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Sentinel lymph node detection in early-stage ovarian cancer: a systematic review and meta-analysis

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Keywords: Ovarian cancer; sentinel lymph node; lymphatic mapping

Abstract:

Objective: A systematic pelvic and para-aortic lymphadenectomy remains part of the surgical standard management of early-stage epithelial ovarian cancer. Sentinel lymph node mapping is being investigated as an alternative procedure; however, data reporting on the sentinel lymph node performance are heterogeneous and limited. This study aimed to evaluate the detection rate and diagnostic accuracy of sentinel lymph node mapping in patients with early-stage ovarian cancer.

Methods: A systematic search was conducted in MEDLINE (through PubMed), Embase, Scopus and The Cochrane Library. We included patients with clinical stage I-II ovarian cancer undergoing a sentinel lymph node biopsy and a pelvic and para-aortic lymphadenectomy as a reference standard. We conducted a meta-analysis for the detection rates and measures of diagnostic accuracy and assessed the risk-of-bias using the Quality Assessment of Diagnostic Accuracy Studies 2 tool. The study was registered in the International Prospective Register of Systematic Reviews (PROSPERO) with identifying number CRD42022351497.

Results: After duplicate removal we identified 540 studies, eighteen were assessed for eligibility and finally, nine studies including 113 patients were analyzed. The pooled detection rates were 92% per patient (95% CI, 77.8%-100%; I2 = 74.3% p<0.0001) and the sentinel lymph node technique correctly identified 11 of 12 patients with lymph node metastases, with a negative predictive value per patient of 100% (95% CI, 97.6%-100%; I2 = 0%). The combination of indocyanine green and [^{99m}Tc]Tc-albumin nanocolloid had the best detection rate (100% (95% CI, 94%-100%; I^2 = 0%) when injected into the utero-ovarian and infundibulo-pelvic ligaments.

Conclusion: Sentinel lymph node biopsy in early-stage ovarian cancer showed a high detection rate and negative predictive value. The utero-ovarian and infundibulo-pelvic injection using the indocyanine green and technetium-99 combination could increase sentinel lymph node detection rates. However, given the limited quality of evidence and the low number of reports results from ongoing trials are awaited before its implementation in routine clinical practice.

WHAT IS ALREADY KNOWN ON THIS TOPIC

The sentinel lymph node technique in apparently early-stage ovarian cancer is an experimental procedure in which multiple tracers, injection methods, and technical procedures have been described. No previous literature has been published analyzing the diagnostic accuracy of the procedure.

WHAT THIS STUDY ADDS

This review provides specific data on sentinel lymph node detection and diagnostic accuracy in patients with early-stage ovarian cancer, including information on which tracer, injection site, and type of surgery showed better detection rates.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE, OR POLICY

The sentinel lymph node technique has shown a high detection rate and negative predictive value in patients with early-stage ovarian cancer. However, the evidence is limited, and information is relatively scarce. So, this review might be a reference for future studies with well-defined protocols and consideration of oncologic outcomes are required before implementing sentinel lymph node detection in routine clinical practice for ovarian cancer.

Introduction:

Ovarian cancer is mainly diagnosed at an advanced stage (FIGO stage III or IV) and only 20 to 30% of ovarian cancer patients are diagnosed with clinically early-stage (FIGO stage I-II) disease at initial evaluation (1). A comprehensive staging surgery, including a systematic pelvic and para-

aortic lymphadenectomy, remains the standard surgical management of early-stage epithelial ovarian cancer patients to determine the prognosis and need for adjuvant treatment (2). However, the incidence of lymph node involvement is about 15 to 20% (3). Performing a lymphadenectomy is an invasive and laborious technique, associated with intraoperative and postoperative morbidity as well as a negative impact on the quality of life (3). Additionally, no evidence suggests a possible therapeutic value of systematic lymphadenectomy (4).

Over the past decade, sentinel lymph node (SLN) mapping emerged as an alternative technique to identify lymph node metastases while reducing the surgical morbidity associated with systematic lymphadenectomies. The SLN mapping technique has proven accurate in other gynecological cancers (5–8). Nevertheless, its application in ovarian cancer is challenging since the tracer injection technique and the ovarian lymphatic drainage are more complex than other gynecological tumors.

Few studies with a limited number of patients have been published and heterogeneously reported the feasibility of the ovarian SLN mapping (9–11). There are still some aspects to be resolved regarding the use of tracers, the injection site, the detection rate according to the technique used, and the diagnostic accuracy. A detailed evaluation of the factors and the consequences of applying different methods of SLN detection and why variation might occur in early-stage ovarian cancer has not been assessed.

The objectives of this systematic review and meta-analysis were to assess the detection rate and diagnostic accuracy of SLN mapping in the staging of patients with early-stage ovarian cancer who underwent full pelvic and para-aortic lymphadenectomy as the reference standard.

Methods:

The protocol was prospectively registered with the International Prospective Register of Systematic Reviews (PROSPERO) under identifying number CRD42022351497, and the systematic review was conducted according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA)(12).

- Eligibility criteria

Inclusion criteria: (1) Studies performing the SLN mapping technique in patients diagnosed with early-stage (FIGO I-II) ovarian cancer and reporting the detection rate and diagnostic accuracy who underwent full pelvic and para-aortic lymphadenectomy. All ages, histological tumor types, grades, surgical access, and all sentinel node detection techniques were allowed.

We excluded patients with benign ovarian pathology, borderline tumors or absence of ovarian pathology, non-human articles, case series, video-articles, review articles, editorial letters, and abstracts. Only the most complete manuscript was included when two or more manuscripts were published using the same data source.

- Information sources and search strategy

A systematic literature search was performed using MEDLINE (through PubMed), Embase, Scopus, and Cochrane Library from inception to September 1st, 2022. The search strategy is reported in the supplementary material (Appendix Table S1). The electronic search was supplemented by evaluating the reference lists of the included studies. We limited articles to English, Spanish, Italian and French language, but search strategies were created only with English terms.

- Study selection and data collection process

Rayyan software (Qatar Computing Research Institute, HBKU, Doha, Qatar) was used for the title and abstract screening for eligibility and, after the removal of duplicates, all citations were reviewed independently by two reviewers (N.A and N.I) at two stages (titles and abstract, and full-text review). Disagreements were resolved by discussion between the reviewers. Reasons for exclusion were recorded.

Data collection included: author, publication year, country, sample size, study period, type of surgery, surgical approach, reference standard, SLN technique (injection site, type of tracer, timing and dose), SLN outcomes (diagnostic accuracy and detection rate), SLN ultrastaging performance and adverse events. The corresponding author was contacted to obtain missing data.

We will provide our data for independent analysis by a selected team by the Editorial Team for the purposes of additional data analysis or for the reproducibility of this study in other centers if such is requested.

- Outcomes

The primary outcomes were the overall detection rate of SLN defined as the proportion of individuals with at least one SLN detected and the diagnostic accuracy of SLN for the staging of ovarian cancer of patients who underwent a complete pelvic and para-aortic lymphadenectomy as a reference standard.

The secondary outcome was to analyze factors related with the SLN mapping detection rate and diagnostic accuracy.

The specific detection rate was analyzed depending on (1) tracers used (2) injection site and (3) type of surgery.

Assessment of risk of bias

The risk of bias were assessed independently by two reviewers (N.A and D.V) using the Quality Assessment of Diagnostic Accuracy Studies 2 tool (QUADAS-2) (13). The risk of bias was

assessed for the following domains: patient selection, index test, reference standard, and flow and timing. The risk of bias was judged as “low”, “high”, or “unclear” in each domain.

Analysis and data synthesis

Data were presented as means or medians for quantitative variables based on the distribution of the data, which has been tested using the Smirnov–Kolmogorov test. Categorical variables were represented using relative frequencies (percentages). P values were reported using the χ2 or Fisher’s exact test in categorical variables according to the sample size in each subgroup. We used Stata 14.0 (StataCorp, College Station,Texas) and JBI SUMARI (The University of Adelaide, Australia) to conduct the meta-analysis. Given the expected heterogeneity, a random-effects model was used. We calculated predictive value estimates from the extracted data.

RESULTS:

1) Study selection

The initial search identified 717 records. Six records were identified via registries and manual searching, and citation tracking. After removing duplicate records, 540 studies were evaluated. Following title and abstract screening, 18 articles were selected for full-text screening. Of the 18 full-text articles, 9 were excluded (14–22) and finally, 9 articles were included (23–31). Reasons for exclusion were outlined in Appendix Table S2. The PRISMA flow diagram shows the complete review process from the original search to the final selection (Figure 1).

2) Study characteristics

A total of 113 patients were included. The studies were conducted between 2014 to 2021. The median age was reported in seven studies (19,20,22,24–27) and it ranged from 45 to 57. Median BMI was reported in five studies (19,20,25–27) ranging from 20.5 to 25.2 kg/m2. Six studies (24–28,31) were considered observational, and three (23,29,30) as clinical trials. Five studies included a total of 58 patients without ovarian cancer and those patients were excluded from the analysis (3 patients with cervical cancer, one with a concomitant endometrial cancer, ten with borderline ovarian tumors, and 44 patients with benign tumors). The most common tracer used in the studies was ICG in 61 patients, followed by the ^{99m}Tc in 51 patients and blue dye in 23 patients. The tracers were used either as a single agent or in combination among them. The main characteristics of the included studies are presented in Table 1.

3. Risk of bias of included studies

The quality assessment of the included studies is presented in Appendix Figure S1. Most studies were at low risk of bias in the patient selection, index test, and reference standard domains. Three studies (26,28,31) were at unclear risk of bias in the patient selection domain

because consecutive recruitment was not well specified. One study (29) was also at an unclear risk of bias in the standard reference domain because it was unclear if a complete systematic lymphadenectomy was performed.

4. Synthesis of results

Overall SLN detection rate

At least one SLN was detected in 94 of 113 patients. The SLN detection rate was 93% (95% CI, 77.8%-100%; p<0.0001; I^2 = 74.3%) and ranged from 27% to 100% in individual studies (Figure 2). Seven studies (23–26,28–30) including 76 patients described the location drainage: in 67 patients (88.8 %) a SLN was detected in the aortic region (in 31 patients (40.8%) the drainage was only aortic and in 35 (46%) the drainage was present in pelvic and aortic regions). In 9 (8%) patients, only pelvic SLN were detected.

Diagnostic accuracy analysis

The SLN technique correctly identified 11 of 12 patients with lymph node metastases. Para-aortic lymph node involvement was reported in 9 patients (23, 24, 26, 27), pelvic involvement in 2 patients (23, 24) and both pelvic and aortic involvement in 1 patient (26). The pooled negative predictive value per patient was 100% (95% CI, 97.6%-100%; p=0.97; I^2 = 0%) (Figure 3). An ultrastaging protocol was used in 5 of 12 patients with lymph node metastases finding two SLNs with isolated tumor cells and four SLNs with macrometastasis (18,23).

Type of tracers

ICG alone was used in 3 studies (19,24,28), including 43 patients (38%) and blue dye alone in one study (27) with 11 patients (9.7%), showing a detection rate of 90.5 (95% CI, 61.25%-100%; I^2 = 65.9%) and 100 (95% CI, 84.9%-100%; I^2 = 0%), respectively (Figure 4).

