analysis confirmed the reliability and stability of the results.

Conclusions: This meta-analysis highlights the accuracy and feasibility of using CNSs for SLNB in patients with cervical cancer, particularly for lesions <2.0 cm and patients untreated with neoadjuvant chemotherapy.

Keywords: detection rate; sentinel lymph nodes; cervical cancer; carbon nanoparticle suspensions; meta-analysis

Introduction

Cervical cancer is a significant health concern worldwide, particularly in developing countries, where its incidence remains high [1]. The prognosis of cervical cancer is closely tied to lymph node metastasis, with the 5-year overall survival (OS) rate declining from 85% and 84.6% in cases of single or localized metastasis to 50% and 20% in those with multiple or extrapelvic metastases [2]. Similarly, 5-year disease-free survival is observed to decrease from 88% in patients with negative nodes to 57% in those with positive nodes [3]. Moreover, the number of positive lymph nodes demonstrates a significant correlation with OS outcomes, with each additional metastatic node substantially reducing the 5-year OS rate [4,5]. Inoue and Morita demonstrated that in stage IB–IIB cervical cancer, 5-year OS rates for patients with 0–3 and ≥4 positive lymph nodes were 89%, 81%, 41%, and 23%, respectively [5]. Additionally, Park and Bae reported the 5-year OS rates for patients with 0, 1, and cervical cancer, 5-year OS rates with OS 0%, and 47%, respectively ($P = .006$) [4]. Therefore, identifying the status of lymph nodes is a critical factor influencing patient survival.

Currently, radical hysterectomy plus bilateral pelvic lymphadenectomy is the standard surgical approach for early-stage cervical cancer [6]. However, postoperative pathological analysis reveals that only 58.5% of these patients are at risk for lymph node metastasis, suggesting that ∼41.5% may undergo bilateral pelvic lymphadenectomy unnecessarily [7]. Furthermore, pelvic lymph node dissection is a complex, time-consuming, and costly procedure with a range of short- and long-term complications that include lymphocele, vascular nerve injury, ureteral injury, venous thrombosis, and pelvic adhesions [8]. Extensive surgical interventions, such as axillary lymph node dissection and the removal of a greater number of lymph nodes, have been strongly linked to the development of lymphedema, which can even progress to severe lower limb swelling known colloquially as "elephant leg," negatively impacting the prognosis of cancer patients [8]. Sentinel lymph node biopsy (SLNB) in early-stage cervical cancer serves as a reliable indicator for the presence of pelvic lymph node metastasis [9]. An analysis of prognosis in 1188 patients with early-stage cervical cancer demonstrated that there were no significant differences in 2-year and 5-year

Received 21 January 2025; **editorial decision** 27 March 2025; **accepted** 31 March 2025

recurrence-free survival rates between those undergoing SLNB alone and those undergoing pelvic lymphadenectomy [9]. This may be attributed to the fact that the sentinel lymph nodes (SLNs) serve as the first stop of lymphatic drainage from the tumor, thus providing a representative assessment of the corresponding regional lymph nodes [10]. The use of SLNB in cervical cancer patients offers the potential to reduce morbidity while still enabling comprehensive evaluation of the pelvic lymph nodes [9]. Moreover, compared to pelvic lymphadenectomy, SLNB alone significantly reduces surgical duration, intraoperative blood loss, transfusion rates, lower limb lymphedema, and the incidence of postoperative infections [9,11]. Consequently, the accurate assessment of SLN metastasis is of paramount significance for the management of cervical cancer, as it not only facilitates the complete resection of both the tumor and metastatic lymph nodes but also minimizes surgical complications.

SLN mapping with tracers is an effective adjunctive method for assessing the status of SLNs. SLN mapping has been endorsed by the National Comprehensive Cancer Network guidelines as a recommended method for surgical lymph node assessment in patients with cervical cancer [1]. Approved by China's National Medical Products Administration (approval number H20041829), carbon nanoparticle suspensions (CNSs) have been widely used in clinical tumor surgery for 20 years. However, CNSs remain limited to China due to a lack of international approval [12]. CNSs are specially smooth spherical particles with an average diameter of 150 nm, exhibiting exceptional lymphatic targeting properties [12]. When administered peritumorally, CNSs preferentially enter lymphatic vessels, which have larger gaps (100–500 nm) compared to blood capillaries (30–50 nm), ensuring exclusive lymphatic uptake [12]. Once within the lymphatic system, CNSs are phagocytosed by macrophages and accumulate in lymph nodes, resulting in distinct black staining [12]. This creates a stark contrast with surrounding tissues, enhancing the visualization and identification of SLNs [13,14]. The identification of lymph nodes using CNSs is straightforward, relying solely on the presence of black staining without the need for extra equipment. Importantly, CNSs remain confined to the lymphatic system, avoiding entry into the bloodstream, which contributes to their safety and efficacy in SLN mapping [15,16]. CNSs have been proven effective in tracing SLNs in various solid tumors, such as colorectal cancer, breast cancer, and thyroid cancer [14,15,17]. Previous research also indicated that CNSs are a safe and feasible tracer with significant potential for application in early-stage cervical cancer [18–20].

Currently, single-center studies have consistently demonstrated the benefits of CNSs, with systematic reviews and meta-analyses further supporting these findings, as seen in breast and thyroid cancer surgery [13,15]. However, a systematic review and quantitative synthesis of the application of CNSs in cervical cancer surgery are currently lacking. Therefore, it is imperative to underscore the necessity for additional investigations to definitively ascertain the efficacy of CNSs in cervical cancer. This meta-analysis aims to systematically evaluate the clinical efficacy of CNSs in guiding SLNB for cervical cancer patients. By synthesizing data from multiple studies, it seeks to identify the key parameters influencing CNSs effectiveness, thereby contributing to informed clinical decision-making and optimized treatment strategies.

Patients and methods

Protocol registration and reporting

The study protocol was registered with PROSPERO, the International Prospective Register of Systematic Reviews, under the registration number CRD42024569290.

Search methodology

A comprehensive literature search was conducted using several databases, including the China National Knowledge Infrastructure, Cqvip, Wanfang Electronic Database, PubMed, EMBASE, Web of Science, and the Cochrane Library. The search encompassed all relevant papers available from the inception of these databases up to July 2024. The Medical Subject Heading (MeSH) terms utilized in the search included: uterine cervical neoplasms/surgery, cervical carcinoma, cervical cancer, cervix cancer, cervix carcinoma, endocervical carcinoma, carbon nanoparticle, nano-carbon, carbon nanoparticles suspensions, CNSs, and SLNB.

Study inclusion and exclusion criteria

Inclusion criteria: (i) Patients diagnosed with cervical cancer. (ii) Concurrent use of CNSs for SLNB mapping. (iii) Availability of diagnostic methods and clinicopathological data. (iv) SLNB as the primary focus of the study. (v) Sufficient primary data to calculate totals for true negative, false negative (FN), false positive, and true positive results.

Exclusion criteria: (i) Letters, editorials, review articles, and case reports. (ii) Studies with overlapping information.

Data extraction

The search data were exported to EndNote X9 (Clarivate Analytics, Philadelphia, PA, USA). After removing duplicates, the data were independently extracted and cataloged by the two primary investigators (Y.G. and G.Z.). Any disagreements were resolved through consultation with a third investigator (T.Q.). The following information was collected: author, year, country, study design, number of recruited patients, detection rate, injection method, concentration of CNSs, the total volume of the CNSs, time of course, injection depth, injection time, pre-surgery injection timing or SLNs black staining time, minimally invasive surgery/open, and tumor stage.

Risk of bias assessment

The Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) protocol was referenced for quality assessment of the selected studies. These guidelines evaluate the degree of bias in the included studies across four major domains: flow and timing, reference standard, index test, and patient selection. The highest possible score is 14, which indicates high-quality study.

Statistical analysis

For this meta-analysis, Stata/MP 17.0 (StataCorp LLC, College Station, TX, USA) was employed. Study heterogeneity was assessed using I^2 and the Chi-square-based Q statistic. Statistical significance was defined as $I^2 > 50\%$ or $P < .05$. A fixed-effect model (Mantel–Haenszel) was utilized when no heterogeneity was detected, while a random-effect model (DerSimonian and Laird) was applied if heterogeneity was present.

Sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), diagnostic score (DS), and diagnostic odds ratio (DOR) were analyzed using a bivariate meta-analysis model. Estimates and their 95% confidence intervals (CI) were derived using appropriate statistical methods. The area under the curve (AUC) and summary receiver operating characteristic (SROC) were also calculated, with higher diagnostic accuracy suggested by an AUC near 1.0. Posttest probability was analyzed using the Fagan nomogram. Publication bias was examined with the Deeks' test for funnel plot asymmetry.

Results

Characteristics of included studies

We initially identified 988 potentially relevant publications. After removing 324 duplicates and excluding 504 irrelevant studies based on titles and abstracts, 160 articles remained for eligibility assessment (Fig. 1). An additional 35 articles were excluded for the following reasons: two studies due to inaccessible full texts, eight studies for duplicate data, five studies were reviews, and 20 studies had incomplete data. Ultimately, 26 studies [18–43], involving a total of 1671 patients, were included in our meta-analysis. CNSs were injected into the normal cervical tissue around the lesions in all articles. The injection methods for CNSs included at the 3 and 9 o'clock positions or at the 3, 6, 9, and 12 o'clock positions (four quadrants). CNS concentrations ranged from 16.67 to 50 mg/ml, with injected volumes varying from 0.4 to 3 ml. The injection duration was typically from 1 to more than 4 min, and the injection depth ranged from 0.1 to 2 cm. CNSs were administered preoperatively in 14 studies and intraoperatively in 12 studies. The pre-surgery injection timing ranged from 15 min to 15 h, while the SLNs black staining time ranged from 3 min to 15 min. Of the surgical procedures reported, 18 studies were minimally invasive surgeries (MIS), four studies were either MIS or open surgeries, and four studies provided no relevant information. The characteristics of the included studies are summarized in Table 1.

Diagnostic accuracy

The overall detection rate of CNSs in SLNB for cervical cancer was 0.92 (95% CI: 0.87–0.96, I^2 = 89.88%, Fig. 2. (A) The bilateral detection rate of CNSs in SLNB for cervical cancer was 0.74 (95% CI: 0.65–0.83, I^2 = 80.86%), while the unilateral detection rate was 0.20 (95% CI: 0.14–0.27, I^2 = 67.31%, Fig. 2. (B) In the subgroup analysis of CNSs detection rates in SLNB for cervical cancer, stratified by lesion size, the following results were observed: For lesions smaller than 2.0 cm, the detection rate was 0.99 (95% CI: 0.97–1.00, I^2 = 53.24%). For lesions ranging from 2.0 to 3.9 cm, the detection rate was 0.94 (95% CI: 0.84–1.00, I^2 = 77%). For lesions equal to or larger than 4 cm, the detection rate was 0.88 (95% CI: 0.79–0.94, I^2 = 15.64%, Fig. 3. (A) In the subgroup analysis of CNSs detection rates in SLNB for cervical cancer, stratified by the administration of neoadjuvant chemotherapy, the following results were observed: Among patients who received neoadjuvant chemotherapy, the detection rate was 0.88 (95% CI: 0.76–0.97, I^2 = 0.00%). In contrast, for patients who did not receive neoadjuvant chemotherapy, the detection rate was 0.99 (95% CI: 0.96–1.00, I^2 = 44.62%, Fig. 3. (B). Figure 4 demonstrates the forest plot of sensitivity, specificity, PLR, NLR, DS, and DOR for CNSs in SLNB of cervical cancer. The overall pooled sensitivity and specificity of all studies were 0.93 (95% CI: 0.88–0.96, I^2 = 35.89%) and 1.00 (95% CI: 0.98–1.00, I^2 = 90.01%). The overall pooled PLR and NLR were 216.84 (95% CI: 77.68–89.01, I^2 = 77.68%) and 0.07 (95% CI: 0.05–0.12, I^2 = 54.96%), respectively. The pooled DS was 7.97 (95% CI: 6.20–9.74, I^2 = 63.04%). The pooled DOR was 2891.96 (95% CI: 491.86–17003.63, I^2 = 100.00%). The SROC curve demonstrated an AUC of 0.97, which indicated excellent diagnostic accuracy (Fig. 5. Additionally, the left upper quadrant in the likelihood ratio scatter diagram was occupied by summary PLR and NLR, indicating that CNSs are useful in improving the diagnostic accuracy of SLNB in cervical cancer (Supplementary Fig. S1). Fagan nomogram analysis demonstrated that a positive value revealed a 100% posttest probability of a correct diagnosis based on CNSs, and a negative value indicated 7% probability of detecting SLNs metastasis CNSs in patients with cervical cancer, based on a 50% pretest probability. The pretest to posttest probability for SLNB detection in cervical cancer using CNSs demonstrated a notable improvement (Supplementary Fig. S2).

There is controversy over the optimal injection method, time, and dose for the CNSs. We compared the combined sensitivity and specificity of SLNB according to different injection method, four quadrants or 3 and 9 o'clock (Supplementary Table S1). For the studies that used four quadrants injection method, the combined sensitivity was 0.90 (95% CI: 0.80–0.95, I^2 = 0.0%) and specificity was 1.00 (95% CI: 0.94–1.00, I^2 = 0.0%). For the studies that used 3 and 9 o'clock injection method, the combined sensitivity and specificity were 0.94 (95% CI: 0.88–0.97, I^2 = 56.76%) and 0.99 (95% CI: 0.95–1.00, I^2 = 92.27%). There were no significant differences between the two groups.

We further compared the effect of different injection time, preoperative or intraoperative, on the SLNB (Supplementary Table S2). The pooled sensitivity for studies using preoperative injection was 0.90 (95% CI: 0.82–0.95, I^2 = 26.72%), the pooled sensitivity for studies using intraoperative injection was 0.94 (95% CI: 0.89–0.97, I^2 = 30.05%). The combined specificity for studies using preoperative and intraoperative injections was 0.99 (95% CI: 0.96–1.00, I^2 = 90.09%) and 1.00 (95% CI: 0.95–1.00, I^2 = 88.11%), respectively. Both groups showed no significant differences.

We further compared the combined sensitivity and specificity of SLNB according to different CNS doses (Supplementary Table S2). For the studies that used 25 mg injection of CNSs, the combined sensitivity was 0.91 (95% CI: 0.83–0.95, I^2 = 37.21%) and specificity was 1.00 (95% CI: 0.93–1.00, I^2 = 85.16%). For the studies that used a 50 mg injection of CNSs, the combined sensitivity and specificity were 0.98 (95% CI: 0.69–1.00, I^2 = 0.0%) and 1.00 (95% CI: 0.91–1.00, I^2 = 22.53%). The results suggested that the diagnostic value of CNSs were not dose-dependent within the tested dose range (25–50 mg).

Publication bias and sensitivity analysis

All studies exhibited significant publication bias, as indicated by the Deeks' funnel plot [Slope (Bias) = −15.61, P = .0001; Supplementary Fig. S3]. Nonetheless, the sensitivity analysis showed that the results were reliable and stable (Supplementary Table S2).

