Sentinel lymph node biopsy in cervical cancer: A meta-analysis

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Abstract. Sentinel lymph node biopsy (SLNB) is used to determine the pathological status of the first lymph node receiving lymphatic drainage from the primary tumor. The diagnostic value of SLNB for the assessment of the nodal status in patients with cervical cancer has not been determined. Therefore, this meta-analysis was conducted to assess the diagnostic value of SLNB in cervical cancer. A search for related literature was performed using PubMed. Data were analyzed using a random effects model and a subgroup analysis was used to assess the diagnostic value of different practices during the process. A total of 17 studies involving a total of 1,112 patients were included in the analysis. The pooled sentinel lymph node (SLN) detection rate, sensitivity and negative predictive values were 92.2% [95% confidence interval (CI): 88.3-94.8%], 88.8% (95% CI: 85.1-91.7%) and 95.0% (95% CI: 92.8-96.6%), respectively. The subgroup analysis revealed that laparoscopy, tracer combination and immunohistochemistry were associated with a higher SLN detection rate. In conclusion, the SLNB in cervical cancer appears to be of diagnostic value, particularly the procedure with the combination of laparoscopy, combined tracers and immunohistochemistry. However, further studies are required to establish the clinical value of SLNB in cervical cancer.

Introduction

The concept of the sentinel lymph node (SLN) refers to the first lymph node to receive lymphatic drainage from the primary tumor. Sentinel lymph node biopsy (SLNB) is used to determine the local and regional lymph node status of solid tumors. It was first described by Cabanas (1) for the management of penile cancer and has been widely used as an effective regional nodal staging procedure after a 1992 landmark study on melanoma

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patients (2). It is currently used in several solid tumors, including breast cancer and melanoma (3,4). The application and validity of SLNB in cervical cancer should be practiced with caution, since the lymphatic drainage of the cervix is significantly more complicated, due to its midline position. Although a number of feasibility studies for SLNB in cervical cancer have been conducted, SLNB does not appear to be suitable for clinical application, due to the wide range of reported detection rates, from 55.5 (5) to 100% (6). A high detection rate may render SLBN in cervical cancer feasible in clinical practice, which may decrease the complications, such as prolonged operation time, blood loss, lymphocyst and lymphedema, experienced by patients undergoing lymph node dissection (7). The pelvic nodal involvement rate in early-stage cervical cancer cases eligible for surgery was reported to be 0-4.8% in stage IA, 17% in stage IB and 12-27% in stage IIA disease (8,9), suggesting that lymph node dissection may not be beneficial in >90% of stage IA cases. Therefore, a reliable SLBN is crucial.

There is currently no clear assessment of SLNB diagnostic performance. Therefore, a meta-analysis of the published studies was conducted, with the aim to provide a comprehensive and up-to-date overview of the feasibility and diagnostic value of SLNB in cervical cancer.

Materials and methods

Search strategy. A comprehensive, systematic search for published studies was performed using the search terms 'cervical cancer', 'sentinel lymph node', 'sensitivity' and 'negative predictive value' in the PubMed database, with a time cutoff of September, 2012. The selected articles were limited to the English language. Reviews, comments, letters, conference abstracts and case reports were excluded from this analysis. Publications with a sample size of <10 were also excluded, since they were considered as case reports (10). The SLNB appears to be a better testing method compared to positron emission tomography, magnetic resonance imaging and computed tomography (11). Furthermore, surgical resection is the preferred therapeutic method for early cervical cancer. Therefore, we analyzed the studies in which sentinel lymph nodes (SLNs) were detected by the blue dye technique and/or by the use of a radiotracer intraoperatively.

Data extraction. Two independent investigators carefully extracted data from the selected articles using predefined tables, including first author, year of publication, sample size, route of

Table I. Characteristics of the 17 studies included in the meta-analysis.