The ^{99m}Tc was used alone in 9 patients (8%) (26) with a detection rate of 88.9 (95% CI, 58.2%-100%; I^2 = 0%) and in combination with patent blue in 20 patients (17.7%) (25,26,29) or ICG in 30 patients (26.5%) (24,30), with a detection rate of 80.9% (95% CI, 22.1%-100%; I^2 = 82.5%) and 100% (95% CI, 94%-100%; I^2 = 0%), respectively. There was no statistically significant difference when the heterogeneity source was explored by tracer type (p = 0.54). The waiting time between the injection of the marker and the detection of SLN reported by most studies averaged 10–15 minutes (Table 1), except for those studies that only used ICG alone, which followed the migration of the tracer immediately after injection.

Injection site and surgical technique

The most used injection site was the infundibulo-pelvic and utero-ovarian ligament (if no previous hysterectomy was performed) in eight studies, including 105 patients (92.2%), on the ipsilateral side of the tumor or bilaterally when both ovaries were involved. However, other injection sites were described: one study (26), including 3 patients (2.7%) , performed the tracer injection on the ovarian cortex; and another study (28) including 5 patients (4.4%), used the hilum of the ovary, the broad ligament and the ovarian parenchyma as the site of injection.

The pooled SLN detection rate when the injection site was in the ovarian ligaments was 92.9% (95% CI, 73.7%-100%; I^2 = 80.5%) in comparison to other injection sites with a pooled detection rate of 88.5 (95% CI, 42.6%-100%; I^2 = 7.4%). This difference was not statistically significant (p = 0.61) (Appendix Figure S2).

In 33 patients (29.2%) the injection was performed to the ovarian ligaments with the mass still *in situ* (25–27,31) and, in 47 patients (41.6%) to the ovarian ligaments stumps of the removed adnexa, just after the frozen' section report of malignancy. Lastly, in 25 patients (22.12%), the injection was performed (23,29,30) in the ovarian ligament stumps during a re-staging intervention surgery. The pooled detection rate was 98.9% (95% CI, 89.8%-100%; I^2 = 0%), 89.7% (95% CI, 58.3%-100%; I^2 = 84.7%), and 78.9% (95% CI, 6.7%-100%; I^2 = 95%), respectively (Appendix Figure S3). There was no statistically significant difference when the heterogeneity source was explored (p = 0.72).

Complications

No complications were reported for the tracer injection. Three studies (23,24,30) described a vascular injury related to the lymphadenectomy and not the SLN dissection.

Discussion:

Summary of Main Results

The SLN mapping was associated with a high detection rate (92%) and negative predictive value (100%) in patients with early-stage ovarian cancer. The individual detection rate from the included studies varied widely, ranging from 27% to 100%. The combination of both tracers ICG and ^{99m}TC resulted in the best detection rate when injected into the ovarian ligaments before the adnexectomy, as was blue dye, but with few patients. The 92% pooled detection rate is comparable with that observed in other gynecological neoplasia like cervical o endometrial cancer (5,7,8).

Results in the Context of Published Literature

The SLN mapping in patients with early-stage ovarian cancer is an experimental procedure in which multiple tracers, injection methods, and technical procedures have been described. No

previous meta-analysis on SLN detection in patients with early-stage ovarian cancer was previously published. Some reviews (9–11) have previously included a miscellaneous of benign and malignant pathology. Only one meta-analysis regarding SLN of the ovary by Ataei et al. was previously published (11), but included information based on an abstract data and analyzed a widely heterogeneous population such as patients with both malignant and benign ovarian tumors, other concomitant gynecological tumors or patients operated for other reasons. This broad selection of patients might lead to a biased conclusion.

According to the two main lymphatic pathways, most of the studies performed the tracer injection into the ovarian ligaments showing a high pooled detection rate. Other injection sites have been described such as the ovarian cortex, but it might be risky due to a possible tumor spillage and dissemination (26).

We found a substantial heterogeneity among used tracers. The interest of the ICG as a single agent is its easy detection, which allows following the migration. However, the combination of ICG and ^{99m}Tc was better in our pooled analyses, although results are just based on one study group (24,30). Interestingly, ICG and ^{99m}Tc combination has been relatively underexplored when considering other neoplasias (32) and may enhance the advantages of both tracers in ovarian cancer patients (33).

Another controversial issue is the optimal time to inject the tracer. Up to five studies (25–28,31) achieved a high detection rate of 98.9% injecting the tracer into the ovarian ligaments prior to the tumor removal, hypothetically the ideal injection time since the lymphatic pathways have not yet been disrupted. Alternatively, four studies (23,24,29,30) assessed the feasibility of performing the tracer injection into the ovarian ligaments' stumps, right after the adnexa removal and malignancy confirmation, to avoid an unnecessarily injection when the intraoperative pathology shows non-malignant histology. In this setting, the pooled detection rate was lower, showing conflicting results among the studies. This discrepancy could be related to the surgical technique and the different tracers used among the studies. Additionally, the high detection rate that Lago et al presented could be due to the injection is performed deep and close to the dorsal/lateral parametrium (34) resulting in tracing uterine lymphatic pathways and obtaining a very high pelvic detection rate.

Performing the SLN mapping in patients undergoing a re-staging surgery is controversial since lymphatic vessels pathways might be significantly altered and the SLN should reflect the distorted result of this manipulated and fibrous tissue. Lago et al. (30) argue that lymphatic drainage still persists after the adnexectomy in a unidirectional flow from the ovarian ligament stumps to the para-aortic and pelvic fields, respectively. However, Uccella et al and Laven et al showed more discouraging results (23, 29)

As reported in the literature (35,36), the para-aortic route was the main lymphatic spread. On the other side, the detection rate in the pelvic region was lower. A possible reason could be the retroperitoneal pelvic extravasation when injecting the tracer, hindering the subsequent SLN

detection. In order to increase pelvic detection rate, Uccella et al. (19) proposed to assess the concordance between two theoretically different lymphatic pathways by performing a cervical injection with ICG and utero-ovarian ligament injection with blue dye in endometrial cancer patients. Interestingly, they found the same pelvic SLN in all cases with both tracers suggesting that two injection sites might be equivalent.

The pooled negative predictive value was 100%. This is probably the best estimate to consider regarding SLN diagnostic accuracy since the main expected benefit of SLN clinical application in patients with early-stage ovarian cancer is to avoid unnecessary systematic lymphadenectomy in node-negative cases. The missing metastasis was in a patient that had a metastatic lymph node in the aortic region in whom no para-aortic SLN was identified, and a pelvic SLN was found as negative (24). As already described in other cancer sites (37), applying a well-defined SLN mapping algorithm going beyond the removal of only the detected SLN could increase the sensitivity and decrease the false negative rate. Therefore, it seems essential to define the ovarian lymphatic drainage pathways as well as a specific algorithm, such as performing a lymphadenectomy in cases of no drainage in a specific anatomical region (2,38).

The MELISA trial (39), SELLY trial (40) and TRSGO-SLN-OO5 (41) are 3 ongoing trials that aim to evaluate the detection rate and diagnostic accuracy of the technique (Appendix Table S2c).

Strengths and Weaknesses

The strength of this review is the rigorous methodology applied. It has a registered protocol, and was conducted following the most relevant guidelines for reporting systematic reviews. Strict selection criteria focused only on the early-stage ovarian cancer population and an adequate reference standard with the pelvic and para-aortic lymph node dissection was used to reduce the risk of biases and heterogeneity. Finally, published tools to assess methodological quality and risk of bias were considered for analyses.

We recognize several limitations, such as the inclusion of different types of studies, the limited sample size from only nine included manuscripts limiting the conclusions regarding diagnostic accuracy, and the subgroup analysis to draw consistent conclusions. Moreover, we found substantial clinical heterogeneity among the studies regarding the tracers used and the technique for the injection.

Implications for Practice and Further Research

The SLN technique is considered the standard of care for other gynecologic neoplasms. Our review showed that SLN mapping resulted in a high detection rate and negative predictive value in patients with early-stage ovarian cancer and provides information on which tracer, injection site, and type of surgery performed better. Although evidence is still limited, this study synthesizes

the current SLN data in ovarian cancer patients and might be a reference for the design of future clinical before considering the technique in a clinical setting.

Conclusions

The SLN mapping in patients with early-stage ovarian cancer showed a high detection rate and negative predictive value. The SLN mapping is a surgical procedure under investigation aiming to be an alternative standard of care in the management of select women with early-stage ovarian cancer. However, given the low quality of available evidence, results from future prospective trials are awaited before its implementation in routine clinical practice.

Declaration of competing interest

The authors declare that there are no conflicts of interest related to the above presented work.

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460 **Table 1:** Characteristics of the included studies

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Author, year; country	Sample size*	Study period	Type of surgery	Surgical approach	Injection site	Tracer used and dose	Time between injection and detection	SLN ultra staging
Kleppe, 2014; Netherlands	5	October 2012-June 2014	PSS	LPT	UO and IP ligaments	0.2–0.5 mL of Tc-99m albumin nanocolloid and Blue dye (each injection)	15 minutes	yes
Hassanzadeh, 2016; Iran	13	January 2010 - October 2014	PSS	LPT	UO and IP ligaments (n=10); Cortex (n=3)	0.2 ml of Tc- 99m Phytate + Blue dye (each injection)	10 minutes	NS
Angelucci,2016; Italy	5	April 2016 - May 2016	PSS	MIS	Hilum of ovary	0.5-1 ml of ICG, 0.5-1mL (1.25 mg/mL)	2 minutes	NS
Buda, 2017; Italy	7	NR	PSS	MIS	UO and IP ligaments	0.5 to 1 ml of ICG (1.25 mg/mL)	Real time	NS
Uccella,2019; Italy	31	March 2018 -	PSS and D	MIS	UO and IP ligamen	2 ml of ICG (1.25 mg/mL)	5-20 minut	yes

		ongoing	SS		ts (after adnexectomy)		es	
Lago, 2018; Spain	10	March 2017-February 2018	PSS and DSS	MIS + LPT	UO and IP ligaments (after adnexectomy)	0.2 ml of Tc99m albumin colloid (37 MBq) + 0.5 ml of ICG (1.25 mg/mL)	15 minutes	Yes
Lago, 2020; Spain	20	March 2018 - July 2019	PSS and DSS	MIS + LPT	UO and IP ligaments (after adnexectomy)	0.2 ml of Tc99m albumin colloid (37 MBq) + 0.5 ml of ICG (1.25 mg/mL)	15 minutes	Yes**
Laven, 2021; Netherlands	11	NR	PSS and DSS	LPT	UO and IP ligaments (after adnexectomy)	0.15 ml of Tc99m albumin nanocolloid (20 MBq) + 0.2 ml blue dye	15 minutes	Yes
Guerra, 2021; Venezuela	28	June 2016-November 2019	DSS	LPT	UO and IP ligaments	0.5 mL of Isosulfan (UO ligament) + 2 mL (IP ligament)	15 minutes	NS

*It refers only to patients with malignant ovarian cancer. **Ultrastaging protocol was applied in a second time* (40). *NR: not reported. UO: utero-ovarian; IP: Infundibulo-pelvic. Abbreviations: PSS, primary staging surgery; DSS, delayed or re-staging surgery; LPT, laparotomy; MIS, minimal invasive surgery; NS, not specified; NE, not evaluable*

Figure 1. PRISMA flow diagram. *Abbreviations: SLN, sentinel lymph node; EOC, epithelial ovarian cancer*

Figure 2. Forest plot showing the overall detection rate

Figure 3. Forest plot showing the negative predictive value

Figure 4. Forest plot showing the detection rate depending on the type of tracers used

Sentinel lymph node detection in early-stage ovarian cancer: a systematic review and meta-analysis

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Keywords: Ovarian cancer; sentinel lymph node; lymphatic mapping

Abstract:

Objective: A systematic pelvic and para-aortic lymphadenectomy remains part of the surgical standard management of early-stage epithelial ovarian cancer. Sentinel lymph node mapping is being investigated as an alternative procedure; however, data reporting on the sentinel lymph node performance are heterogeneous and limited. This study aimed to evaluate the detection rate and diagnostic accuracy of sentinel lymph node mapping in patients with early-stage ovarian cancer.