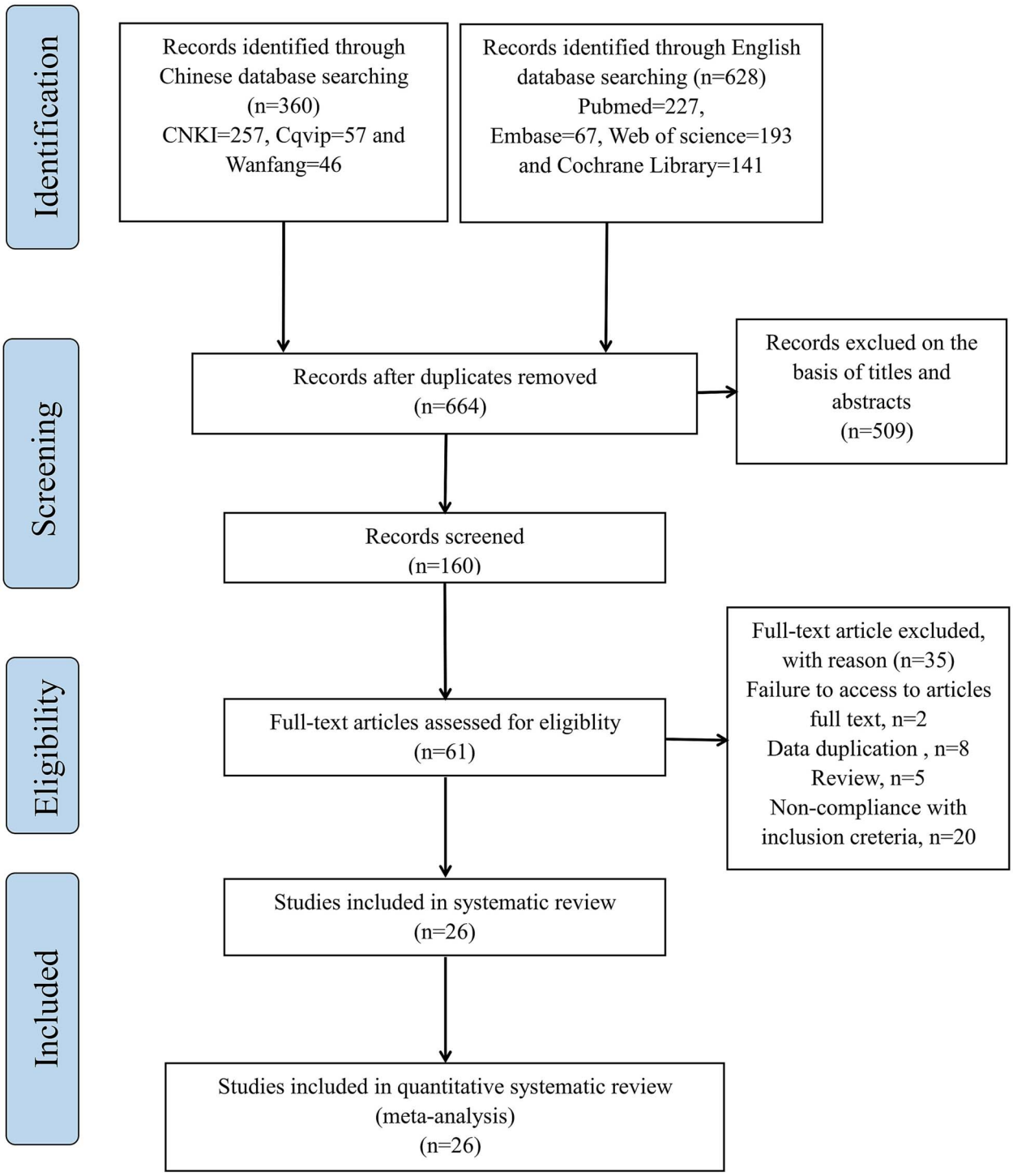

Figure 1. Preferred reporting items for systematic reviews and meta-analyses flowcharts of the article search process.

Discussion

In this study, we investigated the effectiveness of CNSs in lymph node tracing in surgery for cervical cancer. Based on an analysis of 26 studies involving 1671 female patients with cervical cancer undergoing SLNB, it was found that the overall detection rate of CNSs were 0.92. Subgroup analyses revealed that tumor sizes under 2.0 cm and the absence of neoadjuvant chemotherapy were associated with a higher detection rate of SLNs in cervical cancer, with a detection rate of 0.99. The AUC of the SROC was found to be 0.97. Nevertheless, subgroup analyses did not indicate any significant differences related to the injection methods (4 quadrants vs. 3 and 9 o'clock positions), the timing of injections (preoperative vs. intraoperative), or the dosages of CNS injections (25 mg vs. 50 mg).

This is the first meta-analysis to systematically investigate the use of CNSs in SLNB for cervical cancer. The subgroup analysis of CNS detection rates in SLNB for cervical cancer, stratified by lesion size, demonstrates a reduction in detection rates from 0.99 to 0.88 as lesion size increased. In cases where

Table 1. Summary of CNs in SLNB of cervical cancer studies.

Author	Year	Country	Study design	Recruited patients number	Detection rate	Injection method	Concentration of CNSs (mg/ml)	The total volume of the CNSs (ml)	Time of course (min)	Injection depth	Injection time	Pre-surgery injection timing or SLNs black staining time	MIS (minimally invasive surgery)/ open	Tumor stage
Bai	2020	China	A retrospective study	158	136/158	3, 6, 9, and 12 o' clock	50	1	–	2 mm	Preoperative	–	MIS or open	FIGO 2009 stages Ia1–IIa2
Chen	2024	China	RCT	73	36/40	3 and 9 o' clock	25	1	>3	Before 1-3 mm after 1–2 cm	Preoperative	–	MIS or open	FIGO 2018 stages Ia2–IIICp1
Cui-1	2017	China	A retrospective study	50	23/25	3, 6, 9, and 12 o' clock	50	1	–	1 cm	Preoperative	30 min	MIS	FIGO 2009 stages Ib1, Ib2, IIa2
Cui-2	2017	China	A retrospective study	42	40/42	3, 6, 9, and 12 o' clock	50	1	–	1 cm	Intraoperative	–	MIS	FIGO 2009 stages Ib1, Ib2, IIa1, IIa2, IIb1
Du	2011	China	A retrospective study	18	18/18	3, 6, 9, and 12 o' clock	50	1	1	0.5–1 cm	Intraoperative	8.0 ± 1.2 min (5–15 min)	MIS	FIGO 2000 stages Ib–IIa
Guo	2020	China	A retrospective study	75	39/50	3 and 9 o' clock	50	1	–	–	Intraoperative	–	MIS	FIGO stages Ia2–IIa
Lin	2021	China	A retrospective study	79	67/79	3 and 9 o' clock	50	0.5	3	2–3 mm	Preoperative	–	MIS or open	FIGO 2018 stages Ia2–IIICp1
Liu	2013	China	A retrospective study	21	20/21	3, 6, 9, and 12 o' clock	50	0.5	–	1 cm	Preoperative	–	MIS	FIGO 2009 stages Ib1–IIb
Lu	2017	China	A retrospective study	40	38/40	3 and 9 o' clock	50	1	>3	0.3–0.5 cm	Preoperative	8.5 ± 1.5 min (5–10 min)	MIS	FIGO 2009 stages Ia2–IIa
Lu-1	2019	China	A retrospective study	116	111/116	3 and 9 o' clock	50	0.5	>3	0.3–0.5 cm	Preoperative	–	MIS	FIGO 2009 stages Ia2–IIa
Lu-2	2019	China	A prospective study	100	100/100	3 and 9 o' clock	50	0.5	>3	0.2–0.5 cm	Preoperative	–	MIS	FIGO 2009 stages Ia2–IIa2
Pang	2021	China	A retrospective study	90	21/73	3, 6, 9, and 12 o' clock	50	0.4–1.2	3	–	Preoperative	6.71 ± 0.84 min (4–10 min)	MIS	FIGO 2018 stages Ib1–IIa
Qi	2022	China	A retrospective study	124	118/124	3, 6, 9, and 12 o' clock	50	0.5	–	0.5 cm	Intraoperative	–	MIS	FIGO stages Ia2, IIa and Ib
Ren	2019	China	A retrospective study	40	38/40	3, and 9 o' clock	16.67	–	>4	0.2 cm	Preoperative	12–15 h	MIS	FIGO 2009 stages Ia2–IIa
Shi	2016	China	A retrospective study	48	22/24	3, 6, 9, and 12 o' clock	50	0.5	-	1 cm	Preoperative	–	–	FIGO 2009 stages Ib–IIa
Su	2018	China	A retrospective study	39	38/39	3, 6, 9, and 12 o' clock	25	1	3	0.3–0.5 cm	Intraoperative	7.8 ± 1.8 min (3–11 min)	MIS	FIGO 2009 stages Ia2–IIa1
Sun	2020	China	RCT	80	35/40	–	–	–	–	–	Preoperative	–	–	FIGO stages I–III
Wang	2020	China	A retrospective study	45	42/45	3, and 9 o' clock	50	1	2	5 mm	Preoperative	15–20 min	MIS	FIGO 2009 stages Ib1–IIa1
Wei	2017	China	A retrospective study	83	79/83	3, and 9 o' clock	16.67	3	At least 2–3	0.2–0.5 cm	Intraoperative	9.0 ± 1.2 min (7–15 min)	MIS	FIGO 2009 stages Ia2–IIa
Ya	2020	China	A prospective study	356	325/356	3 and 9 o' clock	50	0.5	3	2–3 mm	Intraoperative	8.7 ± 1.5 min (4.5–15.0 min)	–	FIGO 2009 stages Ia2–IIa2
Yang	2014	China	RCT	46	19/23	3, 6, 9, and 12 o' clock	–	1	–	–	Intraoperative	–	MIS	FIGO 2000 stages Ib1–IIa2
Yang	2020	China	A retrospective study	84	41/59	3 and 9 o' clock	50	0.5	3–5	–	Intraoperative	–	–	FIGO 2018 stages I–IV
Zhang	2020	China	A random prospective study	60	60/60	3 and 9 o' clock	–	1	3	0.4 cm	Intraoperative	6.0 ± 1.5 min (4–11 min)	MIS	stages Ia2–IIa2
Zhang	2022	China	A retrospective study	48	48/48	3, and 9 o' clock	25	1	3	Before 5–10 mm, after 1–3 mm	Intraoperative	–	MIS	FIGO 2009 stages Ia2–Ib1
Zhou	2017	China	RCT	60	28/30	–	–	–	–	–	Intraoperative	–	MIS or open	FIGO 2015 stages Ia1–IIa1 <4 cm
Zhu	2019	China	RCT	122	56/58	3 and 9 o' clock or 3, 6, 9 and 12 o' clock	16.67	0.5–1	>2	0.3–1 cm	Preoperative	15 min	MIS	FIGO 2018 stages Ia1–Ib1