First author	Year	Sample size	Route of surgery	Detection method	Pathological assessment	Refs.
Malur	2001	50	Laparoscopy/laparotomy	D+I	HE	(5)
Levenback	2002	39	Laparotomy	D+I	HE	(6)
Rhim	2002	26	Laparotomy	D+I	HE+IHC	(14)
Lambaudie	2003	12	Laparoscopy	D+I	HE+IHC	(15)
Plante	2003	70	Laparoscopy	D+I	HE+IHC	(16)
Niikura	2004	20	Laparotomy	D+I	HE+IHC	(17)
Roca	2005	40	Laparoscopy/laparotomy	D+I	HE+IHC	(18)
Silva	2005	56	Laparotomy	Isotope	HE+IHC	(19)
Wydra	2006	100	Laparotomy	D+I	HE+IHC	(20)
Zhang	2006	27	ND	D+I	HE	(21)
Schwendinger	2006	47	Laparotomy	Dye	HE+IHC	(22)
Kara	2008	32	Laparotomy	Isotope	HE+IHC	(23)
Pazin	2009	50	ND	Dye	ND	(24)
Darlin	2010	105	Laparoscopy/laparotomy	Isotope	HE+IHC	(25)
Ogawa	2010	82	ND	Isotope	HE	(26)
Lecuru	2011	145	Laparoscopy	D+I	HE+IHC	(27)
Roy	2011	211	Laparoscopy	D+I	HE+IHC	(28)

D+I, dye + isotope; HE, hematoxylin-eosin staining; IHC, immunohistochemistry; ND, not described.

surgery, detection method, type of pathological assessment and diagnostic results (detection rate, mean SLN number, bilateral detection rate, sensitivity and negative predictive value).

Statistical analysis. The detection rate, sensitivity and negative predictive values were pooled with the random effects model of DerSimonian and Laird (13), using MetaAnalyst Beta 3.13 software (Tufts Medical Center, Boston, MA, USA) (12). The potential heterogeneity among the studies was assessed using the Q-statistic and P<0.1 was considered to indicate a statistically significant difference. If heterogeneity was present, a subgroup analysis was used for further assessment.

Results

Study selection and description. A total of 38 studies were identified with the established search strategy. Studies that were clearly not eligible, as indicated by the information provided in the abstract, were excluded. For the remaining studies, the full text was read. Finally, a total of 17 studies were included in the analysis, involving a total of 1,112 patients (5,6,14-28). The study selection process is summarized in Fig. 1. The median number of included patients per study was 50 (range, 12-211). The detailed characteristics of the 17 eligible studies are summarized in Table I and the diagnostic performance of SLNB is summarized in Table II.

Analysis of the 17 studies. The diagnostic value of SLNB was affected by several factors and significant heterogeneity was identified (Table I). Therefore, data were pooled using a random effects model.
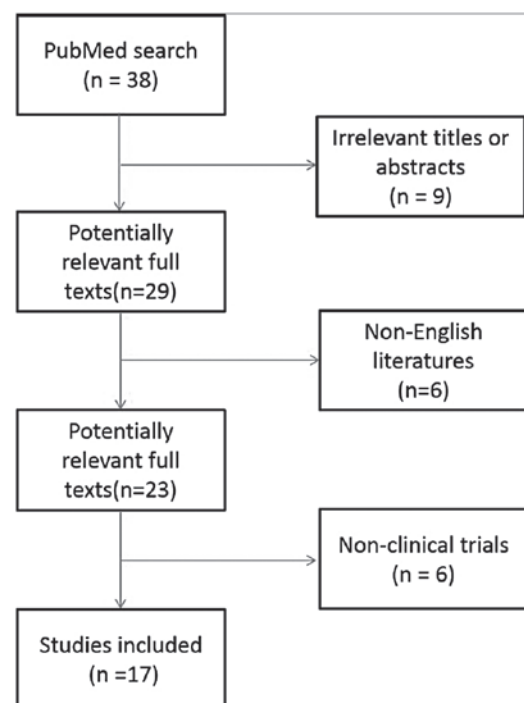

Figure 1. Flow chart of study selection process for the meta-analysis.

The pooled detection rate of SLN was 92.2% (95% CI: 88.3-94.8%; Fig. 2), whereas the pooled sensitivity and negative predictive values were 88.8 and 95.0%, respectively (Fig. 3A and B).