Methods: A systematic search was conducted in MEDLINE (through PubMed), Embase, Scopus and The Cochrane Library. We included patients with clinical stage I-II ovarian cancer undergoing a sentinel lymph node biopsy and a pelvic and para-aortic lymphadenectomy as a reference standard. We conducted a meta-analysis for the detection rates and measures of diagnostic accuracy and assessed the risk-of-bias using the Quality Assessment of Diagnostic Accuracy Studies 2 tool. The study was registered in the International Prospective Register of Systematic Reviews (PROSPERO) with identifying number CRD42022351497.

Results: After duplicate removal we identified 540 studies, eighteen were assessed for eligibility and finally, nine studies including 113 patients were analyzed. The pooled detection rates were 92% per patient (95% CI, 77.8%-100%; I2 = 74.3% p<0.0001) and the sentinel lymph node technique correctly identified 11 of 12 patients with lymph node metastases, with a negative predictive value per patient of 100% (95% CI, 97.6%-100%; I2 = 0%). The combination of indocyanine green and [^{99m}Tc]Tc-albumin nanocolloid had the best detection rate (100% (95% CI, 94%-100%; I^2 = 0%) when injected into the utero-ovarian and infundibulo-pelvic ligaments.

Conclusion: Sentinel lymph node biopsy in early-stage ovarian cancer showed a high detection rate and negative predictive value. The utero-ovarian and infundibulo-pelvic injection using the indocyanine green and technetium-99 combination could increase sentinel lymph node detection rates. However, given the limited quality of evidence and the low number of reports results from ongoing trials are awaited before its implementation in routine clinical practice.

WHAT IS ALREADY KNOWN ON THIS TOPIC

The sentinel lymph node technique in apparently early-stage ovarian cancer is an experimental procedure in which multiple tracers, injection methods, and technical procedures have been described. No previous literature has been published analyzing the diagnostic accuracy of the procedure.

WHAT THIS STUDY ADDS

This review provides specific data on sentinel lymph node detection and diagnostic accuracy in patients with early-stage ovarian cancer, including information on which tracer, injection site, and type of surgery showed better detection rates.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE, OR POLICY

The sentinel lymph node technique has shown a high detection rate and negative predictive value in patients with early-stage ovarian cancer. However, the evidence is limited, and information is relatively scarce. So, this review might be a reference for future studies with well-defined protocols and consideration of oncologic outcomes are required before implementing sentinel lymph node detection in routine clinical practice for ovarian cancer.

Introduction:

Ovarian cancer is mainly diagnosed at an advanced stage (FIGO stage III or IV) and only 20 to 30% of ovarian cancer patients are diagnosed with clinically early-stage (FIGO stage I-II) disease at initial evaluation (1). A comprehensive staging surgery, including a systematic pelvic and para-

aortic lymphadenectomy, remains the standard surgical management of early-stage epithelial ovarian cancer patients to determine the prognosis and need for adjuvant treatment (2). However, the incidence of lymph node involvement is about 15 to 20% (3). Performing a lymphadenectomy is an invasive and laborious technique, associated with intraoperative and postoperative morbidity as well as a negative impact on the quality of life (3). Additionally, no evidence suggests a possible therapeutic value of systematic lymphadenectomy (4).

Over the past decade, sentinel lymph node (SLN) mapping emerged as an alternative technique to identify lymph node metastases while reducing the surgical morbidity associated with systematic lymphadenectomies. The SLN mapping technique has proven accurate in other gynecological cancers (5–8). Nevertheless, its application in ovarian cancer is challenging since the tracer injection technique and the ovarian lymphatic drainage are more complex than other gynecological tumors.

Few studies with a limited number of patients have been published and heterogeneously reported the feasibility of the ovarian SLN mapping (9–11). There are still some aspects to be resolved regarding the use of tracers, the injection site, the detection rate according to the technique used, and the diagnostic accuracy. A detailed evaluation of the factors and the consequences of applying different methods of SLN detection and why variation might occur in early-stage ovarian cancer has not been assessed.

The objectives of this systematic review and meta-analysis were to assess the detection rate and diagnostic accuracy of SLN mapping in the staging of patients with early-stage ovarian cancer who underwent full pelvic and para-aortic lymphadenectomy as the reference standard.

Methods:

The protocol was prospectively registered with the International Prospective Register of Systematic Reviews (PROSPERO) under identifying number CRD42022351497, and the systematic review was conducted according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA)(12).

- Eligibility criteria

Inclusion criteria: (1) Studies performing the SLN mapping technique in patients diagnosed with early-stage (FIGO I-II) ovarian cancer and reporting the detection rate and diagnostic accuracy who underwent full pelvic and para-aortic lymphadenectomy. All ages, histological tumor types, grades, surgical access, and all sentinel node detection techniques were allowed.

We excluded patients with benign ovarian pathology, borderline tumors or absence of ovarian pathology, non-human articles, case series, video-articles, review articles, editorial letters, and abstracts. Only the most complete manuscript was included when two or more manuscripts were published using the same data source.

- Information sources and search strategy

A systematic literature search was performed using MEDLINE (through PubMed), Embase, Scopus, and Cochrane Library from inception to September 1st, 2022. The search strategy is reported in the supplementary material (Appendix Table S1). The electronic search was supplemented by evaluating the reference lists of the included studies. We limited articles to English, Spanish, Italian and French language, but search strategies were created only with English terms.

- Study selection and data collection process

Rayyan software (Qatar Computing Research Institute, HBKU, Doha, Qatar) was used for the title and abstract screening for eligibility and, after the removal of duplicates, all citations were reviewed independently by two reviewers (N.A and N.I) at two stages (titles and abstract, and full-text review). Disagreements were resolved by discussion between the reviewers. Reasons for exclusion were recorded.

Data collection included: author, publication year, country, sample size, study period, type of surgery, surgical approach, reference standard, SLN technique (injection site, type of tracer, timing and dose), SLN outcomes (diagnostic accuracy and detection rate), SLN ultrastaging performance and adverse events. The corresponding author was contacted to obtain missing data.

We will provide our data for independent analysis by a selected team by the Editorial Team for the purposes of additional data analysis or for the reproducibility of this study in other centers if such is requested.

- Outcomes

The primary outcomes were the overall detection rate of SLN defined as the proportion of individuals with at least one SLN detected and the diagnostic accuracy of SLN for the staging of ovarian cancer of patients who underwent a complete pelvic and para-aortic lymphadenectomy as a reference standard.

The secondary outcome was to analyze factors related with the SLN mapping detection rate and diagnostic accuracy.

The specific detection rate was analyzed depending on (1) tracers used (2) injection site and (3) type of surgery.

Assessment of risk of bias

The risk of bias were assessed independently by two reviewers (N.A and D.V) using the Quality Assessment of Diagnostic Accuracy Studies 2 tool (QUADAS-2) (13). The risk of bias was

assessed for the following domains: patient selection, index test, reference standard, and flow and timing. The risk of bias was judged as “low”, “high”, or “unclear” in each domain.

Analysis and data synthesis

Data were presented as means or medians for quantitative variables based on the distribution of the data, which has been tested using the Smirnov–Kolmogorov test. Categorical variables were represented using relative frequencies (percentages). P values were reported using the $\chi 2$ or Fisher’s exact test in categorical variables according to the sample size in each subgroup. We used Stata 14.0 (StataCorp, College Station,Texas) and JBI SUMARI (The University of Adelaide, Australia) to conduct the meta-analysis. Given the expected heterogeneity, a random-effects model was used. We calculated predictive value estimates from the extracted data.

RESULTS:

1) Study selection

The initial search identified 717 records. Six records were identified via registries and manual searching, and citation tracking. After removing duplicate records, 540 studies were evaluated. Following title and abstract screening, 18 articles were selected for full-text screening. Of the 18 full-text articles, 9 were excluded (14–22) and finally, 9 articles were included (23–31). Reasons for exclusion were outlined in Appendix Table S2. The PRISMA flow diagram shows the complete review process from the original search to the final selection (Figure 1).

2) Study characteristics

A total of 113 patients were included. The studies were conducted between 2014 to 2021. The median age was reported in seven studies (19,20,22,24–27) and it ranged from 45 to 57. Median BMI was reported in five studies (19,20,25–27) ranging from 20.5 to 25.2 kg/m2. Six studies (24–28,31) were considered observational, and three (23,29,30) as clinical trials. Five studies included a total of 58 patients without ovarian cancer and those patients were excluded from the analysis (3 patients with cervical cancer, one with a concomitant endometrial cancer, ten with borderline ovarian tumors, and 44 patients with benign tumors). The most common tracer used in the studies was ICG in 61 patients, followed by the ^{99m}Tc in 51 patients and blue dye in 23 patients. The tracers were used either as a single agent or in combination among them. The main characteristics of the included studies are presented in Table 1.

3. Risk of bias of included studies

The quality assessment of the included studies is presented in Appendix Figure S1. Most studies were at low risk of bias in the patient selection, index test, and reference standard domains. Three studies (26,28,31) were at unclear risk of bias in the patient selection domain

because consecutive recruitment was not well specified. One study (29) was also at an unclear risk of bias in the standard reference domain because it was unclear if a complete systematic lymphadenectomy was performed.

4. Synthesis of results

Overall SLN detection rate

At least one SLN was detected in 94 of 113 patients. The SLN detection rate was 93% (95% CI, 77.8%-100%; p<0.0001; I^2 = 74.3%) and ranged from 27% to 100% in individual studies (Figure 2). Seven studies (23–26,28–30) including 76 patients described the location drainage: in 67 patients (88.8 %) a SLN was detected in the aortic region (in 31 patients (40.8%) the drainage was only aortic and in 35 (46%) the drainage was present in pelvic and aortic regions). In 9 (8%) patients, only pelvic SLN were detected.

Diagnostic accuracy analysis

The SLN technique correctly identified 11 of 12 patients with lymph node metastases. Para-aortic lymph node involvement was reported in 9 patients (23, 24, 26, 27), pelvic involvement in 2 patients (23, 24) and both pelvic and aortic involvement in 1 patient (26). The pooled negative predictive value per patient was 100% (95% CI, 97.6%-100%; p=0.97; I^2 = 0%) (Figure 3). An ultrastaging protocol was used in 5 of 12 patients with lymph node metastases finding two SLNs with isolated tumor cells and four SLNs with macrometastasis (18,23).