RCT, random control trial; MIS, minimally invasive surgery; FIGO, the International Federation of Gynecology and Obstetrics; "-", not available

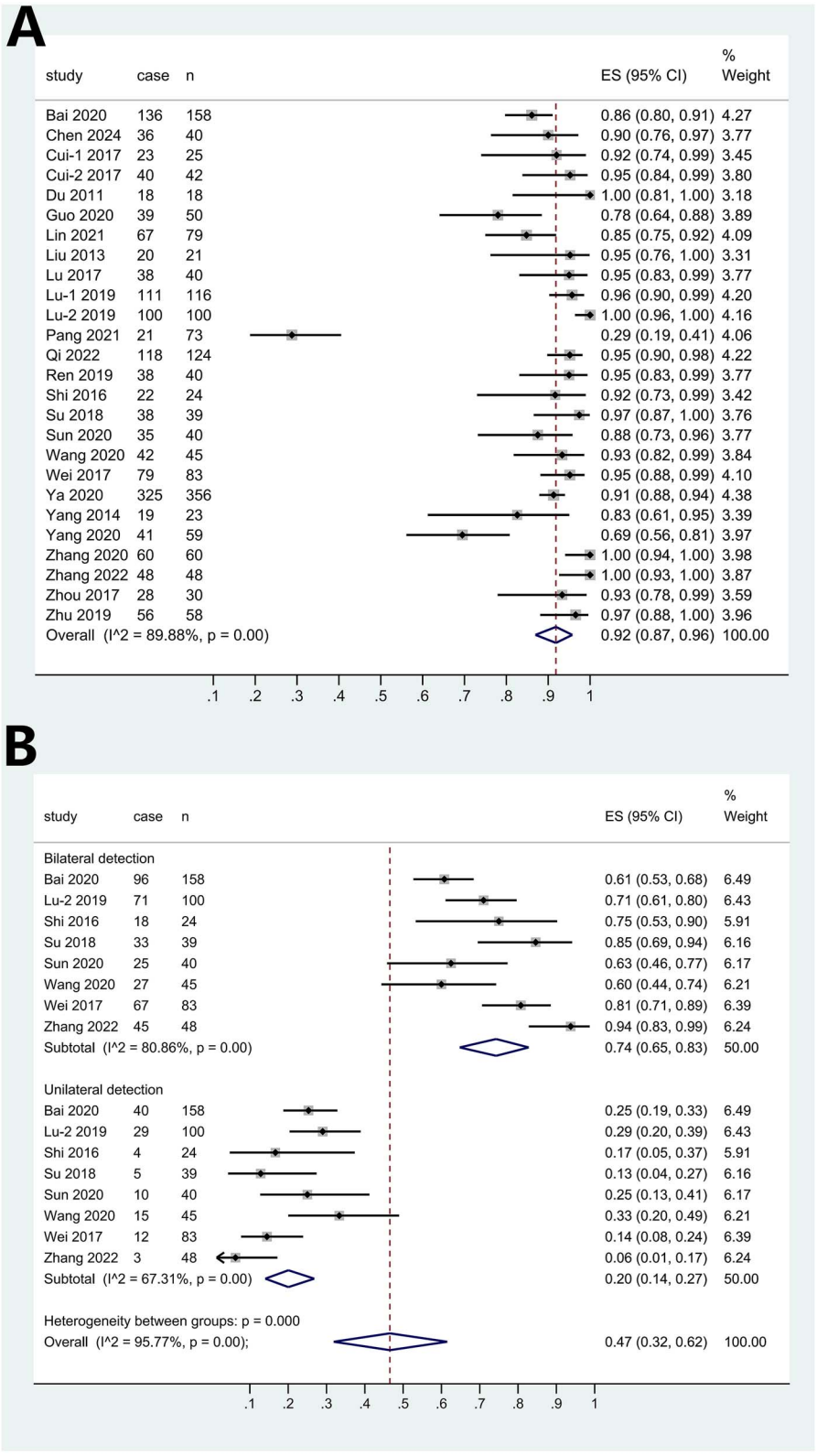

Figure 2. Forest plot for the (A) overall detection rate and (B) bilateral and unilateral detection rate of CNSs in SLNB of cervical cancer.

the cervical tumor is significantly enlarged, identifying a suitable injection site may prove challenging, potentially resulting in tracer reflux into surrounding tissues. As tumor volume increased, central necrosis significantly escalated, which may lead to CNS retrograde leakage through the cervical canal into the vagina [44]. Furthermore, tumor invasion of lymphatic vessels could alter the original lymphatic drainage pathways [45]. These phenomena may consequently contribute to the lower detection rate of SLNs in cases of large cervical cancer tumors. The depth of stromal invasion and the presence of