Table II. Diagnostic performance of the 17 studies included in the meta-analysis.

First author	Year	Sample size	Detection rate (%)	Bilateral detection rate (%)	Mean no. of SLNs (%)	Sensitivity	Negative predictive value (%)	Refs.
Malur	2001	50	78	NA	2	83.3	97	(5)
Levenback	2002	39	100	72	4	87.5	97	(6)
Rhim	2002	26	100	NA	2	80	95.2	(14)
Lambaudie	2003	12	92	83	3.1	66.7	90	(15)
Plante	2003	70	87	60	1.9	100	100	(16)
Niikura	2004	20	90	75	2.3	100	100	(17)
Roca	2005	40	100	NA	2.5	100	100	(18)
Silva	2005	56	93	41	2.3	82.3	92.1	(19)
Wydra	2006	100	84	66	1.8	86.4	95.5	(20)
Zhang	2006	27	100	74	2.6	85.7	95.2	(21)
Schwendinger	2006	47	83	NA	2	90	97	(22)
Kara	2008	32	100	50	2.1	100	100	(23)
Pazin	2009	50	92	38	2.6	85	89.6	(24)
Darlin	2010	105	90	59	1	94	99	(25)
Ogawa	2010	82	88	64	2.2	100	100	(26)
Lecuru	2011	145	98	76	3	92	98.2	(27)
Roy	2011	211	99	86	NA	90.6	94.2[a]	(28)

[a]Calculated from 181 patients in whom bilateral sentinel lymph nodes were identified. SLN, sentinel lymph node; NA, not available.
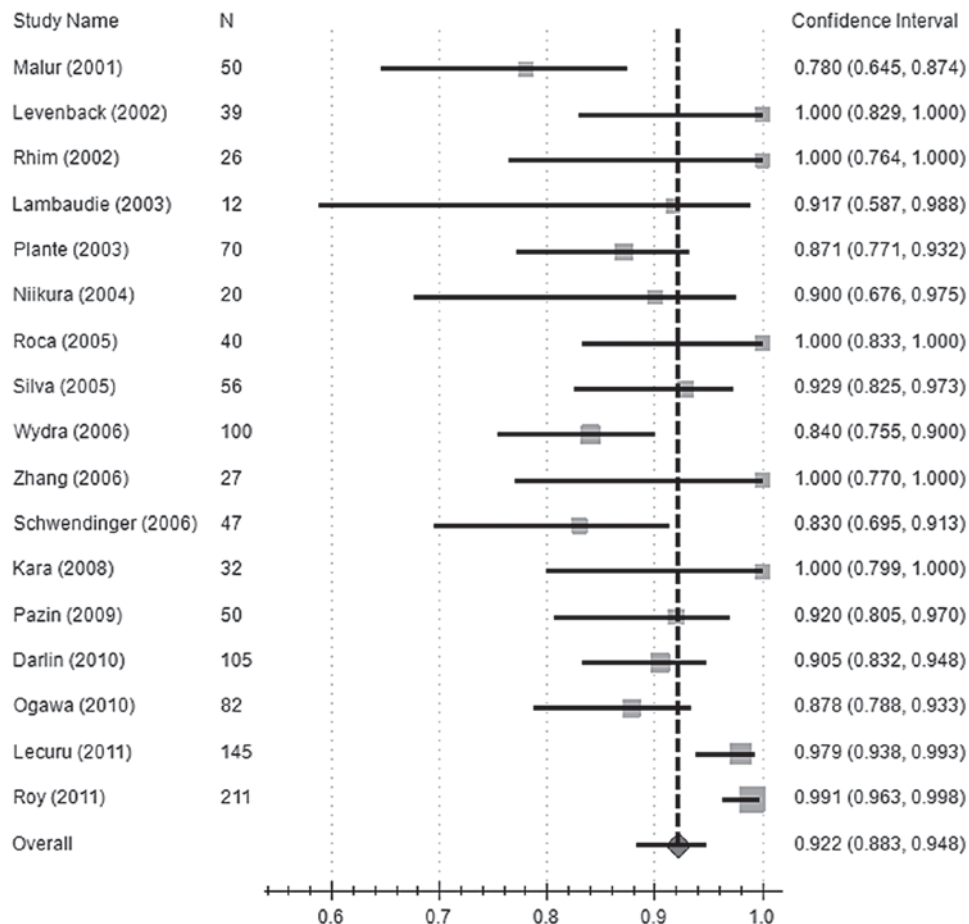

Figure 2. Forest plot showing the detection rate of sentinel lymph node biopsy in the 17 studies.