Type of tracers

ICG alone was used in 3 studies (19,24,28), including 43 patients (38%) and blue dye alone in one study (27) with 11 patients (9.7%), showing a detection rate of 90.5 (95% CI, 61.25%-100%; I^2 = 65.9%) and 100 (95% CI, 84.9%-100%; I^2 = 0%), respectively (Figure 4).

The ^{99m}Tc was used alone in 9 patients (8%) (26) with a detection rate of 88.9 (95% CI, 58.2%-100%; I^2 = 0%) and in combination with patent blue in 20 patients (17.7%) (25,26,29) or ICG in 30 patients (26.5%) (24,30), with a detection rate of 80.9% (95% CI, 22.1%-100%; I^2 = 82.5%) and 100% (95% CI, 94%-100%; I^2 = 0%), respectively. There was no statistically significant difference when the heterogeneity source was explored by tracer type (p = 0.54). The waiting time between the injection of the marker and the detection of SLN reported by most studies averaged 10–15 minutes (Table 1), except for those studies that only used ICG alone, which followed the migration of the tracer immediately after injection.

Injection site and surgical technique

The most used injection site was the infundibulo-pelvic and utero-ovarian ligament (if no previous hysterectomy was performed) in eight studies, including 105 patients (92.2%), on the ipsilateral side of the tumor or bilaterally when both ovaries were involved. However, other injection sites were described: one study (26), including 3 patients (2.7%) , performed the tracer injection on the ovarian cortex; and another study (28) including 5 patients (4.4%), used the hilum of the ovary, the broad ligament and the ovarian parenchyma as the site of injection.

The pooled SLN detection rate when the injection site was in the ovarian ligaments was 92.9% (95% CI, 73.7%-100%; I^2 = 80.5%) in comparison to other injection sites with a pooled detection rate of 88.5 (95% CI, 42.6%-100%; I^2 = 7.4%). This difference was not statistically significant (p = 0.61) (Appendix Figure S2).

In 33 patients (29.2%) the injection was performed to the ovarian ligaments with the mass still *in situ* (25–27,31) and, in 47 patients (41.6%) to the ovarian ligaments stumps of the removed adnexa, just after the frozen' section report of malignancy. Lastly, in 25 patients (22.12%), the injection was performed (23,29,30) in the ovarian ligament stumps during a re-staging intervention surgery. The pooled detection rate was 98.9% (95% CI, 89.8%-100%; I^2 = 0%), 89.7% (95% CI, 58.3%-100%; I^2 = 84.7%), and 78.9% (95% CI, 6.7%-100%; I^2 = 95%), respectively (Appendix Figure S3). There was no statistically significant difference when the heterogeneity source was explored (p = 0.72).

Complications

No complications were reported for the tracer injection. Three studies (23,24,30) described a vascular injury related to the lymphadenectomy and not the SLN dissection.

Discussion:

Summary of Main Results

The SLN mapping was associated with a high detection rate (92%) and negative predictive value (100%) in patients with early-stage ovarian cancer. The individual detection rate from the included studies varied widely, ranging from 27% to 100%. The combination of both tracers ICG and ^{99m}TC resulted in the best detection rate when injected into the ovarian ligaments before the adnexectomy, as was blue dye, but with few patients. The 92% pooled detection rate is comparable with that observed in other gynecological neoplasia like cervical o endometrial cancer (5,7,8).

Results in the Context of Published Literature

The SLN mapping in patients with early-stage ovarian cancer is an experimental procedure in which multiple tracers, injection methods, and technical procedures have been described. No

previous meta-analysis on SLN detection in patients with early-stage ovarian cancer was previously published. Some reviews (9–11) have previously included a miscellaneous of benign and malignant pathology. Only one meta-analysis regarding SLN of the ovary by Ataei et al. was previously published (11), but included information based on an abstract data and analyzed a widely heterogeneous population such as patients with both malignant and benign ovarian tumors, other concomitant gynecological tumors or patients operated for other reasons. This broad selection of patients might lead to a biased conclusion.

According to the two main lymphatic pathways, most of the studies performed the tracer injection into the ovarian ligaments showing a high pooled detection rate. Other injection sites have been described such as the ovarian cortex, but it might be risky due to a possible tumor spillage and dissemination (26).

We found a substantial heterogeneity among used tracers. The interest of the ICG as a single agent is its easy detection, which allows following the migration. However, the combination of ICG and ^{99m}Tc was better in our pooled analyses, although results are just based on one study group (24,30). Interestingly, ICG and ^{99m}Tc combination has been relatively underexplored when considering other neoplasias (32) and may enhance the advantages of both tracers in ovarian cancer patients (33).

Another controversial issue is the optimal time to inject the tracer. Up to five studies (25–28,31) achieved a high detection rate of 98.9% injecting the tracer into the ovarian ligaments prior to the tumor removal, hypothetically the ideal injection time since the lymphatic pathways have not yet been disrupted. Alternatively, four studies (23,24,29,30) assessed the feasibility of performing the tracer injection into the ovarian ligaments' stumps, right after the adnexa removal and malignancy confirmation, to avoid an unnecessarily injection when the intraoperative pathology shows non-malignant histology. In this setting, the pooled detection rate was lower, showing conflicting results among the studies. This discrepancy could be related to the surgical technique and the different tracers used among the studies. Additionally, the high detection rate that Lago et al presented could be due to the injection is performed deep and close to the dorsal/lateral parametrium (34) resulting in tracing uterine lymphatic pathways and obtaining a very high pelvic detection rate.

Performing the SLN mapping in patients undergoing a re-staging surgery is controversial since lymphatic vessels pathways might be significantly altered and the SLN should reflect the distorted result of this manipulated and fibrous tissue. Lago et al. (30) argue that lymphatic drainage still persists after the adnexectomy in a unidirectional flow from the ovarian ligament stumps to the para-aortic and pelvic fields, respectively. However, Uccella et al and Laven et al showed more discouraging results (23, 29)

As reported in the literature (35,36), the para-aortic route was the main lymphatic spread. On the other side, the detection rate in the pelvic region was lower. A possible reason could be the retroperitoneal pelvic extravasation when injecting the tracer, hindering the subsequent SLN

detection. In order to increase pelvic detection rate, Uccella et al. (19) proposed to assess the concordance between two theoretically different lymphatic pathways by performing a cervical injection with ICG and utero-ovarian ligament injection with blue dye in endometrial cancer patients. Interestingly, they found the same pelvic SLN in all cases with both tracers suggesting that two injection sites might be equivalent.

The pooled negative predictive value was 100%. This is probably the best estimate to consider regarding SLN diagnostic accuracy since the main expected benefit of SLN clinical application in patients with early-stage ovarian cancer is to avoid unnecessary systematic lymphadenectomy in node-negative cases. The missing metastasis was in a patient that had a metastatic lymph node in the aortic region in whom no para-aortic SLN was identified, and a pelvic SLN was found as negative (24). As already described in other cancer sites (37), applying a well-defined SLN mapping algorithm going beyond the removal of only the detected SLN could increase the sensitivity and decrease the false negative rate. Therefore, it seems essential to define the ovarian lymphatic drainage pathways as well as a specific algorithm, such as performing a lymphadenectomy in cases of no drainage in a specific anatomical region (2,38).

The MELISA trial (39), SELLY trial (40) and TRSGO-SLN-OO5 (41) are 3 ongoing trials that aim to evaluate the detection rate and diagnostic accuracy of the technique (Appendix Table S2c).

Strengths and Weaknesses

The strength of this review is the rigorous methodology applied. It has a registered protocol, and was conducted following the most relevant guidelines for reporting systematic reviews. Strict selection criteria focused only on the early-stage ovarian cancer population and an adequate reference standard with the pelvic and para-aortic lymph node dissection was used to reduce the risk of biases and heterogeneity. Finally, published tools to assess methodological quality and risk of bias were considered for analyses.

We recognize several limitations, such as the inclusion of different types of studies, the limited sample size from only nine included manuscripts limiting the conclusions regarding diagnostic accuracy, and the subgroup analysis to draw consistent conclusions. Moreover, we found substantial clinical heterogeneity among the studies regarding the tracers used and the technique for the injection.

Implications for Practice and Further Research

The SLN technique is considered the standard of care for other gynecologic neoplasms. Our review showed that SLN mapping resulted in a high detection rate and negative predictive value in patients with early-stage ovarian cancer and provides information on which tracer, injection site, and type of surgery performed better. Although evidence is still limited, this study synthesizes

the current SLN data in ovarian cancer patients and might be a reference for the design of future clinical before considering the technique in a clinical setting.

Conclusions

The SLN mapping in patients with early-stage ovarian cancer showed a high detection rate and negative predictive value. The SLN mapping is a surgical procedure under investigation aiming to be an alternative standard of care in the management of select women with early-stage ovarian cancer. However, given the low quality of available evidence, results from future prospective trials are awaited before its implementation in routine clinical practice.

Declaration of competing interest

The authors declare that there are no conflicts of interest related to the above presented work.

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Analysis of 276 pelvic and paraaortic lymphadenectomies and surgical implications. *J Am Coll Surg*. 2003;197(2):198–205.

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41. US National Library of Medicine. Sentinel Lymph Node Assessment in Ovarian Cancer (TRSGO-SLN-OO5). Available at: https://clinicaltrials.gov/ct2/show/NCT04714931. Accessed 1st June, 2023

460 **Table 1:** Characteristics of the included studies

461

Author, year; country	Sample size*	Study period	Type of surgery	Surgical approach	Injection site	Tracer used and dose	Time between injection and detection	SLN ultra staging
Kleppe, 2014; Netherlands	5	October 2012-June 2014	PSS	LPT	UO and IP ligaments	0.2–0.5 mL of Tc-99m albumin nanocolloid and Blue dye (each injection)	15 minutes	yes
Hassanzadeh, 2016; Iran	13	January 2010 - October 2014	PSS	LPT	UO and IP ligaments (n=10); Cortex (n=3)	0.2 ml of Tc- 99m Phytate + Blue dye (each injection)	10 minutes	NS
Angelucci,2016; Italy	5	April 2016 - May 2016	PSS	MIS	Hilum of ovary	0.5-1 ml of ICG, 0.5-1mL (1.25 mg/mL)	2 minutes	NS
Buda, 2017; Italy	7	NR	PSS	MIS	UO and IP ligaments	0.5 to 1 ml of ICG (1.25 mg/mL)	Real time	NS
Uccella,2019; Italy	31	March 2018 -	PSS and D	MIS	UO and IP ligamen	2 ml of ICG (1.25 mg/mL)	5-20 minut	yes

		ongoing	SS		ts (after adnexectomy)		es	
Lago, 2018; Spain	10	March 2017-February 2018	PSS and DSS	MIS + LPT	UO and IP ligaments (after adnexectomy)	0.2 ml of Tc99m albumin colloid (37 MBq) + 0.5 ml of ICG (1.25 mg/mL)	15 minutes	Yes
Lago, 2020; Spain	20	March 2018 - July 2019	PSS and DSS	MIS + LPT	UO and IP ligaments (after adnexectomy)	0.2 ml of Tc99m albumin colloid (37 MBq) + 0.5 ml of ICG (1.25 mg/mL)	15 minutes	Yes**
Laven, 2021; Netherlands	11	NR	PSS and DSS	LPT	UO and IP ligaments (after adnexectomy)	0.15 ml of Tc99m albumin nanocolloid (20 MBq) + 0.2 ml blue dye	15 minutes	Yes
Guerra, 2021; Venezuela	28	June 2016-November 2019	DSS	LPT	UO and IP ligaments	0.5 mL of Isosulfan (UO ligament) + 2 mL (IP ligament)	15 minutes	NS