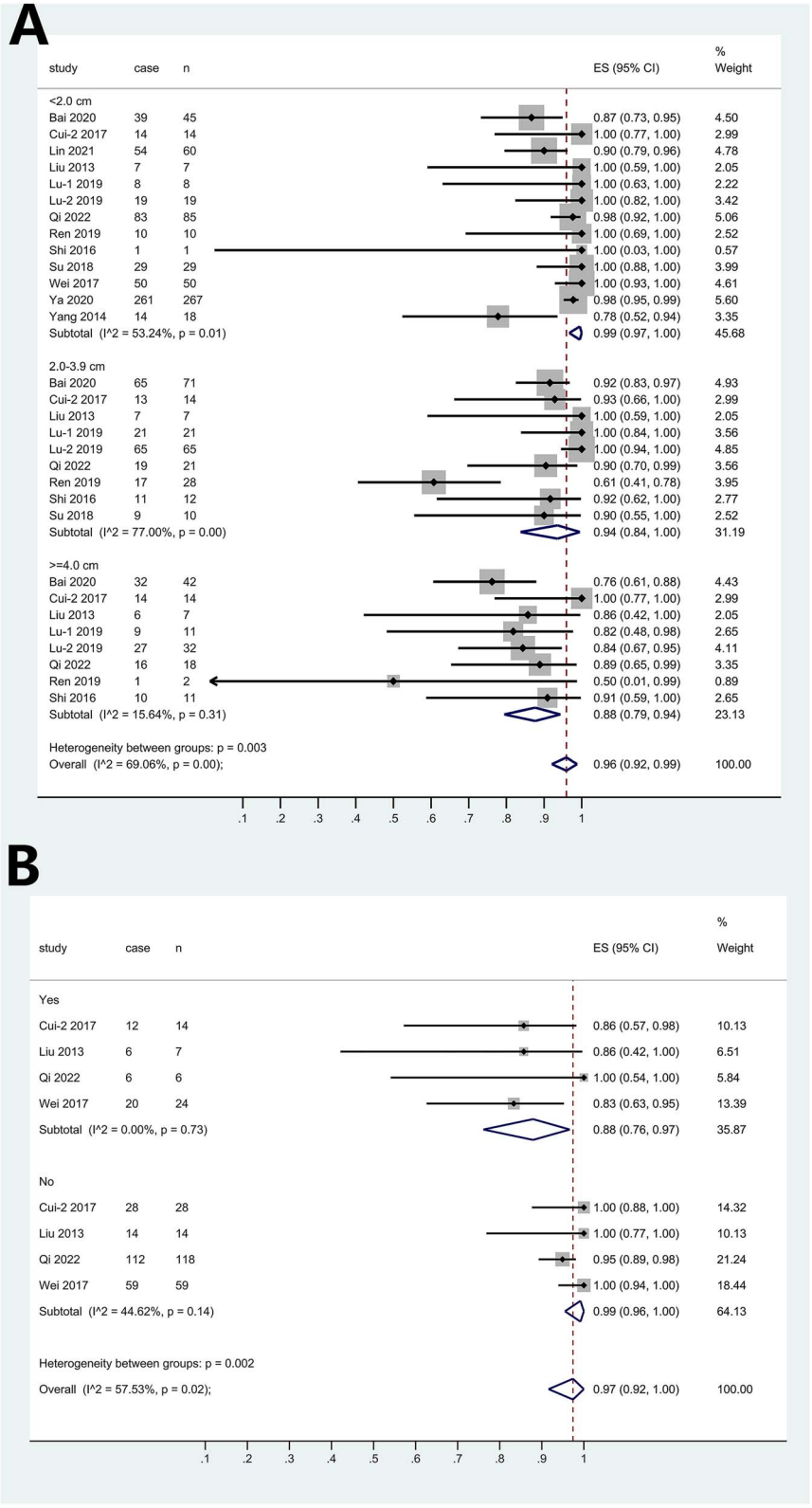

Figure 3. Subgroup analysis of the detection rate of CNSs in SLNB of cervical cancer, stratified by (A) lesion size and (B) the administration of neoadjuvant chemotherapy.

lymphovascular space invasion are robustly correlated with the expansion of tumor dimensions and the progression to advanced cancer stages, as evidenced by a multitude of pathological assessments and clinical outcomes [46,47]. These factors have been consistently identified as pivotal indicators in the prognostication of various cancers, particularly in gynecological malignancies such as cervical and endometrial cancers [46,47]. Ya *et al.* observed that the FN rate of CNSs in

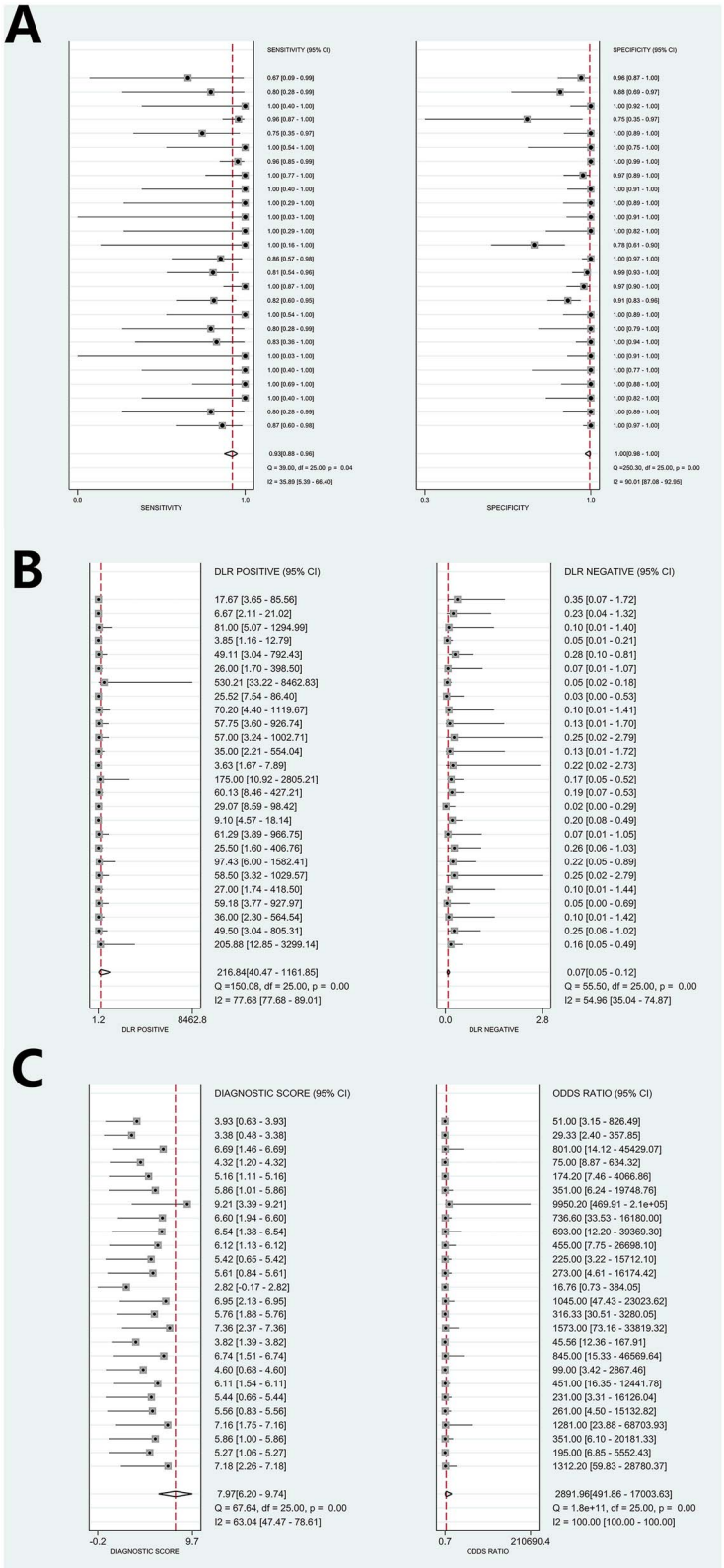

Figure 4. Forest plot of pooled (A) the sensitivity and specificity, (B) the positive and negative diagnosis likelihood ratio, and (C) the diagnostic score and odds ratio of CNSs in SLNB of cervical cancer.

cervical cancer was also elevated for significant DLS ($\geq$ 50%), and the presence of LVSI [20]. Cervical cancer patients without neoadjuvant chemotherapy have higher CNS detection rates in SLNB (0.99) than those treated with chemotherapy (0.88). Following neoadjuvant chemotherapy, lymph nodes may exhibit histiocytic accumulation, lymphoid depletion, fibrosis, and hyalinization [48]. These alterations can variably affect lymphatic drainage. Consequently, this

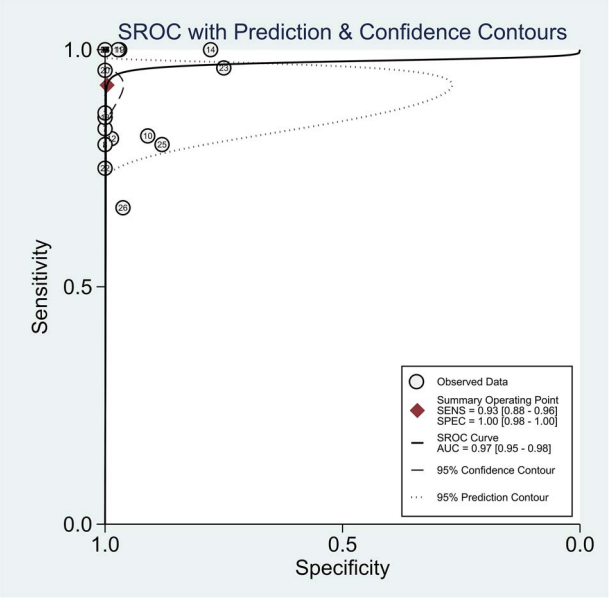

Figure 5. Summary of the receiver operating characteristic plot of CNSs in SLNB of cervical cancer.

may lead to an increased FN rate, thereby adversely impacting the detection rate of SLNs. The lymph nodes may also decrease in size or vanish as a result of lymphocytic toxicity and fibrotic involution [49]. The increased fibrosis post-chemotherapy not only affects the ease of dissection but also the assessment of lymphatic drainage, thereby potentially rendering the true SLNs unidentifiable [50]. Previous studies also have demonstrated that neoadjuvant radiotherapy affects lymph node detection rates [51,52]. High doses of radiotherapy result in lymphocyte depletion and stromal atrophy, which may be replaced by adipocytes, potentially rendering lymph nodes indistinguishable under microscopic examination [51]. Furthermore, fibrosis and size reduction of lymph nodes caused by radiotherapy can complicate their identification during the sample processing phase [52]. However, there is no available literature with comparative data between the group that received neoadjuvant radiotherapy and the group that did not. Thus, a subgroup analysis for the effect of neoadjuvant radiotherapy cannot be conducted.

