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Risk factors associated with false negative rate of sentinel lymph node biopsy in endometrial cancer: a systematic review and meta-analysis

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Objective: Currently, sentinel lymph node biopsy (SLNB) is increasingly used in endometrial cancer, but the rate of missed metastatic lymph nodes compared to systemic lymph node dissection has been a concern. We conducted a systematic review and meta-analysis to evaluate the false negative rate (FNR) of SLNB in patients with endometrial cancer and to explore the risk factors associated with this FNR.

Data sources: Three databases (PubMed, Embase, Web of Science) were searched from initial database build to January 2023 by two independent reviewers.

Research eligibility criteria: Studies were included if they included 10 or more women diagnosed with International Federation of Gynecology and Obstetrics (FIGO) stage I or higher endometrial cancer, the study technique used sentinel lymph node localization biopsy, and the reported outcome metrics included false negative and/or FNR.

Study appraisal and synthesis methods: Two authors independently reviewed the abstracts and full articles. The FNR and factors associated with FNR were synthesized through random-effects meta-analyses and meta-regression.

The results: We identified 62 eligible studies. The overall FNR for the 62 articles was 4% (95% CL 3-5).There was no significant difference in the FNR in patients with high-risk endometrial cancer compared to patients with low-risk endometrial cancer. There was no difference in the FNR for whether frozen sections were used intraoperatively. The type of dye used intraoperatively (indocyanine green/blue dye) were not significantly associated with the false negative rate. Cervical injection reduced the FNR compared with alternative injection techniques. Indocyanine green reduced the FNR compared with alternative Tc-99m. Postoperative pathologic ultrastaging reduced the FNR.

Conclusions: Alternative injection techniques (other than the cervix), Tc-99m dye tracer, and the absence of postoperative pathologic ultrastaging are risk factors for a high FNR in endometrial cancer patients who undergo SLNB; therefore, we should be vigilant for missed diagnosis of metastatic lymph nodes after SLNB in such populations.

Systematic review registration: http://www.crd.york.ac.uk/PROSPERO/, identifier CRD42023433637.

Introduction

Endometrial cancer is one of the three major malignant tumors of the female reproductive tract. In recent years, EC, with its increasing incidence and mortality worldwide, has become the most common gynecologic cancer in high-income countries (1, 2), posing a serious threat to public health worldwide.

Surgery is currently the main modality for the treatment of endometrial cancer. Despite the low rate of metastasis in patients with early endometrial cancer, the standard of care still includes complete or elective pelvic and para-aortic lymph node dissection for proper staging, which is the most important prognostic factor (3, 4). Benedetti Panici et al. and the ASTEC trial have demonstrated that lymphadenectomy has a staging role and does not improve overall survival in low risk populations (5, 6). In addition, the number of lymph nodes removed during staging is associated with potential side effects (7). Since 2016, SLNB has been introduced as an alternative to lymph node dissection for surgical staging (8). The majority of SLNs were located in the pelvic area, with the external iliac vessels being the most common area (9). Theoretically, sentinel lymph node (SLN) should reflect the status of the entire nodal basin. If there is no metastasis in the sentinel lymph nodes, the likelihood of metastasis to other lymph nodes in the pelvis is extremely low. At present, lymphadenectomy is primarily used for staging and should be considered in women with high- risk factors; however, sentinel lymph node biopsy is an acceptable alternative to systematic lymphadenectomy in early- stage endometrial cancer (10). The recent guidelines from the European Society of Gynecological Oncology-European Society for Radiotherapy and Oncology-European Society of Pathology (ESGO-ESTRO-ESP) have expressed unanimous consensus to consider SLN biopsy for staging purposes in patients with low risk, intermediate risk, and high risk of endometrial cancer (11). Retrospective studies showed similar prognosis of patients after full lymphadenectomy and sentinel lymph node biopsy only (12–14). In addition, compared to complete lymph node dissection, this procedure avoids complications associated with systemic lymph node dissection, such as neurovascular damage, lymphedema and lymphoid cyst formation (15, 16).