*It refers only to patients with malignant ovarian cancer. **Ultrastaging protocol was applied in a second time* (40). *NR: not reported. UO: utero-ovarian; IP: Infundibulo-pelvic. Abbreviations: PSS, primary staging surgery; DSS, delayed or re-staging surgery; LPT, laparotomy; MIS, minimal invasive surgery; NS, not specified; NE, not evaluable*

Figure 1. PRISMA flow diagram. *Abbreviations: SLN, sentinel lymph node; EOC, epithelial ovarian cancer*

Figure 2. Forest plot showing the overall detection rate

Figure 3. Forest plot showing the negative predictive value

Figure 4. Forest plot showing the detection rate depending on the type of tracers used

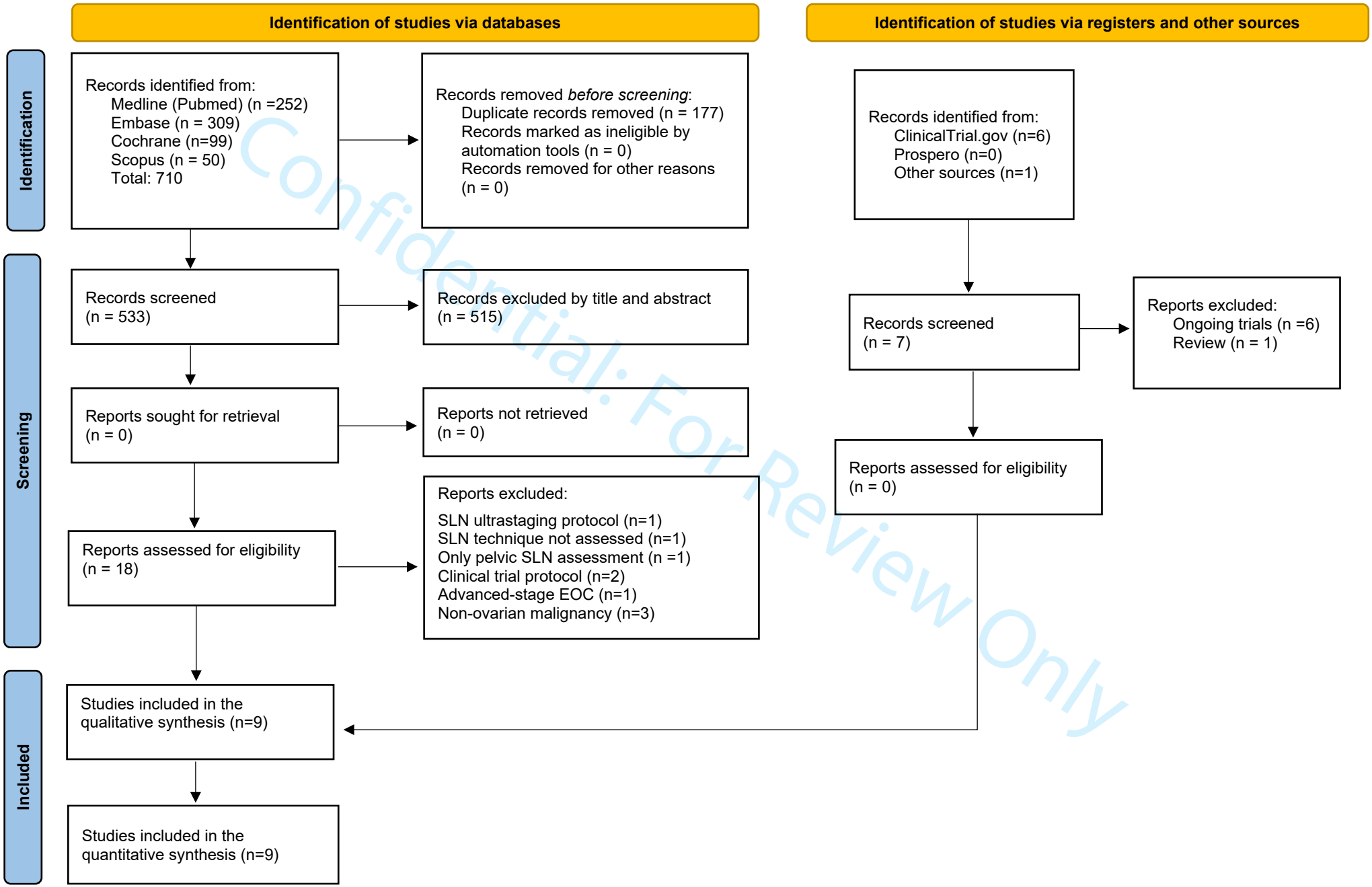


Figure 1. PRISMA flow diagram. *Abbreviations: SLN, sentinel lymph node; EOC, epithelial ovarian cancer*

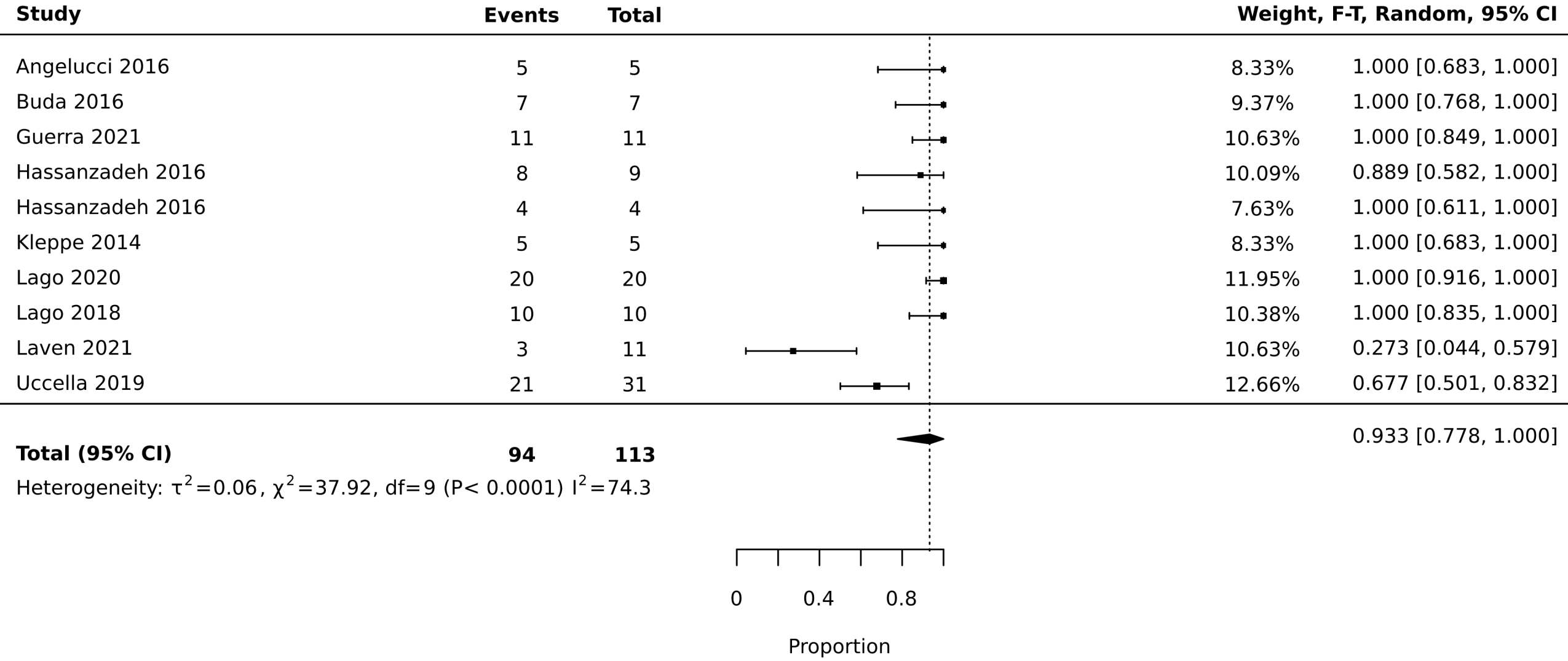


Figure 2. Forest plot showing the overall detection rate

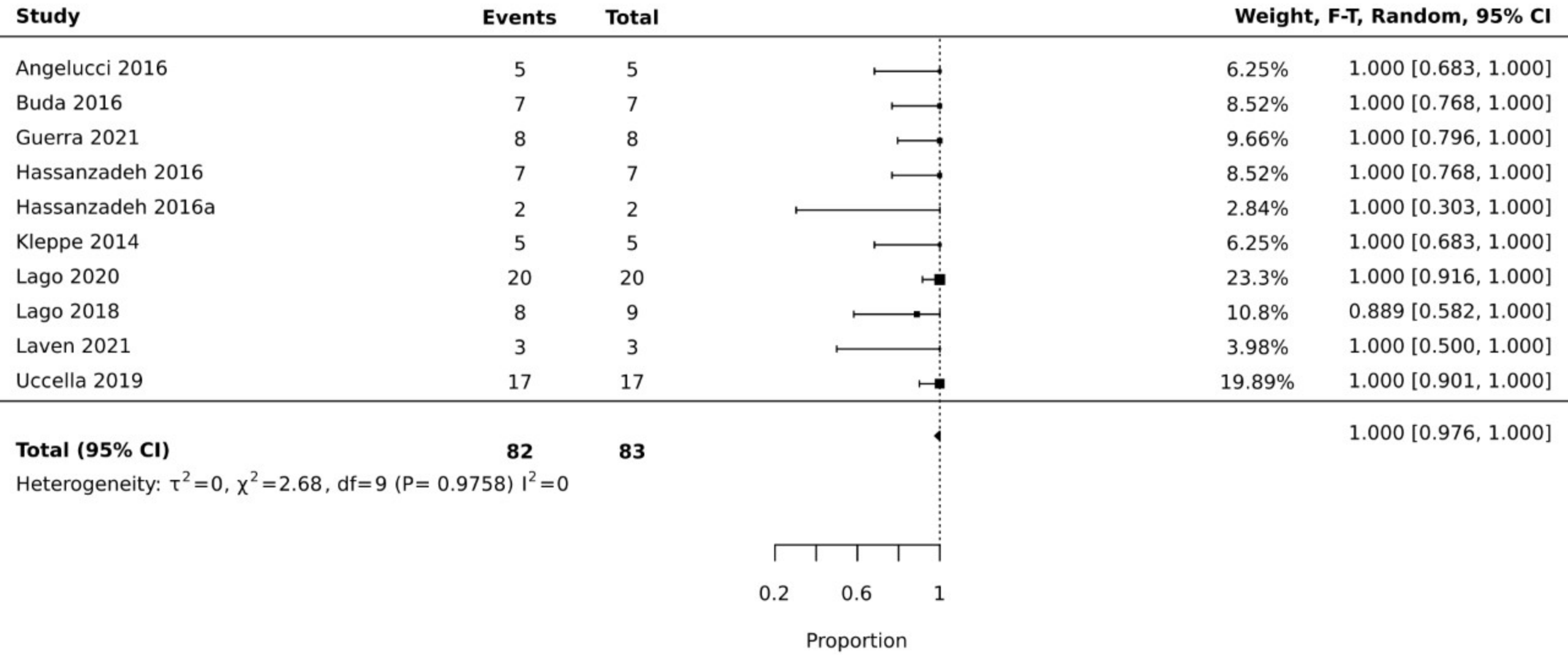
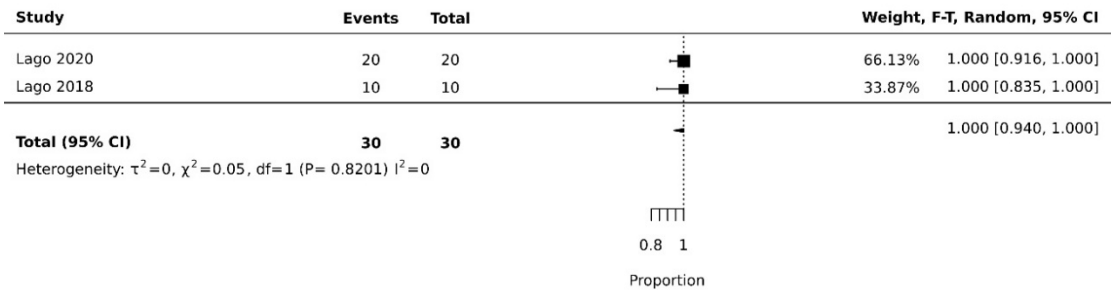
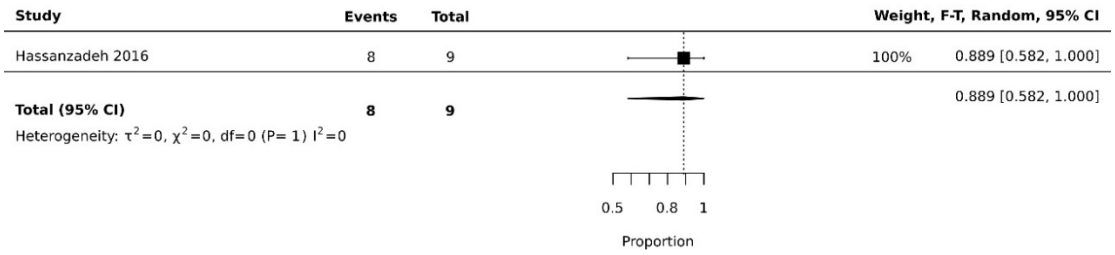