Traditional lymph node tracing methods, such as dye staining and radioactive isotopes, have been widely used, but they each have limitations that can impact their effectiveness and safety [53]. A meta-analysis indicated that the sensitivities for SLN detection using blue dye, Technetium-99 m (^{99}mTc) colloid, and the combined technique are 81%, 92%, and 92%, respectively, while the corresponding detection rates are 84%, 88%, and 97%, respectively [54]. Notwithstanding, the utilization of blue dye is accompanied by the risk of adverse reactions, including pruritus, rash, and allergic responses, which in extreme instances can culminate in life-threatening consequences [55]. Furthermore, the intraoperative application of ^{99}mTc necessitates the presence of specialized technical personnel, sophisticated equipment, and rigorous management of radioactive materials, thereby introducing additional logistical complexities. Indocyanine green (ICG) is a promising fluorescent tracer that surpasses blue dye, ^{99}mTc, and the combined method in improving bilateral SLN detection rates [56]. ICG has a good visibility in laparoscopic and robotic surgeries. However, identification of ICG requires specialized fluorescence laparoscopy, making the procedure complex and costly, thereby limiting its application in certain cancer research centers, particularly in developing countries [56]. In recent years, mitoxantrone has emerged as a novel agent for the identification of SLNs in breast cancer, demonstrating a high detection rate of ~97.6% [57]. However, its use is associated with certain safety concerns. The most adverse reaction observed with mitoxantrone administration during surgery was an abnormal biochemical indicator related to liver function [57]. This suggests that caution should be exercised for patients with abnormal liver function or those with a history of liver damage [57]. Sulfur hexafluoride and sonozoid are regarded as safe and manageable ultrasound contrast agents for the detection of SLNs in breast cancer; however, their success rates and accuracy in clinical applications remain relatively low, ~80% [58]. The SentiMAG multicenter clinical trial compared superparamagnetic iron oxide (SPIO) with a combined method (radioactive tracer- ^{99}mTc and blue dye-Patent Blue V) and demonstrated the non-inferiority of SPIO as a single-tracer agent [59]. However, the SPIO technique is not without its limitations, as it necessitates the use of plastic retractors in the surgical field instead of metal instruments during detection. CNSs are particularly advantageous in resource-limited settings, with no reported cases of anaphylactic reactions or serious adverse effects across the studies analyzed. In contrast to blue dyes, which rapidly diffuse into surrounding tissues, CNSs demonstrate slow dispersion within the lymphatic system, facilitating prolonged accumulation in SLNs without leakage [16]. CNSs provide flexible administration options, with injection possible ranging from 15 min to 15 h before lymph node dissection [20]. These properties ensure a clear surgical field, allowing sufficient time for precise intraoperative dissection and enhancing postoperative lymph node detection. However, CNSs have been noted to have a tendency to discolor the skin at the injection site, similar to what is found after injection of blue dye, mitoxantrone, and SPIO [57,59]. Unlike blue dye, mitoxantrone, and SPIO, CNSs used for SLNs detection cannot be completely metabolized by the body, leading to prolonged retention in tissues [57,59,60]. This leads to skin staining that can last for months, which can affect aesthetics [60]. This characteristic is particularly problematic in the context of superficial tumors, such as breast cancer, where lymphatic mapping is often performed in visible areas [15]. Consequently, patients may be more hesitant to accept CNSs for such applications, given the potential for long-term cosmetic impairment. CNSs have been utilized in various cancer types, including breast cancer, colorectal cancer, and thyroid cancer, with no reported adverse reactions in the studies analyzed [14,15,17]. Consequently, SLN detection utilizing CNSs can be considered a safe procedure.

All articles are from China; three are written in English, while the remaining twenty-three are in Chinese. This can be attributed to the fact that CNSs have only obtained marketing approval in China, with no such approval granted in other countries. The patients were recruited based on the International Federation of Gynecology and Obstetrics (FIGO) standard; however, the four included studies did not provide clear information regarding the specific version of the FIGO staging criteria applied [26,32,36,40]. This lack of clarity raises the possibility that variations in the FIGO staging criteria version could have influenced the results. Notably,

the study by Pang *et al.* shows an extremely poor detection rate, which was quite different from other studies [31]. The study lacks detailed methodology and sufficient references, potentially affecting the accuracy of its findings. Discrepancies exist between the initial sample size of 90 patients and the reported results for only 73 patients, with no explanation provided for the missing data. Despite these limitations, the study was included in the analysis to ensure comprehensiveness. Several factors, including different pathological and operation techniques, tumor embolus formation, and occasional skip metastasis in lymph nodes, all of these factors may result in the failure to identify microscopic metastases within the SLNs. Consequently, in patients with advanced clinical staging of cervical cancer, those with larger tumor lesions, or individuals exhibiting extensive lymph node metastasis, the use of CNSs may lead to a heightened incidence of FN lymph node results, thereby diminishing the clinical relevance of SLNs detection. Wang *et al.*'s research also indicated that elevated body mass index is a significant impediment to the accurate detection of SLNs due to the excessive adipose tissue surrounding the lymph nodes, which can impede the detection process [19]. Additionally, information related to complications and the survival data of SLNB in cervical cancer using CNSs were limited. Despite the encouraging findings, the adoption of CNSs in clinical practice requires further validation through large-scale studies and long-term follow-up.

In conclusion, CNSs represent a promising advancement in the field of lymphatic mapping for cervical cancer. Their distinctive properties and clinical advantages underscore their potential to improve the accuracy and safety of lymph node tracing, particularly in patients with a lesion diameter smaller than 2.0 cm or those who have not received neoadjuvant chemotherapy. Continued research and validation are needed to fully establish CNSs as a standard method, but the current evidence suggests a bright future for this innovative technology in improving cervical cancer management.

Supplementary data

Supplementary data are available at *Japanese Journal of Clinical Oncology* online.

Author contributions

Ting Qu (Conceptualization, Methodology, Writing—original draft, Data search, extraction, and checks), Guangfu Zeng (Data curation, Literature collection and organization, Data search, extraction, and checks), Jinmei Yang (Data curation, Literature collection and organization, Data search, extraction, and checks), Kexin Tang (Data analysis and Creation of tables and figures), Ping Xie (Supervision, Writing—review & editing), Xiaohai Tang (Conceptualization, Supervision, Writing—original draft, Data search, extraction, and checks, Writing—review & editing), and all authors made significant contributions to drafting and/or revising the article. All authors approved the final version of the article for publication.

Conflict of interest

None declared.

Funding

We acknowledge financial support from the Sichuan Province (No. 2024NSFSC1676) and Special Support for Postdoctoral Research Project of Sichuan Province in 2024 (No. TB2024077).