A

Study Name	N		Confidence Interval
Malur (2001)	50		0.833 (0.703, 0.913)
Levenback (2002)	39		0.875 (0.730, 0.948)
Rhim (2002)	26		0.800 (0.605, 0.913)
Lambaudie (2003)	12		0.667 (0.376, 0.869)
Plante (2003)	70		1.000 (0.897, 1.000)
Niikura (2004)	20		1.000 (0.713, 1.000)
Roca (2005)	40		1.000 (0.833, 1.000)
Silva (2005)	56		0.823 (0.701, 0.902)
Wydra (2006)	100		0.864 (0.782, 0.918)
Zhang (2006)	27		0.857 (0.671, 0.946)
Schwendinger (2006)	47		0.900 (0.776, 0.959)
Kara (2008)	32		1.000 (0.799, 1.000)
Pazin (2009)	50		0.850 (0.723, 0.925)
Darlin (2010)	105		0.940 (0.875, 0.972)
Ogawa (2010)	82		1.000 (0.911, 1.000)
Lecuru (2011)	145		0.920 (0.863, 0.954)
Roy (2011)	211		0.906 (0.859, 0.939)
Overall			0.888 (0.851, 0.917)

0.4   0.5   0.6   0.7   0.8   0.9   1.0

B

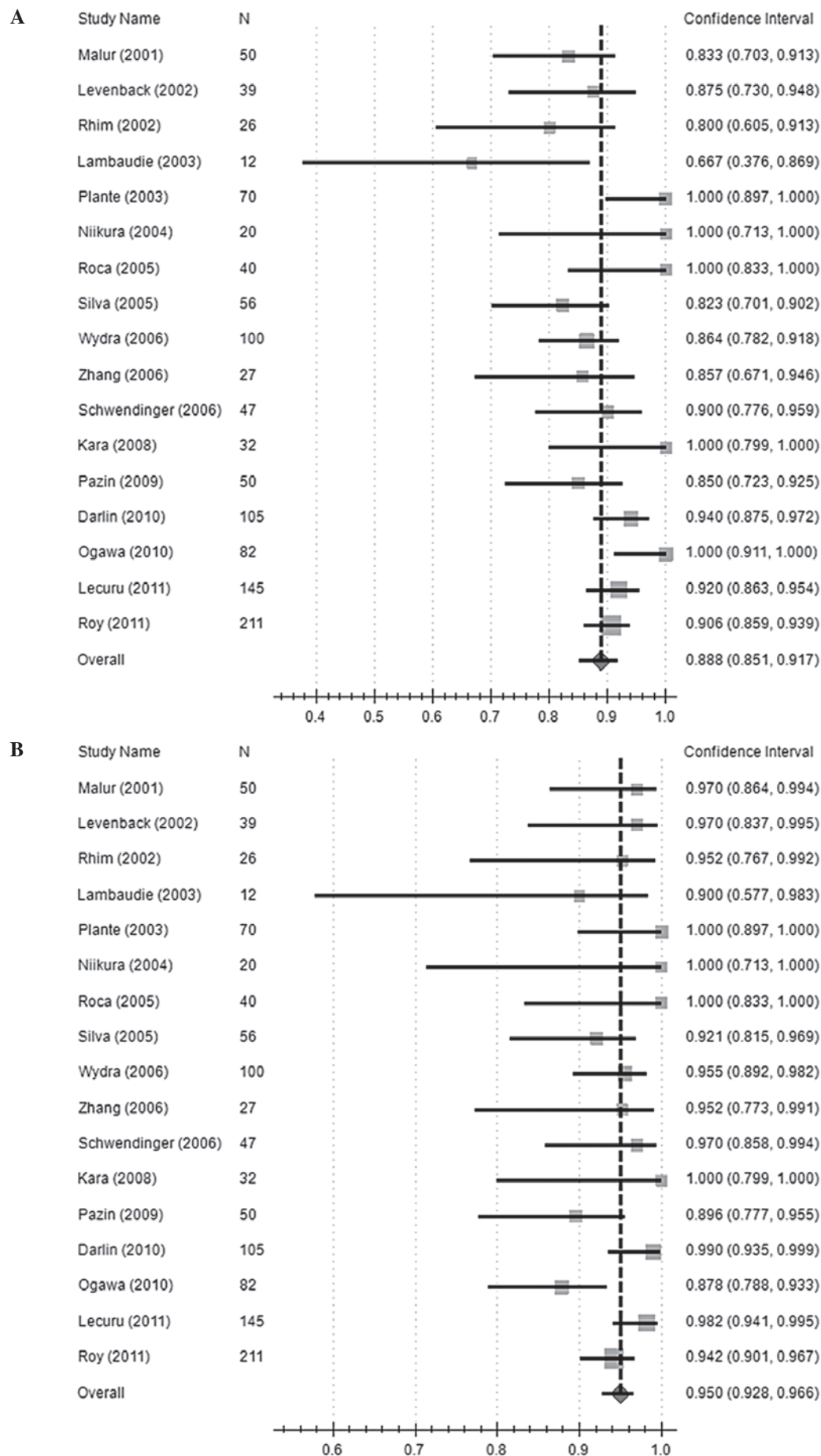| Study Name	N		Confidence Interval
Malur (2001)	50		0.970 (0.864, 0.994)
Levenback (2002)	39		0.970 (0.837, 0.995)
Rhim (2002)	26		0.952 (0.767, 0.992)
Lambaudie (2003)	12		0.900 (0.577, 0.983)
Plante (2003)	70		1.000 (0.897, 1.000)
Niikura (2004)	20		1.000 (0.713, 1.000)
Roca (2005)	40		1.000 (0.833, 1.000)
Silva (2005)	56		0.921 (0.815, 0.969)
Wydra (2006)	100		0.955 (0.892, 0.982)
Zhang (2006)	27		0.952 (0.773, 0.991)
Schwendinger (2006)	47		0.970 (0.858, 0.994)