Although SLN localization has many advantages, the rate of missed metastatic lymph nodes compared to systemic lymph node dissection has been a concern. In particular, the value of sentinel lymph node biopsy in patients with high-risk types of endometrial cancer for its application remains controversial (17). At the same time, the presence of micrometastases in some SLNs, which are undiagnosed by conventional histology (18), has recently increased the rate of missed metastatic lymph nodes. In recent years, scholars in several studies have reported false negatives in endometrial cancer using SLNB (19–21). Scholars in current studies point out that in endometrial cancer, SLN biopsy combined with standard algorithms and ultrastaging has been shown to significantly reduce the false negative rate and improve sensitivity and negative predictive value (22). However, even when different intraoperative algorithms for sentinel lymph nodes are followed and pathologic ultrastaging is used, some patients with lymph node metastases are still missed to the point of compromising postoperative adjuvant therapy and presenting a poor prognosis.

Although there is a proliferation of articles examining false negative rates of sentinel lymph node biopsies for endometrial cancer, they are mostly limited to reports of individual rates of false negative rates. Few studies have been performed on the risk factors affecting the false negative rate. Therefore, the aim of this meta-analysis was to evaluate the false negative rate of SLNB performed in patients with endometrial cancer, as well as to explore the risk factors affecting the FNR, to rationally prevent and minimize the incidence of the false negative rate and to evaluate whether sentinel sentinel lymph node biopsy is a feasible technological option in patients with high-risk endometrial cancer.

Methods

Information sources and search strategy

We searched three databases (PubMed, Embase, and Web of Science) for articles from the time of their creation to January 2023.

The following Medical Subject Headings were used: "Sentinel Lymph Node," "Sentinel Lymph Node Biopsy," and "Endometrial Neoplasms" (Table 1). The titles and abstracts of each retrieved article were reviewed to confirm that the article reported false negative sentinel lymph node biopsies in patients with endometrial cancer, and those articles that met the criteria for inclusion were retrieved in full and

TABLE 1 Search terms.