References

1. Abu-Rustum NR, Yashar CM, Arend R. *et al.* NCCN guidelines® insights: cervical cancer, version 1.2024. *J Natl Compr Cancer Netw* 2023;**21**:1224–33. https://doi.org/10.6004/jnccn.2023.0062.
2. Holman LL, Levenback CF, Frumovitz M. Sentinel lymph node evaluation in women with cervical cancer. *J Minim Invasive Gynecol* 2014;**21**:540–5. https://doi.org/10.1016/j.jmig.2013.12.095.
3. Sartori E, Tisi G, Chiudinelli F. *et al.* Early stage cervical cancer: adjuvant treatment in negative lymph node cases. *Gynecol Oncol* 2007;**107**:S170–4. https://doi.org/10.1016/j.ygyno.2007.07.026.
4. Park JW, Bae JW. Prognostic significance of positive lymph node number in early cervical cancer. *Mol Clin Oncol* 2016;**4**:1052–6. https://doi.org/10.3892/mco.2016.837.
5. Inoue T, Morita K. The prognostic significance of number of positive nodes in cervical carcinoma stages IB, IIA, and IIB. *Cancer* 1990;**65**:1923–7. https://doi.org/10.1002/1097-0142(19900501)65:9<1923::aid-cncr2820650909>3.0.co;2-m.
6. Bogani G, Di Donato V, Scambia G. *et al.* Radical hysterectomy for early stage cervical cancer. *Int J Environ Res Public Health* 2022;**19**:11641. https://doi.org/10.3390/ijerph191811641.
7. Ferrandina G, Pedone Anchora L, Gallotta V. *et al.* Can we define the risk of lymph node metastasis in early-stage cervical cancer patients? A large-scale. *Ann Surg Oncol* 2017;**24**:2311–8. https://doi.org/10.1245/s10434-017-5917-0.
8. DiSipio T, Rye S, Newman B, Hayes S. Incidence of unilateral arm lymphoedema after breast cancer: a systematic review and meta-analysis. *Lancet Oncol* 2013;**14**:500–15. https://doi.org/10.1016/s1470-2045(13)70076-7.
9. Lennox GK, Covens A. Can sentinel lymph node biopsy replace pelvic lymphadenectomy for early cervical cancer? *Gynecol Oncol* 2017;**144**:16–20. https://doi.org/10.1016/j.ygyno.2016.08.337.
10. Margioula-Siarkou C, Almperis A, Gullo G. *et al.* Sentinel lymph node staging in early-stage cervical cancer: a comprehensive review. *J Clin Med* 2023;**13**:27. https://doi.org/10.3390/jcm13010027.
11. Alonso-Espías M, Gorostidi M, García-Pineda V. *et al.* Survival impact of sentinel lymph node biopsy in patients with early-stage cervical cancer. *Reprod Sci* 2024;**31**:3066–73. https://doi.org/10.1007/s43032-024-01687-5.
12. Tian Y, Yang P, Lin Y. *et al.* Assessment of carbon nanoparticle suspension lymphography-guided distal gastrectomy for gastric cancer. *JAMA Netw Open* 2022;**5**:e227739. https://doi.org/10.1001/jamanetworkopen.2022.7739.
13. Lu D, Pan B, Tang E. *et al.* Intraoperative strategies in identification and functional protection of parathyroid glands for patients with thyroidectomy: a systematic review and network meta-analysis. *Int J Surg* 2024;**110**:1723–34. https://doi.org/10.1097/js9.0000000000000991.
14. Zhao J, Wang J, Cheng R. *et al.* Safety and effectiveness of carbon nanoparticles suspension-guided lymph node dissection during thyroidectomy in patients with thyroid papillary cancer: a prospective, multicenter, randomized, blank-controlled trial. *Front Endocrinol (Lausanne)* 2024;**14**:1251820. https://doi.org/10.3389/fendo.2023.1251820.
15. Jiang Y, Li J, Chen B. *et al.* Sentinel lymph node biopsy mapped with carbon nanoparticle suspensions in patients with breast cancer: a systematic review and meta-analysis. *Front Oncol* 2022;**12**:818812. https://doi.org/10.3389/fonc.2022.818812.
16. Du J, Zhang Y, Ming J. *et al.* Evaluation of the tracing effect of carbon nanoparticle and carbon nanoparticle-epirubicin suspension in axillary lymph node dissection for breast cancer treatment. *World J Surg Oncol* 2016;**14**:164. https://doi.org/10.1186/s12957-016-0925-2.
17. Wang R, Mo S, Liu Q. *et al.* The safety and effectiveness of carbon nanoparticles suspension in tracking lymph node metastases of colorectal cancer: a prospective randomized controlled trial.

Jpn J Clin Oncol 2020;**50**:535–42. https://doi.org/10.1093/jjco/hyaa011.
18. Lu Y, Wei J-Y, Yao D-S. *et al.* Application of carbon nanoparticles in laparoscopic sentinel lymph node detection in patients with early-stage cervical cancer. *PLoS One* 2017;**12**:e0183834. https://doi.org/10.1371/journal.pone.0183834.
19. Wang Y, Dan Z, Yuan G. *et al.* Detection of sentinel lymph node in laparoscopic surgery for uterine cervical cancer using carbon nanoparticles. *J Surg Oncol* 2020;**122**:934–40. https://doi.org/10.1002/jso.26100.
20. Ya X, Qian W, Huiqing L. *et al.* Role of carbon nanoparticle suspension in sentinel lymph node biopsy for early-stage cervical cancer: a prospective study. *BJOG* 2021;**128**:890–8. https://doi.org/10.1111/1471-0528.16504.
21. Bai B, Zhang W, Jiang J, Zou Q. Application value of carbon nanoparticles in sentinel lymph node biopsy of early cervical cancer and its influencing factors. *Modern Oncology* 2020;**28**:1530–4. https://doi.org/10.3969/j.issn.1672-4992.2020.09.024.
22. Chen Y, Yu F, Sun X, Lou Y. Comparison of tracing effects between nanocarbon and indocyanine green in the treatment of early cervical cancer. *Advances in Clinical Medicine* 2024;**14**:1514–22. https://doi.org/10.12677/acm.2024.143873.
23. Cui Y, Qe F, Xiao L. *et al.* Predictive value of nanometer carbon suspension injection as SLN tracer in predicting pelvic lymph node metastasis of early cervical carcinoma. *The Chinese Journal of Human Sexuality* 2017;**26**:33–6. https://doi.org/10.3969/j.issn.1672-1993.2017.10.011.
24. Cui Y, Liu X, Li J. *et al.* Comparison of two lymphatic tracers in laparoscopic radical resection of cervical cancer. *Chin Clin Oncol* 2017;**22**:650–3. https://doi.org/10.3969/j.issn.1009-0460.2017.07.016.
25. Du P, Zhang X, Deng Z. Clinical study on carbon nanoparticles labeled sentinel lymph nodes in cervical cancer by laparoscopy. *Academic Journal of Guangzhou Medical College* 2011;**39**:20–4. https://doi.org/10.3969/j.issn.1008-1836.2011.04.006.
26. Guo X, Wang Q, Li L. *et al.* Comparison of sentinel lymph node tracking effect between carbon nanoparticles and indocyanine green in laparoscopic radical hysterectomy for early cervical cancer. *Journal of Xinxiang Medical University* 2020;**37**:955–7. https://doi.org/10.7683/xxyxyxb.2020.10.012.
27. Lin X, He J, Lu J. *et al.* Carbon nanoparticle tracing of sentinel lymph nodes in diagnosis and treatment of cervical cancer and clinical value of lymph node ultrastaging detection. *Nan Fang Yi Ke Da Xue Xue Bao* 2022;**42**:1896–901. https://dx.doi.org/10.12122/j.issn.1673-4254.2022.12.20.
28. Liu KJ, Lu XW, Liu Q. *et al.* Application of carbon nanoparticles in the laparoscopic sentinel lymph node detection in patients with cervical cancer. *Zhongguo Yi Xue Ke Xue Yuan Xue Bao* 2013;**35**:150–4. https://doi.org/10.3881/j.issn.1000-503X.2013.02.005.
29. Lu Y. *Application of Carbon Nanoparticles in Sentinel Lymph Node Mapping and Detection of Lymph Node Micrometastasis in Cervical Cancer*. Guangxi: Guangxi Medical University, 2019; https://cdmd.cnki.com.cn/Article/CDMD-10598-1020068741.htm.
30. Lu Y, Qin W-y, Yao D-s. Prospective study of ultrastaging of sentinel lymph node in diagnostic value of early-stage cervical cancer. *Chinese Journal of Cancer Prevention and Treatment* 2019;**26**:494–8. https://doi.org/10.16073/j.cnki.cjcpt.20190426.001.
31. Pang X, Wu X, Su Y. *et al.* Study on the diagnostic efficiency and clinical treatment guidance value of nanocarbon in sentinel lymph nodes of early cervical cancer. *Oriental Medicated Diet* 2021;**23**:84. https://d.wanfangdata.com.cn/periodical/Ch9QZXJpb2RpY2FsQ0hJTmV3UzIwMjUwMTE2MTYzNjE0Eg95c3NseWoyMDIxMjMxNzYaCHRhN2p0aHlv.
32. Qi M, Wang J, Zhang Z. Clinical application of carbon nanoparticles tracing sentinel lymph nodes to detect metastasis status in early-stage cervical cancer. *Journal of Ningxia Medical University* 2022;**44**:1121–4. https://doi.org/10.16050/j.cnki.issn1674-6309.2022.11.008.
33. Ren J, Liu X, Zhang X. *et al.* The value of nano-carbon labeled sentinel lymph node in the diagnosis and treatment of early cervical cancer. *Acta Academiae Medicinae Weifang* 2019;**41**:215–7. https://doi.org/10.16846/j.issn.1004-3101.2019.03.017.
34. Shi S. *Sentinel Lymph Node Maping in Patients Subjected to Cervical Carcinoma after Neoadjuvant Chemoradiotherapy*. Fujian: Fujian Medical University, 2016.
35. Su N, Liu R, Luo Y. *et al.* The application value of nanocarbon tracing sentinel lymph nodes in laparoscopic radical surgery for early cervical cancer. *Henan Medical Research* 2018;**27**:3693–5. https://doi.org/10.3969/j.issn.1004-437X.2018.20.016.
36. Sun N. Explore the effect of methylene blue and nano-carbon injection to identify pelvic sentinel lymph nodes in cervical cancer. *Guide of China Medicine* 2020;**18**:3–5. https://doi.org/10.15912/j.cnki.gocm.2020.27.003.
37. Wei J. *Application of Carbon Nanoparticles in Laparoscopic Sentinel Lymph Node Detection in Patients with Early Cervical Cancer*. Guangxi: Guangxi Medical University, 2017; https://d.wanfangdata.com.cn/thesis/Y3246027.
38. Yang L, Wang J, Li W. *et al.* Comparison between methylene blue and carbon nanoparticles on the sentinel lymph node biopsy in cervical cancer laparoscopic surgery. *Shandong Medical Journal* 2014;**54**:44–6. https://doi.org/10.3969/j.issn.1002-266X.2014.18.016.
39. Yang S. *Study of Sentinel Lymph Node Mapping with Carbon Nanoparticles in the Operation of Uterine Cancer*. Liaoning: Dalian Medical University, 2020; https://cdmd.cnki.com.cn/Article/CDMD-10161-1020081609.htm.
40. Zhang J, Liu Q, Chen J, Luo Y. Clinical study on carbon nanoparticles for sentinel lymph node tracing in early cervical cancer under laparoscopy. *China Science and Technology Journal Database — Medicine and Health* 2020;**12**:0229–30. http://qikan.cqvip.com/Qikan/Article/Detail?id=1000002759990.
41. Zhang G, You X, Wang Y. *et al.* The value of carbon Nano-Labeled sentinel lymph nodes in the diagnosis and treatment of early cervical cancer. *Modern Oncology* 2022;**30**:2813–7. https://doi.org/10.3969/j.issn.1672-4992.2022.15.026.
42. Zhou B, Yang Y. Clinical application of different tracers in early cervical cancer sentinel lymph node localization. *The Practical Journal of Cancer* 2017;**32**:1174–6. https://doi.org/10.3969/j.issn.1001-5930.2017.07.040.
43. Zhu H, Zhao X, Liu K. *et al.* Comparative analysis of sentinel lymph node biopsy with two tracers in laparoscopic surgery for early-stage cervical cancer. *Progress in Modern Biomedicine* 2019;**19**:4651–4. https://doi.org/10.13241/j.cnki.pmb.2019.24.011.
44. Milross CG, Tucker SL, Mason KA. *et al.* The effect of tumor size on necrosis and polarographically measured pO2. *Acta Oncol* 1997;**36**:183–9. https://doi.org/10.3109/02841869709109228.
45. Zhang Q, Liu S, Wang H. *et al.* ETV4 mediated tumor-associated neutrophil infiltration facilitates Lymphangiogenesis and lymphatic metastasis of bladder cancer. *Adv Sci (Weinh)* 2023;**10**:e2205613. https://doi.org/10.1002/advs.202205613.
46. Tortorella L, Restaino S, Zannoni GF. *et al.* Substantial lymphovascular space invasion (LVSI) as predictor of distant relapse and poor prognosis in low-risk early-stage endometrial cancer. *J Gynecol Oncol* 2021;**32**:e11. https://doi.org/10.3802/jgo.2021.32.e11.
47. Malek M, Rahmani M, Pourashraf M. *et al.* Prediction of lymphovascular space invasion in cervical carcinoma using diffusion kurtosis imaging. *Cancer Treat Res Commun* 2022;**31**:100559. https://doi.org/10.1016/j.ctarc.2022.100559.
48. Newman LA, Pernick NL, Adsay V. *et al.* Histopathologic evidence of tumor regression in the axillary lymph nodes of patients treated with preoperative chemotherapy correlates with breast cancer outcome. *Ann Surg Oncol* 2003;**10**:734–9. https://doi.org/10.1245/aso.2003.03.081.
49. Bélanger J, Soucy G, Sidéris L. *et al.* Neoadjuvant chemotherapy in invasive breast cancer results in a lower axillary lymph node