Kara (2008)	32		1.000 (0.799, 1.000)
Pazin (2009)	50		0.896 (0.777, 0.955)
Darlin (2010)	105		0.990 (0.935, 0.999)
Ogawa (2010)	82		0.878 (0.788, 0.933)
Lecuru (2011)	145		0.982 (0.941, 0.995)
Roy (2011)	211		0.942 (0.901, 0.967)
Overall			0.950 (0.928, 0.966)

0.6   0.7   0.8   0.9   1.0

Figure 3. Forest plot showing (A) the sensitivity and (B) the negative predictive value of sentinel lymph node biopsy in the 17 studies.

Table III. Meta-analysis results of the 17 studies.

Diagnostic parameters	Detection rate % (95% CI)	Sensitivity % (95% CI)	Negative predictive value% (95% CI)
Overall (17 studies)	92.2 (88.3-94.8)	88.8 (85.1-91.7)	95.0 (92.8-96.6)
Laparoscopy (4 studies)	96.1 (85.5-99.0)	89.8 (79.5-95.2)	96.2 (90.9-98.5)
Laparotomy (7 studies)	90.2 (83.1-94.5)	86.3 (81.4-90.1)	95.3 (92.2-97.2)
Dye (2 studies)	87.5 (75.3-94.1)	87.2 (78.9-92.6)	93.2 (79.9-97.9)
Isotope (4 studies)	90.3 (86.0-93.4)	94.4 (82.6-98.4)	94.5 (85.6-98.1)
D+I (11 studies)	94.3 (88.5-97.2)	88.0 (83.2-91.6)	95.7 (93.8-97.0)
HE (4 studies)	89.4 (75.8-95.8)	88.0 (77.3-94.1)	93.7 (86.1-97.3)
HE+IHC (12 studies)	93.1 (88.6-96.0)	89.6 (85.0-92.9)	95.7 (93.7-97.1)

CI, confidence interval; D+I, dye + isotope; HE, hematoxylin-eosin staining; IHC, immunohistochemistry.