Pubmed	Embase	Web of seince
1.(((((((("Sentinel Lymph Node"[Mesh]) OR (Lymph Node, Sentinel[Title/Abstract])) OR (Lymph Nodes, Sentinel[Title/Abstract])) OR (Sentinel Lymph Nodes[Title/Abstract])) OR (Sentinel Node[Title/Abstract])) OR (Node, Sentinal[Title/Abstract])) OR (Nodes, Sentinal[Title/Abstract])) OR (Sentinel Nodes[Title/Abstract])) OR ((((((((("Sentinel Lymph Node Biopsy"[Mesh]) OR (Lymph Node Biopsy, Sentinel[Title/Abstract])) OR (Biopsy, Sentinel Lymph Node[Title/Abstract])) OR (sentinel axillary lymph node biopsy[Title/Abstract])) OR (sentinel lymph node biopsies[Title/Abstract])) OR (sentinel lymphatic node biopsy[Title/Abstract])) OR (sentinel nodal biopsy[Title/Abstract])) OR (sentinel node biopsy[Title/Abstract])) OR (SLN biopsy[Title/Abstract])) 2.((((((((((((((((((((("Endometrial Neoplasms"[Mesh]) OR (endometrium tumor[Title/Abstract])) OR (endometrial neoplasms[Title/Abstract])) OR (endometrial tumor[Title/Abstract])) OR (endometrial tumour[Title/Abstract])) OR (endometrioma[Title/Abstract])) OR (endometrium tumour[Title/Abstract])) OR (Endometrial Neoplasm[Title/Abstract])) OR (Neoplasm, Endometrial[Title/Abstract])) OR (Neoplasms, Endometrial[Title/Abstract])) OR (Endometrial Carcinoma[Title/Abstract])) OR (Carcinoma, Endometrial[Title/Abstract])) OR (Carcinomas, Endometrial[Title/Abstract])) OR (Endometrial Carcinomas[Title/Abstract])) OR (Endometrial Cancer[Title/Abstract])) OR (Cancer, Endometrial[Title/Abstract])) OR (Cancers, Endometrial[Title/Abstract])) OR (Endometrial Cancers[Title/Abstract])) OR (Endometrium Cancer[Title/Abstract])) OR (Cancer, Endometrium[Title/Abstract])) OR (Cancers, Endometrium[Title/Abstract])) OR (Cancer of the Endometrium[Title/Abstract])) OR (Carcinoma of Endometrium[Title/Abstract])) OR (Endometrium Carcinoma[Title/Abstract])) OR (Endometrium Carcinomas[Title/Abstract])) OR (Cancer of Endometrium[Title/Abstract])) OR (Endometrium Cancers[Title/Abstract]) 3.1AND2	1.'sentinel lymph node'/exp OR 'sentinel lymph node' OR (('sentinel'/exp OR sentinel) AND ('lymph'/exp OR lymph) AND node) OR 'lymph node, sentinel' OR (('lymph'/exp OR lymph) AND node, AND ('sentinel'/exp OR sentinel)) OR 'lymph nodes, sentinel' OR (('lymph'/exp OR lymph) AND nodes, AND ('sentinel'/exp OR sentinel)) OR 'sentinel lymph nodes' OR (('sentinel'/exp OR sentinel) AND ('lymph'/exp OR lymph) AND nodes) OR 'sentinel node' OR (sentinal AND node) OR 'node, sentinal' OR (node, AND sentinal) OR 'nodes, sentinal' OR (nodes, AND sentinal) OR 'sentinel nodes' OR (sentinal AND nodes) 2.'sentinel lymph node biopsy'/exp OR 'sentinel lymph node biopsy' OR (('sentinel'/exp OR sentinel) AND ('lymph'/exp OR lymph) AND node AND ('biopsy'/exp OR biopsy)) OR 'lymph node biopsy, sentinel'/exp OR 'lymph node biopsy, sentinel' OR (('lymph'/exp OR lymph) AND node AND ('biopsy,'/exp OR biopsy,) AND ('sentinel'/exp OR sentinel)) OR 'biopsy, sentinel lymph node'/exp OR 'biopsy, sentinel lymph node' OR (('biopsy,'/exp OR biopsy,) AND ('sentinel'/exp OR sentinel) AND ('lymph'/exp OR lymph) AND node) OR 'sentinel axillary lymph node biopsy'/exp OR 'sentinel axillary lymph node biopsy' OR (('sentinel'/exp OR sentinel) AND axillary AND ('lymph'/exp OR lymph) AND node AND ('biopsy'/exp OR biopsy)) OR 'sentinel lymph node biopsies'/exp OR 'sentinel lymph node biopsies' OR (('sentinel'/exp OR sentinel) AND ('lymph'/exp OR lymph) AND node AND ('biopsies'/exp OR biopsies)) OR 'sentinel lymphatic node biopsy'/exp OR 'sentinel lymphatic node biopsy' OR (('sentinel'/exp OR sentinel) AND ('lymphatic'/exp OR lymphatic) AND node AND ('biopsy'/exp OR biopsy)) OR 'sentinel nodal biopsy'/exp OR 'sentinel nodal biopsy' OR (('sentinel'/exp OR sentinel) AND nodal AND ('biopsy'/exp OR biopsy)) OR 'sentinel node biopsy'/exp OR 'sentinel node biopsy' OR (('sentinel'/exp OR sentinel) AND node AND ('biopsy'/exp OR biopsy)) OR 'sln biopsy'/exp OR 'sln biopsy' OR (sln AND ('biopsy'/exp OR biopsy)) 3.'endometrium tumor'/exp OR 'endometrium tumor' OR (('endometrium'/exp OR 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'endometrial carcinomas' OR (endometrial AND carcinomas) OR 'endometrial cancer'/exp OR 'endometrial cancer' OR (endometrial AND ('cancer'/exp OR cancer)) OR 'cancer, endometrial' OR (('cancer,'/exp OR cancer,) AND endometrial) OR 'cancers, endometrial' OR (('cancers,'/exp OR cancers,) AND endometrial) OR 'endometrial cancers' OR (endometrial AND ('cancers'/exp OR cancers)) OR 'endometrium cancer'/exp OR 'endometrium cancer' OR (('endometrium'/exp OR endometrium) AND ('cancer'/exp OR cancer)) OR 'cancer, endometrium'/exp OR 'cancer, endometrium' OR (('cancer,'/exp OR cancer,) AND ('endometrium'/exp OR endometrium)) OR 'cancers, endometrium' OR (('cancers,'/exp OR cancers,) AND ('endometrium'/exp OR endometrium)) OR 'cancer of the endometrium' OR (('cancer'/exp OR cancer) AND of AND the AND ('endometrium'/exp OR endometrium)) OR 'carcinoma of endometrium' OR (('carcinoma'/exp OR carcinoma) AND of AND ('endometrium'/exp OR endometrium)) OR 'endometrium carcinoma'/exp OR 'endometrium carcinoma' OR (('endometrium'/exp OR endometrium) AND ('carcinoma'/exp OR carcinoma)) OR 'endometrium carcinomas' OR (('endometrium'/exp OR endometrium) AND carcinomas) OR 'cancer of endometrium' OR (('cancer'/exp OR cancer) AND of AND ('endometrium'/exp OR endometrium)) OR 'endometrium cancers' OR (('endometrium'/exp OR endometrium) AND ('cancers'/exp OR cancers)) 4.(1OR2)AND3	1.((((((((TS=(Sentinel Lymph Node)) OR AB=(Lymph Node, Sentinel)) OR AB=(Lymph Nodes, Sentinel)) OR AB=(Sentinel Lymph Nodes)) OR AB=(Sentinel Node)) OR AB=(Node, Sentinal)) OR AB=(Nodes, Sentinal)) OR AB=(Sentinal Nodes)(14163) 2. 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further reviewed for literature supplementation using references cited in articles that met the criteria for inclusion. Details of the review protocol were registered in PROSPERO, number CRD42023433637.