count. *J Am Coll Surg* 2008;**206**:704–8. https://doi.org/10.1016/j.jamcollsurg.2007.10.016.
50. Boughey JC, Suman VJ, Mittendorf EA. *et al.* Sentinel lymph node surgery after neoadjuvant chemotherapy in patients with node-positive breast cancer: the ACOSOG Z1071 (alliance) clinical trial. *JAMA* 2013;**310**:1455–61. https://doi.org/10.1001/jama.2013.278932.
51. Fajardo LF. Effects of ionizing radiation on lymph nodes. a review. *Front Radiat Ther Oncol* 1994;**28**:37–45. https://doi.org/10.1159/000423371.
52. Shvero J, Koren R, Marshak G. *et al.* Histological changes in the cervical lymph nodes after radiotherapy. *Oncol Rep* 2001;**8**:909–11. https://doi.org/10.3892/or.8.4.909.
53. Baeten IGT, Hoogendam JP, Jeremiasse B. *et al.* Indocyanine green versus technetium-99m with blue dye for sentinel lymph node detection in early-stage cervical cancer: a systematic review and meta-analysis. *Cancer Rep (Hoboken)* 2022;**5**:e1401. https://doi.org/10.1002/cnr2.1401.
54. van de Lande J, Torrenga B, Raijmakers PG. *et al.* Sentinel lymph node detection in early stage uterine cervix carcinoma: a systematic review. *Gynecol Oncol* 2007;**106**:604–13. https://doi.org/10.1016/j.ygyno.2007.05.010.
55. Perenyei M, Barber ZE, Gibson J. *et al.* Anaphylactic reaction rates to blue dyes used for sentinel lymph node mapping: systematic review and meta-analysis. *Ann Surg* 2021;**273**:1087–93. https://doi.org/10.1097/sla.0000000000004061.
56. Dijkstra BM, Jeltema HJR, Kruijff S, Groen RJM. The application of fluorescence techniques in meningioma surgery-a review. *Neurosurg Rev* 2019;**42**:799–809. https://doi.org/10.1007/s10143-018-01062-4.
57. Jiao D, Yang B, Chen J. *et al.* Efficacy and safety of mitoxantrone hydrochloride injection for tracing axillary sentinel nodes in breast cancer: a self-controlled clinical trial. *Front Oncol* 2022;**12**:914057. https://doi.org/10.3389/fonc.2022.914057.
58. Wubulihasimu M, Maimaitusun M, Xu XL. *et al.* The added value of contrast-enhanced ultrasound to conventional ultrasound in differentiating benign and malignant solid breast lesions: a systematic review and meta-analysis. *Clin Radiol* 2018;**73**:936–43. https://doi.org/10.1016/j.crad.2018.06.004.
59. Karakatsanis A, Christiansen PM, Fischer L. *et al.* The Nordic SentiMag trial: a comparison of super paramagnetic iron oxide (SPIO) nanoparticles versus Tc(99) and patent blue in the detection of sentinel node (SN) in patients with breast cancer and a meta-analysis of earlier studies. *Breast Cancer Res Treat* 2016;**157**:281–94. https://doi.org/10.1007/s10549-016-3809-9.
60. Yang B, Zheng S, Huang X. *et al.* A single-center, self-controlled, phase I clinical trial of mitoxantrone hydrochloride injection for lymph tracing for sentinel lymph node identification of breast cancer. *Gland Surg* 2021;**10**:992–1001. https://doi.org/10.21037/gs-20-694.

Japanese Journal of Clinical Oncology, 2025, 1–12
https://doi.org/10.1093/jjco/hyaf063
Original Article