Subgroup analysis of three factors. The Q-statistic P-values of the heterogeneity test were <0.1. We performed subgroup analyses according to the route of surgery (laparoscopy or laparotomy), the detection method (dye, isotope or a combination of the two), pathological assessment type [hematoxylin-eosin staining (HE) or HE + immunohistochemistry (IHC)]. The results of the subgroup analyses are presented in Table III.

When considering the route of surgery, the pooled SLN detection rate in the laparoscopy subgroup (4 studies) was 96.1%, compared to 90.2% in the laparotomy subgroup (7 studies). The sensitivity and negative predictive values of the two subgroups were 89.8 vs. 86.3% and 96.2 vs. 95.3%, respectively.

When considering the detection method, the pooled SLN detection rate in dye subgroup (2 studies), the isotope subgroup (4 studies) and the combination of the two subgroup (11 studies) was 87.5, 90.3 and 94.3%, respectively. The pooled negative predictive value of the combination subgroup was higher compared to that of the dye and isotope subgroups.

When considering the pathological assessment type, the pooled detection rates in the HE+IHC subgroup (12 studies) was 93.1% and in the HE subgroup 89.4% (4 studies).

Discussion

In the present meta-analysis we pooled the detection rate, sensitivity and negative predictive values with data extracted from 17 studies. The overall SLN detection rate was 92.2%, which was satisfactory in the SLNB of cervical cancer, whereas the high pooled sensitivity (88.8%) and negative predictive values (95.0%) also indicated that this procedure is feasible.

However, the diagnostic parameters were affected by several factors, such as the route of surgery, the detection method, the pathological assessment type and other predictable/unpredictable factors. Subgroup analyses were performed for the three factors mentioned above.

First, in the subgroup analysis according to the route of surgery, we observed that the detection rate of laparoscopy was superior to that of laparotomy (96.1 vs. 90.2%). Furthermore, laparoscopy exhibited a higher sensitivity compared to laparotomy (89.8 vs. 86.3%), with wide visual fields and minimal incisions. Therefore, the technologically improved laparo-

scopic equipment is recommended for the surgical treatment of cervical cancer.

Second, the SLN detection rate in cervical cancer with the combination of dye and isotope (94.3%) was higher compared to that of dye (87.5%) or isotope (90.3%) alone. In addition, the pooled negative predictive value exhibited the same trend. Van de Lande *et al* (29) also reported that the combination of a radionuclide with a blue dye was the optimal method of SLN detection in a systematic review that mainly compared the three methods.

Finally, when the pathological assessment with HE + IHC was used to determine the lymph node status, higher detection and sensitivity rates were achieved compared to the HE group (93.1 vs. 89.4% and 89.6 vs. 88.0%, respectively). IHC may accurately determine the lymph node status, since it is able to detect micrometastases, compared to HE alone (30). Therefore, under the appropriate conditions, IHC is recommended in SLNB.

In this meta-analysis, the predetermined search strategy described above was used for the selection of studies from the available literature. Several studies on SLNB in cervical cancer were identified; however, the data used by each study to describe the performance characteristics were inconsistent, due to the different objectives of the studies. Several studies reported data that were not sufficient to calculate sensitivity or negative predictive values, leading to the exclusion of those studies.

Furthermore, in view of the limited time and capacity, newly published literature was not included in our study.

In conclusion, we analyzed the performance characteristics of SLNB in cervical cancer using data from 17 studies, including a total of 1,112 patients. Although SLNB appears to exhibit a satisfactory diagnostic performance in the meta-analysis, further studies are required to determine the true performance of the clinical application of SLNB in cervical cancer.

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