Eligibility criteria

Inclusion criteria included 10 or more women diagnosed with FIGO stage 1 or higher endometrial cancer; study technique using sentinel lymph node localization biopsy; after sentinel lymph node dissection was performed pelvic lymphadenectomy with or without paraaortic lymphadenectomy; and reported outcome metrics including but not limited to false negative/false negative rates. The exclusion criteria were as follows: articles that did not meet the inclusion criteria; secondary lesions and repeat populations or nonoriginal studies (e.g., systematic reviews); and narrative reviews, letters, editorials, conferences, and abstracts. If duplicate data sets were encountered, the most recent or informative study was included in the analysis.

Study selection

We managed the literature screening using EndNote X 20, and after removing duplicates, 2 researchers browsed the titles and abstracts by mutual blindness, performed preliminary screening of the literature according to the inclusion and exclusion criteria, excluded the literature that did not meet the inclusion criteria, and performed full-text browsing for articles that met the inclusion criteria, while cross-checking them afterward and exchanging opinions through discussion or seeking third-party opinions in case of disagreement. The cross-checking was followed by cross-checking, and disagreements were resolved by discussing and exchanging opinions or seeking opinions from third parties. Subsequently, a standardized form was used to extract information from the included literature, including the authors, year, sample size, tumor histology type, surgical route, and other basic information.

Data extraction

Data were extracted by two independent reviewers using a standardized form. Extracted data included authors, year of publication, sample size, study method, tumor histology type, tracer, injection site, surgical route, age, BMI, tumor risk grade, intraoperative frozen sections, pathological ultrastaging, and quality assessment items. The surgical route included (robotic, laparoscopic, open), injection site included (cervical vs. intrauterine), tracer included (indocyanine green, blue dye, Tc-99 m), intraoperative frozen section and pathological ultrastaging included (yes/no).