Figure 3. Forest plot showing the negative predictive value

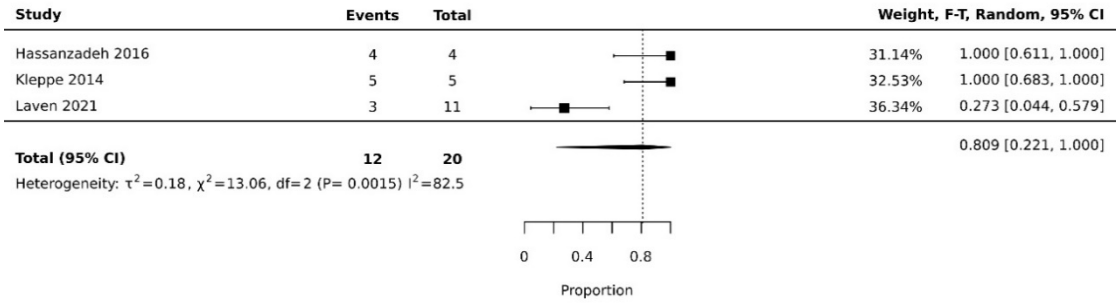
a) Indocyanine green and [^{99m}Tc]Tc-albumin nanocolloid



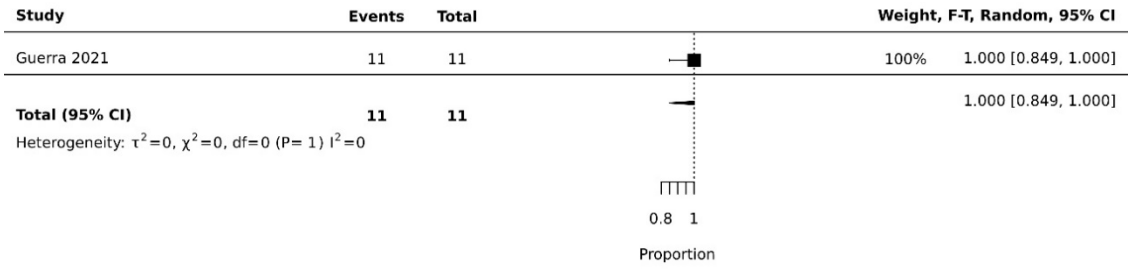
b) [^{99m}Tc]Tc-albumin nanocolloid



c) [^{99m}Tc]Tc-albumin nanocolloid and blue dye



d) Blue dye



e) Indocyanine green

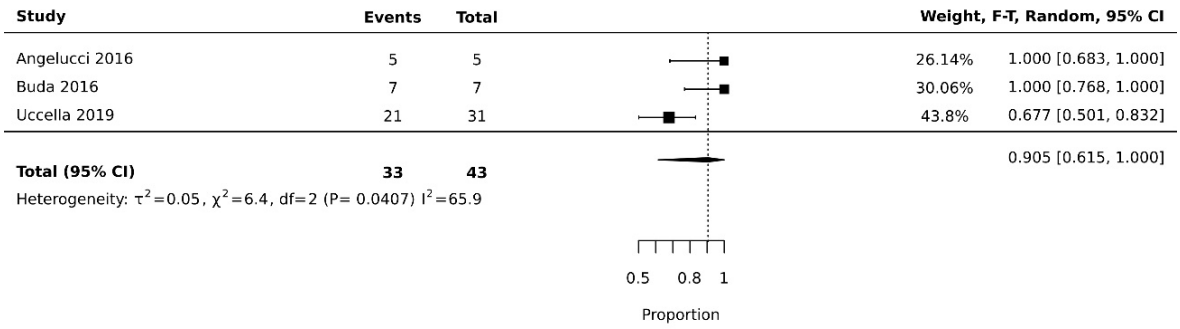


Figure 4. Forest plot showing the detection rate depending on the type of tracers used

Supplementary Online Information

Appendix Table S1: Search strategy

Search strategy (1st July 2022)			
Database	**MeSH / Emtree terms**	**Search terms in database**	**Hits (*n*)**
MEDLINE (PubMed)	#1 Sentinel Lymph Node Biopsy	"Sentinel Lymph Node Biopsy"[Mesh] OR (sentinel [tiab] AND (node*[tiab] OR lymph*[tiab] OR biops*[tiab])) OR (lymphatic*[tiab] AND mapping[tiab])	20270
	#2 Ovarian Neoplasms	ovarian neoplasms[Mesh]) or (ovar*[tiab] AND (neoplasm*[tiab] OR cancer*[tiab] OR carcinoma*[tiab] OR adenocarcinoma*[tiab] OR tumor*[tiab] OR ((early[tiab] OR I[tiab] OR 1[tiab] OR II[tiab] OR 2[tiab]) AND stage*[tiab]))	154995
	#3	#1 AND #2	252
	Total: 252 results		
Embase (Elsevier)	#1 Sentinel Lymph Node Biopsy	sentinel:ab,ti,kw AND lymph*:ab,ti,kw OR (sentinel:ab,ti,kw AND node*:ab,ti,kw) OR (sentinel:ab,ti,kw AND biops*:ab,ti,kw) OR (sentinel:ab,ti,kw AND (dissection*:ab,ti,kw OR excision*:ab,ti,kw)) OR (lymphatic:ab,ti,kw AND mapping:ab,ti,kw) OR ('sentinel'/exp AND 'lymph'/exp AND node AND 'biopsy'/exp) OR ('sentinel'/exp AND 'lymph'/exp AND node)	30,063
	#2 Ovary Cancer	(ovarian Neoplasm*):ab,ti,kw OR (ovary neoplasm*):ab,ti,kw OR (Ovarian Cancer*):ab,ti,kw OR (ovary cancer)/exp OR (Ovary Cancer*):ab,ti,kw OR (Ovarian Carcin*):ab,ti,kw OR (Ovary Carcin*):ab,ti,kw OR (Ovarian tumor*):ab,ti,kw OR (Ovary tumor*):ab,ti,kw OR (Ovarian Malign*):ab,ti,kw OR (Ovarian surgery):ab,ti,kw OR (Ovarian mass*):ab,ti,kw	194,555
	#3	#1 AND #2	309
	Total: 309 results		
Cochrane	#1 Sentinel Lymph Node	[Sentinel Lymph Node] explode all trees	48
	#2	(Sentinel lymph node OR (sentinel AND node) OR (sentinel AND lymph) OR (lymphatic mapping) OR (sentinel biops*)):ab AND (Sentinel lymph node OR (sentinel AND node) OR (sentinel AND lymph) OR (lymphatic mapping) OR (sentinel biops*)):ti	691
	#3	#1 OR #2	702
	#4 Ovarian Neoplasms	[Ovarian Neoplasms] explode all trees	2207
	#5	((ovary) OR ((adnex*) OR early-stage AND ovarian AND (cancer OR neoplasm)) OR (early-stage AND epithelial AND ovarian AND (cancer OR neoplasm OR mass*)) OR (ovarian AND cancer) OR (ovarian AND mass) OR (ovarian AND neoplasm) OR (ovarian AND surgery)):ti,ab	20605
	#6	#3 AND (#4 OR #5)	99
	Total: 99 results		
Scopus (Elsevier)	#1	ABSTRACT((sentinel AND (lymph OR node)) OR (sentinel AND node) OR (lymphatic AND mapping) OR (lymph AND node)) AND ((ovary) OR (early-stage AND ovarian AND (cancer OR neoplasm)) OR (early-stage AND epithelial AND ovarian AND (cancer OR neoplasm)) OR (ovarian AND cancer) OR (ovarian AND tumor) OR (ovarian AND mass) OR (ovarian AND neoplasm) OR (ovarian AND surgery))	4525
	#2	TITLE (((sentinel) OR (lymphatic) OR (map*)) AND ((ovary) OR (adnex*) OR (ovarian AND (cancer OR neoplasm OR tumor)) OR (early-stage AND ovarian AND (cancer OR neoplasm OR tumor)) OR (ovarian AND (neoplasm OR cancer OR tumor))))	334
	Total: 50 results		
Total: 710			

Appendix Table S2: References excluded at abstract stage (a), at full-text stage (b) and (c) ongoing trials