There are many methods of SLN ultrastaging, and the one currently used is the Memorial Sloan Kettering Cancer Center (MSKCC) superstaging method: first, paraffin sections are routinely stained for H&E, and if the results are negative, two consecutive 5-μm-thick sections (one for H&E and one for cytokeratin AE1/AE3) at 50-μm intervals from each paraffin block are rowed, with one of the

levels providing another section as a negative control for immunohistochemistry (23). Ultrastaging was defined in this meta-analysis asl any additional treatment of the sentinel lymph nodes beyond routine lymph node evaluation, usually including additional sectioning and hematoxylin and eosin (H&E) staining of the SLN; ultrastaging was considered in all cases where immunohistochemistry was used. Intraoperative frozen section was defined as postoperative pathological examination of sentinel lymph node sections after rapid frozen sectioning. The false negative rate was defined as metastatic patients without a positive SLN divided by all metastatic patients (false negative tests/false negative + true positive tests) (24). High-risk tumors were defined as fulfilling one of the following conditions: high-grade tumor (endometrioid grade 3 and nonendometrioid histologies: serous, clear cell, or carcinosarcoma), deep myometrial invasion (MI) (≥50%), or the presence of angiolymphatic invasion (LVSI) (25). When different definitions were used for reporting outcomes, we recalculated the original study results according to our proposed definitions.

Assessment of risk of bias

Two reviewers independently assessed the risk of bias for inclusion in the study using the QUADAS-2 tool. Differences were resolved through review of the original articles. The risk of bias was assessed in four domains: patient selection, index test, reference standard, and flow and timing. Bias in the patient selection domain could occur if recruitment was not consecutive, not random, or if inappropriate exclusion criteria were used. Bias in the index test domain could occur if the interpretation of the results of the test to be evaluated is performed with knowledge of the results of the gold standard test, or if the test threshold is chosen to optimize sensitivity and/or specificity. Bias in the reference standard domain could occur if the interpretation of the gold standard results is performed with knowledge of the results of the test to be evaluated. Bias in the flow and timing domain could occur If only a certain percentage of the study group received the gold standard, or if some patients received a different gold standard, or if not all cases included in the study were included in the analysis. A study was judged to be at "low", "unclear", or "high" risk of bias in each domain, based on a set of signaling questions for each domain. If all signaling questions for a domain were answered "yes" then the risk of bias was judged as "low" for that domain; similarly, if any signaling question was answered "no" then the risk of bias was judged to be "high" for that domain. The "unclear" category was used when there was insufficient data to allow the judgment. For clinical applicability, only the first three components (patient selection, index test and reference standard) are evaluated, and the determination method is the same as that of the risk of bias, which is based on the degree of matching with the evaluation question, and is also graded according to the levels of "high", "low", and "unclear".

Data synthesis

We used the 'meta' package v4.15-1 in R v3.5.0 for statistical analysis. We evaluated statistical heterogeneity with the use of

thestatistic and defined heterogeneity as notable when >50%. We calculated the overall false negative rate based on the data provided in the original paper, and we performed a meta-analysis of the false negative rate using a random-effects model. We used stratified meta-analysis and meta-regression to explore the impact of patient (tracer, injection site, tumor risk class, intraoperative frozen section, pathological ultrastaging) characteristics on the combined outcomes. When studies reported outcomes for multiple subgroups (e.g., comparing injection sites), we included the overall false negative rate in the main meta-analysis and the subgroup false negative rate in the stratified meta-analysis and meta-regression. A value of p < 0.05 was considered significant.

Results

Study selection

The study obtained a total of 3030 relevant studies by searching three databases ((PubMed, Embase, Web of Science), 1861 remaining studies after excluding duplicate items, 125 remaining relevant studies after reading the titles and abstracts of the literature to exclude studies not relevant to the study, and 125 full-text studies after reading to exclude studies not consistent with the purpose of the study. Finally, a total of 62 studies were included for qualitative synthesis and meta-analysis, and the literature screening process and results are shown in Figure 1.

Study characteristics

Of the 62 articles included in this study (19–21, 25–83), we used only those with endometrial cancer patients who had at least pelvic lymph node dissection after sentinel lymph node dissection as the study population. The total included sample size was 6304 cases, the maximum sample size for a single study was 414 cases, and the minimum sample size for a single study was 17 cases; pelvic ± para-aortic lymphadenectomy biopsy was the most commonly used reference standard; all literature reported relevant study outcome indicators; specific description of the included literature (Table 2).
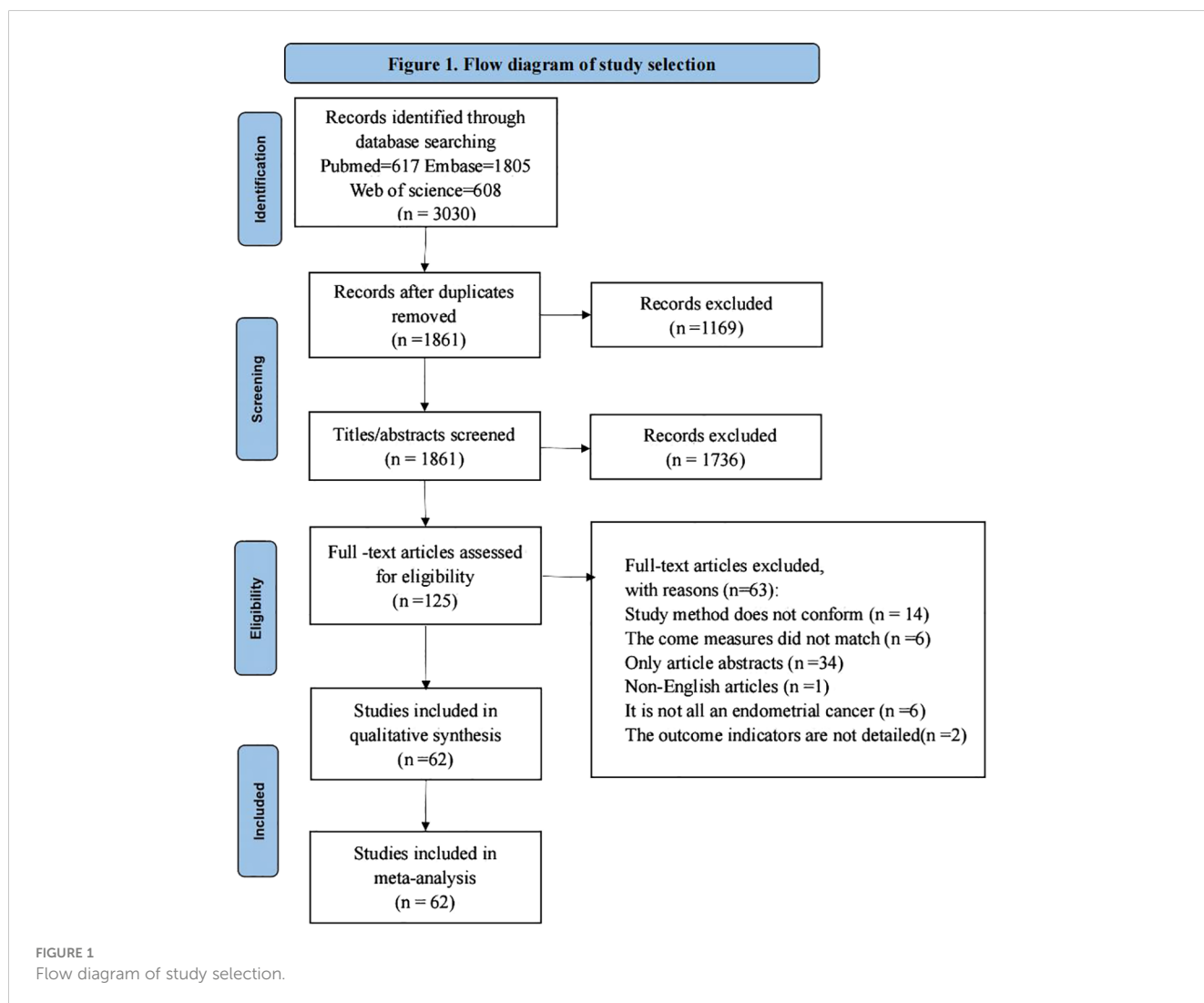

FIGURE 1
Flow diagram of study selection.