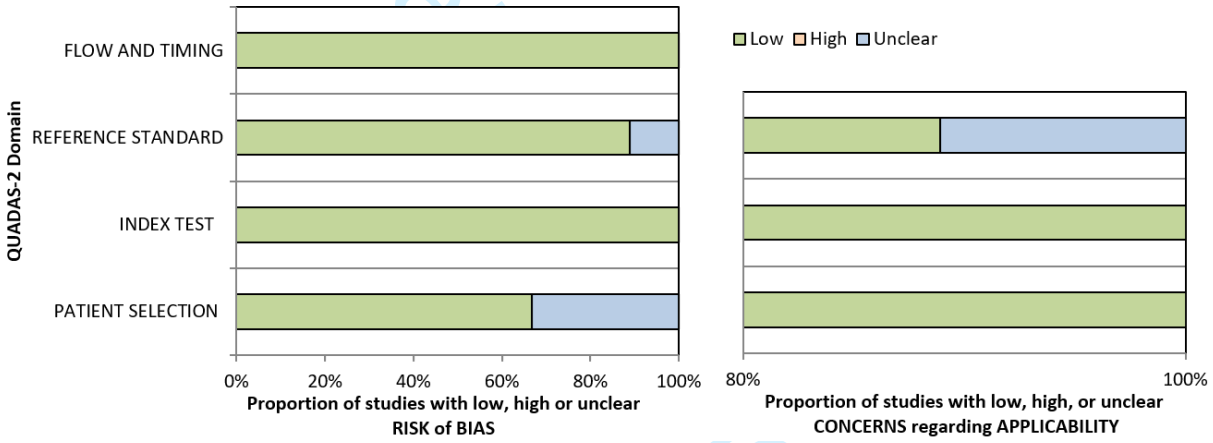
(a) References excluded at abstract stage	Reason for exclusion
Nyberg RH, Korkola P, Mäenpää JU. Sentinel Node and Ovarian Tumors: A Series of 20 Patients. Int J Gynecol Cancer. 2017 May;27(4):684-689	Case series: only 1 case of early-stage OC.
Speth SC, Kruitwagen RF, Kleppe M, Pooters IN, Van Gorp T, Slangen BF, Brans B. Comparison of Intraoperative γ-Probe Imaging and Postoperative SPECT/CT in Detection of Sentinel Nodes Related to the Ovary. J Nucl Med. 2017 Feb;58(2):243-245	Case series
Buda A, Passoni P, Reato C, Di Martino G. Laparoscopic Minimally Invasive Approach to Sentinel Lymph Node Mapping of the Ovary Using the Near-infrared Fluorescent S1 HD Pinpoint System with Indocyanine Green Dye. J Minim Invasive Gynecol. 2018 Feb;25(2):336-337.	Case-report (video-article)
Kimmig R, Buderath P, Rusch P, Mach P, Aktas B. Early ovarian cancer surgery with indocyanine-green-guided targeted compartmental lymphadenectomy (TCL, pelvic part). J Gynecol Oncol. 2017 Sep;28(5):e68.	Case-report (video-article) Part II
Kimmig R, Buderath P, Mach P, Rusch P, Aktas B. Surgical treatment of early ovarian cancer with compartmental resection of regional lymphatic network and indocyanine-green-guided targeted compartmental lymphadenectomy (TCL, paraaortic part). J Gynecol Oncol. 2017 May;28(3):e41.	Case-report (video-article) Part I
Uccella S, Gisone B, Stevenazzi G, Ghezzi F. Laparoscopic sentinel node detection with ICG for early ovarian cancer: Description of a technique and literature review. Eur J Obstet Gynecol Reprod Biol. 2018 Feb;221:193-194.	Case-report
Uccella S, Fagotti A, Zannoni GF, Coleman RL. Presumed early ovarian cancer with isolated tumor cells in para-aortic sentinel nodes. Int J Gynecol Cancer. 2019 Jan;29(1):216-220.	Case report
Lago V, Bello P, Marina Martín MT, Montero B, Padilla-Iserte P, Lopez S, Matute L, Domingo S. Sentinel lymph node in apparent early ovarian cancer: open technique. Int J Gynecol Cancer. 2019 Nov;29(9):1449.	Case-report (video article)
Turco LC, Vargiu V, Nero C, Fagotti A, Scambia G, Cosentino F. Laparotomy approach to sentinel lymph node detection in ovarian cancer using a near-infrared fluorescent system camera with indocyanine green dye. Int J Gynecol Cancer. 2020 May;30(5):712-713.	Case-report (video-article)
Lago V, Bello P, Matute L, Padilla-Iserte P, Marina T, Agudelo M, Domingo S. Sentinel Lymph Node Technique in Apparent Early Ovarian Cancer: Laparoscopic Technique. J Minim Invasive Gynecol. 2020 Jul-Aug;27(5):1019-1020.	Case-report (video-article)
Farazestanian M, Ataei S, Azad A, Jahani N, Sadeghi R. Unusual location of sentinel node in the inferior gluteal region in a patient with ovarian tumor. Revista Española de Medicina Nuclear e Imagen Molecular (English Edition),Volume 41, Supplement 1,2022,Pages S6-S7,ISSN 2253-8089,	Case-Report
D, Scambia G, Franchi M. Isolated tumour cells in a sentinel lymph node of apparent early-stage ovarian cancer: Ultrastaging of all other 27 lymph nodes. Gynecol Oncol Rep. 2022 Jul 20;42:101047.	Case-Report
Matanes E, Gupta V, Kogan L, Racicot J, Salvador S, Gotlieb WH, Lau S. Surgical Technique for Sentinel Lymph Node Sampling in Presumed Early-stage Ovarian Cancer. J Minim Invasive Gynecol. 2021 Aug;28(8):1446.	Video-article (description of the technique)
Agusti N, Paredes P, Vidal-Sicart S, Glickman A, Torne A, Díaz-Feijoo B. Sentinel lymph node mapping in early-stage ovarian cancer: surgical technique in 10 steps. Int J Gynecol Cancer. 2022 Aug 1;32(8):1082-1083	Video-article (description of the technique)
Agustí N., Paredes P., VidalSicart S., Glickman A.G., Fusté P., Carreras N., Pahisa J., Del Pino M., Fristch A., Torne A., Diaz-Feijoo B. Study of the lymphatic map and detection of the sentinel lymph node in ovaric masses with suspected malignancy. Int J Gynecol Cancer. 2021 31:SUPPL 1 (A278-A279)	Conference abstract

Laven P., Kruitwagen R., Lambrechts S., Van Gorp T., Slangen B., Zusterzeel P., Van Der Pol J. Sentinel lymph node identification in early stage ovarian cancer: Is it still possible after prior tumor resection? Int J Gynecol Cancer. 2021 31:SUPPL 4 (A109-A110)	Conference abstract
Ataei S.,Farazestanian M.,Mostafavi S.,Sadri K.,Azad A.,Jahani N.,Esmaeil Poor M.,Yousefi Z.,Hassanzadeh M.,Sadeghi R. Sentinel Node Mapping in Patients with Ovarian Tumors: A Study Using Intraoperative 99mTc-Phytate Gamma Probing and Post-Operative SPECT/CT Lymphoscintigraphy. Eur. J. Nucl. Med. 2021 48:SUPPL 1 (S376-S377)	Conference abstract
Laven P., Kruitwagen R., Lambrechts S. Sentinel lymph node identification in early stage ovarian cancer: Is it still possible after prior tumor resection? Int J Gynecol Cancer. 2020 30:SUPPL 3 (A45-)	Conference abstract
Lago V., Bello P., Montero B., Matute L., Lopez S., Marina T., Agudelo M., Domingo S.Sentinel lymph node technique in early stage ovarian cancer (SENTOV): A phase II clinical trial. Int J Gynecol Cancer. 2019 29 Supplement 4 (A645-)	Conference abstract
Lago V., Bello P., Montero B., Matute L., Padilla-Iserte P., Lopez S., Agudelo M., Domingo S. Clinical application of the sentinel lymph node technique in early ovarian cancer: Phase II clinical trial. Int J Gynecol Cancer. 2019 29 Supplement 4 (A485-)	Conference abstract
Lago V., Bello P., Padilla-Iserte P., Matute L., Marina T., Gurrea M., Domingo S. Sentov (sentinel lymph node technique in ovarian cancer): Video technique. Int J Gynecol Cancer 2019 29 Supplement 4 (A652-)	Conference abstract
Utrera A., Agudelo-Cifuentes M., Bernal J., Bello-Arques P., Matute L., Lago V., Yepes-Agudelo A., Figueroa G., Vera V.Findings in sentinel lymph node biopsy in 19 patients with ovarian cancer. Eur. J. Nucl. Med. 2019 46:1 Supplement 1 (S518-S519)	Conference abstract
Lago Leal V., Domingo Del Pozo S., Matute Tobias L., Padilla Iserte P., Gurrea Soteras M., Díaz García C. Sentov I: Tailoring clinical feasibility of sentinel lymph node technique in early ovarian cancer. Int J Gynecol Cancer 2017 27 Supplement 4 (1559-)	Conference abstract
Kleppe M., Van Gorp T., Slangen B.F.M., Krüse A.J., Brans B., Pooters I.N.A., Van De Vijver K.K., Kruitwagen R.F.P.M. Sentinel node in ovarian cancer: A feasibility study. Int J Gynecol Cancer 2013 23:8 SUPPL. 1 (558-)	Conference abstract
Ataei Nakhaei S, Mostafavi SM, Farazestanian M, Hassanzadeh M, Sadeghi R. Feasibility of sentinel lymph node mapping in ovarian tumors: A systematic review and meta-analysis of the literature. Front Med (Lausanne). 2022 Aug 1;9:950717.	Review
Van NT, Nguyen-Xuan HT, Koual M, Bentivegna E, Bats AS, Azaïs H. Place du ganglion sentinelle dans la prise en charge du cancer de l'ovaire de stade précoce : revue de la littérature [Sentinel lymph node biopsy in the management of early-stage ovarian cancer: A systematic review of the literature]. Gynecol Obstet Fertil Senol. 2022 Jan;50(1):75-81. French	Review
Yujia WANG; Jing CAI; Si SUN; Zehua WANG. The feasibility and effectiveness of sentinel lymph node detection in ovarian neoplasms: a systematic review / 中国医师杂志. (2021) Journal of Chinese Physician, 23 (2), pp. 171-177.	Review. Not English, Spanish, Italian or French
Dell'Orto F, Laven P, Delle Marchette M, et al Feasibility of sentinel lymph node mapping of the ovary: a systematic review International Journal of Gynecologic Cancer 2019;29:1209-1215.	Review
Uccella S, Zorzato PC, Lanzo G, Fagotti A, Cianci S, Gallina D, Gueli Alletti S, Monterossi G, Franchi M, Ghezzi F, Zannoni GF, Scambia G. The role of sentinel node in early ovarian cancer: a systematic review. Minerva Med. 2019 Aug;110(4):358-366.	Review
Sadeghi R. Sentinel lymph node biopsy in ovarian cancers: Are intracervical injections necessary? Eur J Obstet Gynecol Reprod Biol. 2018 May;224:204-205	Letter to the editor
Sadeghi R. Feasibility of Sentinel Node Mapping in Ovarian Tumors: What Is the Evidence? Int J Gynecol Cancer. 2018 Feb;28(2):421-422	Letter to the editor
Lago V, Domingo S. New horizons of sentinel lymph node technique in early ovarian cancer. Am J Obstet Gynecol. 2020 Jan;222(1):94.	Letter to the editor