TABLE 2 Characteristics of included studies.

Author	Year	Study Size	Study Method	Cancer Histology	Tracer Used	Injection Site	Route of Surgery	Reference Standard	Pathology Assessment
E. Barranger	2004	17	Prospective	All	Patent Blue and Tc-99m	Cervical	Laparoscopic	Systematic pelvic lymphadenectomy, para-aortic lymphadenectomy was performed when a para-aortic SN was detected or when positive SNs were found by intraoperative histological examination	H&E, IHC、 ultrastaging
H. Niikura	2004	28	NR	All	Tc-99m	Uterine	Open	Pelvic and paraaoPrtic lymphadenectomy	H&E, IHC、 ultrastaging
C. Altgassen	2007	25	Prospective	All	Blue dye	Uterine	Open	Depending on tumor size (>2 cm), grading (>G1) and invasion (>Ia) a complete pelvic lymphadenectomy was performed. A para-aortic lymphadenectomy followed if the general state of the patient was considered to be sufficient by the gynecologist and the anesthesiologist intra-operatively	H&E
L. A. Lopes	2007	40	NR	All	Patent Blue	Uterine	Open	Bilateral para-aortic and pelvic lymphadenectomies	H&E, IHC、 ultrastaging
A. S. Bats	2008	43	Prospective	All	Tc-99m and blue dye	Cervical	Laparoscopic	Pelvic lymphadenectomy was performed with or without para-aortic lymphadenectomy	H&E, IHC、 ultrastaging
Barranger E	2009	33	Prospective	All	Tc-99m and patent blue	Cervical	Laparoscopic	Laparoscopic bilateral pelvic lymphadenectomy	H&E, IHC、 ultrastaging
J. How	2012	100	Prospective	All	Tc-99m and patent blue	Cervical	Robotic	Complete pelvic lymphadenectomy in all cases regardless of surgical pathology diagnosis. If the patient had a pre-operative type II endometrial cancer (clear cell, serous,adeno-squamous) or grade 2 or 3 endometrioid carcinomas, or carcinosarcoma, positive SLN on intra-operative frozen section, or grossly enlarged pelvic LNs suspicious for malignancy, the surgeon would continue with a para-aortic lymphadenectomy	H&E, IHC、 ultrastaging
E. Solima	2012	59	Prospective	All	Tc-99m	Uterine	Open or Laparoscopic	Patients with one of the following criteria underwent systematic pelvic and paraaortic lymphadenectomy: 1) endometrioid adenocarcinoma with intraoperative staging equal to or higher than IBG2 (FIGO 1988); and 2) clear cell or serous carcinoma. All surgeries were performed by 4 senior gynecologists with proficiency in oncologic surgery, experienced in radio guided surgery in endometrial cancer.	H&E, IHC、 ultrastaging
E. C. Rossi	2013	29	Prospective	All	ICG	Cervical & Uterine	Robotic	Bilateral pelvic and paraaortic lymphadenectomy	H&E 、 ultrastaging
A. Torné	2013	74	Prospective	All	Tc-99m	Uterine	Laparoscopic	Laparoscopic pelvic and paraaortic lymphadenectomy	H&E, IHC、 ultrastaging

(Continued)