Kleppe M, Kraima AC, Kruitwagen RF, Van Gorp T, Smit NN, van Munsteren JC, DeRuiter MC. Understanding Lymphatic Drainage Pathways of the Ovaries to Predict Sites for Sentinel Nodes in Ovarian Cancer. Int J Gynecol Cancer. 2015 Oct;25(8):1405-14.	Non-human
(b) References excluded at full text stage	
Matsuo K, Klar M, Barakzai SK, Jooya ND, Nusbaum DJ, Shimada M, Roman LD, Wright JD. Utilization of sentinel lymph node biopsy in the early ovarian cancer surgery. Arch Gynecol Obstet. 2022 May 20.	SLN technique not assessed
Lago V, Montero B, López S, Padilla-Iserte P, Matute L, Marina T, Gurrea M, Montoliu G, Bello P, Domingo S. Ultrastaging protocol in sentinel lymph node for apparent early stage ovarian cancer. Gynecol Oncol. 2021 May;161(2):408-413.	SLN ultrastaging protocol
Uccella S, Garzon S, Bosco M, Porcari I, Lanzo G, Laganà AS, Chiantera V, Cliby WA, Mariani A, Franchi M, Zorzato PC. Cervical versus utero-ovarian ligament injection of the tracer for the pelvic sentinel lymph node mapping in gynecologic oncology: a prospective observational study. Gynecol Obstet Invest. 2022 May 18.	Only pelvic SLN evaluation
Scambia G, Nero C, Uccella S, Vizza E, Ghezzi F, Cosentino F, Chiantera V, Fagotti A. Sentinel-node biopsy in early stage ovarian cancer: a prospective multicentre study (SELLY). Int J Gynecol Cancer. 2019 Nov;29(9):1437-1439	Clinical trial protocol
Pop CF, Veys I, Gomez Galdon M, Moreau M, Larsimont D, Donckier V, Bourgeois P, Liberale G. Ex vivo indocyanine green fluorescence imaging for the detection of lymph node involvement in advanced-stage ovarian cancer. J Surg Oncol. 2018 Dec;118(7):1163-1169.	Advanced-stage ovarian cancer
Kleppe M, Van Gorp T, Slangen BF, Kruse AJ, Brans B, Pooters IN, Van de Vijver KK, Kruitwagen RF. Sentinel node in ovarian cancer: study protocol for a phase 1 study. Trials. 2013 Feb 15;14:47.	Clinical trial protocol
Nyberg RH, Korkola P, Mäenpää J. Ovarian sentinel node: is it feasible? Int J Gynecol Cancer. 2011 Apr;21(3):568-72.	Non-ovarian malignancy
Negishi H, Takeda M, Fujimoto T, Todo Y, Ebina Y, Watari H, Yamamoto R, Minakami H, Sakuragi N. Lymphatic mapping and sentinel node identification as related to the primary sites of lymph node metastasis in early-stage ovarian cancer. Gynecol Oncol. 2004 Jul;94(1):161-6.	Non-ovarian malignancy
Vanneuville G, Mestas D, Le Bouedec G, Veyre A, Dauplat J, Escande G, Guillot M. The lymphatic drainage of the human ovary in vivo investigated by isotopic lymphography before and after the menopause. Surg Radiol Anat. 1991;13(3):221-6.	Non-ovarian malignancy
(c) Ongoing trials	
US National Library of Medicine. Mapping Sentinel Lymph Node in Initial Stages of Ovarian Cancer (MELISA). Available at: https://clinicaltrials.gov/ct2/show/NCT05184140. Accessed 1st July, 2022	Ongoing
US National Library of Medicine. SEntine Lymph Node in earLY Ovarian Cancer (SELLY). Available at: https://clinicaltrials.gov/ct2/show/NCT03563781. Accessed 18th August, 2022.	Ongoing
US National Library of Medicine. Sentinel Lymph Node Assessment in Ovarian Cancer (TRSGO-SLN-OO5). Available at: https://clinicaltrials.gov/ct2/show/NCT04714931. Accessed 18th August, 2022.	Ongoing
US National Library of Medicine. Magtrial: Magtrace® as Tracer for Sentinel Lymph Node Detection in Early-Stage Epithelial Ovarian Cancer. Available at: https://clinicaltrials.gov/ct2/show/NCT05375526. Accessed 18th August, 2022.	Ongoing
US National Library of Medicine. ICG-Enabled Mapping of Ovarian Sentinel Lymph Nodes: A Feasibility Study. Available at: https://clinicaltrials.gov/ct2/show/NCT04051502. Accessed 18th August, 2022.	Ongoing
US National Library of Medicine. Fluorescence for Sentinel Lymph Node Identification in Cancer Surgery (GASVERT). Available at: https://clinicaltrials.gov/ct2/show/NCT02997553. Accessed 18th August, 2022.	Ongoing

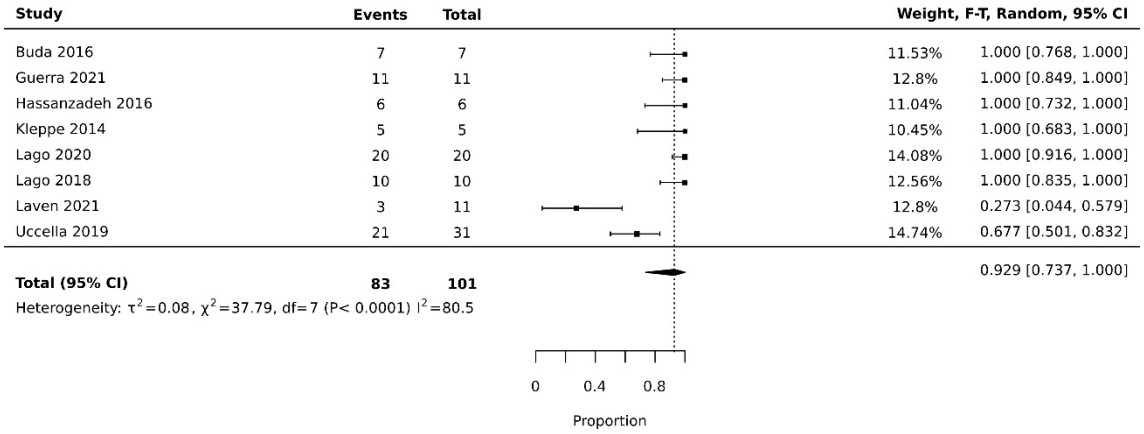
Appendix Figure S1. Graphical presentation of the QUADS-2

Study	RISK OF BIAS				APPLICABILITY CONCERNS		
	PATIENT SELECTION	INDEX TEST	REFERENCE STANDARD	FLOW AND TIMING	PATIENT SELECTION	INDEX TEST	REFERENCE STANDARD
Kleppe, 2014	☺	☺	☺	☺	☺	☺	☺
Hassanzadeh, 2016	?	☺	☺	☺	☺	☺	☺
Angelucci, 2016	?	☺	☺	☺	☺	☺	☺
Buda, 2017	?	☺	☺	☺	☺	☺	☺
Uccella, 2019	☺	☺	☺	☺	☺	☺	☺
Lago, 2018	☺	☺	☺	☺	☺	☺	☺
Lago, 2020	☺	☺	☺	☺	☺	☺	☺
Laven, 2021	☺	☺	?	☺	☺	☺	?
Guerra, 2021	☺	☺	☺	☺	☺	☺	☺

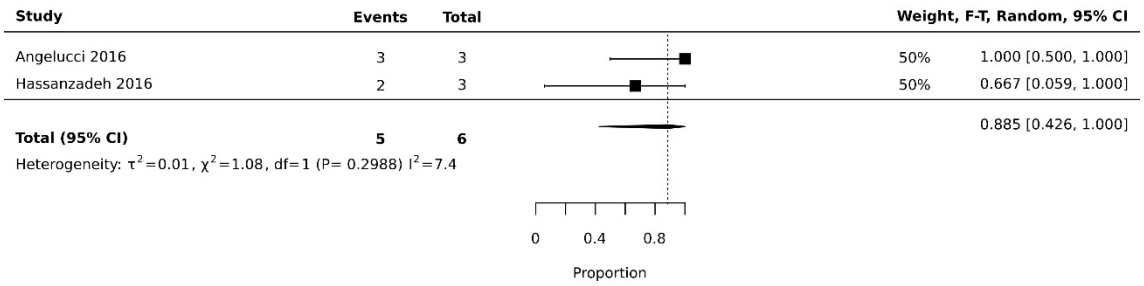


Appendix Figure S2. Forest plot showing the detection rate depending on the injection site

a) Uter-ovarian and infundibulo-pelvic ligaments

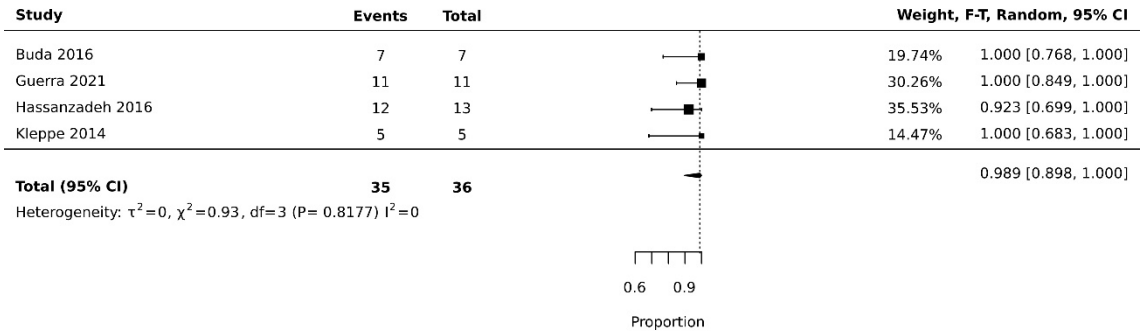


b) Other sites

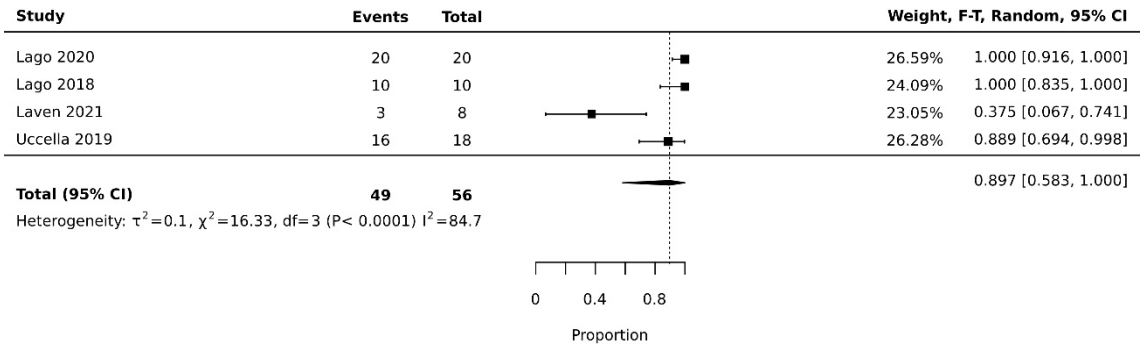


Appendix Figure S3. Forest plot showing the detection rate depenging on the type of surgery

a) Primary surgery with the tracer injection prior to the adnexa removal



b) Primary surgery with the tracer injection after the adnexa removal



c) Re-staging surgery