TABLE 2   Continued

Author	Year	Study Size	Study Method	Cancer Histology	Tracer Used	Injection Site	Route of Surgery	Reference Standard	Pathology Assessment
C. L. D. Cano	2014	50	Prospective	All	Tc-99m and blue dye	Cervical	Open or Laparoscopic	Pelvic and/or paraaortic lymphadenectomy	H&E、ultrastaging
E. Raimond	2014	156	Retrospective	All	Patent blue	Cervical	NR	Pelvic lymphadenectomy was systematically	H&E, IHC、ultrastaging
M. M. Farghali	2015	93	Retrospective	Endometrioid adenocarcinoma、Clear Cell Carcinoma 、Papillary serous carcinoma	Methylene blue dye	Uterine	Open	Pelvic and para-aortic lymphadenectomy. Extent of lymphadenectomy was decided by senior surgeon intra-operatively depending on grade of tumor, depth of invasion, size, location of endometrial carcinoma and patient`s fitness to such risky intervention	H&E, IHC、ultrastaging
G. Favero	2015	42	Prospective	Endometrioid adenocarcinoma、Serous papillary adenocarcinoma、Clear cell adenocarcinoma	Tc-99m	Uterine	Laparoscopic	Pelvic and Bpara-aortic lymphadenectomy	H&E
J. How	2015	100	Prospective	All	Tc-99m、ICGandBlue day	Cervical	Robotic	Pelvic lymphadenectomy. A para-aortic lymphadenectomy was per-formed if the patient had one or more of the following characteristics:pre-operative type II endometrial cancers (clear cell, serous, carcinosarcoma, or adenosquamous), grade 3 endometrioid carcinomas, positive SLN on intraoperative frozen section, or grossly enlarged para-aortic LNs suspicious for malignancy	H&E, IHC、ultrastaging
Naoura I	2015	180	Retrospective	All	Tc-99m and patent blue	Cervical	Open or Laparoscopic	SLN procedure completed by a systematic pelvic lymphadenectomy.Para-aortic lymphadenectomy (PAAL) was recommended for patients with positive SLN at intraoperative examination or final histology and for those with high-risk EC according to the current guidelines	H&E, IHC、ultrastaging
Sawicki S	2015	60	NR	Endometrioid 、Clear cell 、Serous	(Tc-99m and blue) dye or blue dye	cervical and Uterine	Open	Pelvic and para-aortic lymphadenectomy (with SLNB) was performed in patients with grade 3 tumors, with more than 50% myometrial invasion or cervical involvement (in the latter 2 cases, the extent of para-aortic lymph node dissection was at a surgeon' s discretion).	H&E、ultrastaging
Touhami O	2015	39	Retrospective	Uterine Serous Carcinoma	Tc-99m and patent blue	Uervical	Open or Laparoscopic	Pelvis lymph nodes + para-aortic lymph nodes.	NR
P. Valha	2015	18	Prospective	All	Blue dye	Uterine	Open	Pelvic and para-aortic lymphadenectomies	H&E, IHC、ultrastaging

(Continued)

TABLE 2 Continued

Author	Year	Study Size	Study Method	Cancer Histology	Tracer Used	Injection Site	Route of Surgery	Reference Standard	Pathology Assessment
A. Buda	2016	118	Retrospective	All	Tc-99m and blue dye or blue day or ICG	Cervical	Open or Laparoscopic	Complete pelvic lymphadenectomy and in the absence of SLN mapping or unilateral mapping	H&E, IHC、 ultrastaging
J. Ehrisman	2016	36	Retrospective	All	Meth-ylene blue or indocyanine green (ICG)	Cervical	Laparoscopic	Complete pelvic lymphadenectomy	H&E, IHC、 ultrastaging
R. W. Holloway	2016	119	Retrospective	All	ICG	Cervical	Robotic	A pelvic lymphadenectomy or pelvic-plus-aortic lymphadenectomy Para-aortic lymphadenectomy was reserved for Grade 3 tumors/Type II histologies with any depth-of-invasion (DOI),grossly positive pelvic lymph nodes confirmed on frozen section,and low-grade tumors with middle or outer-third myometrial invasion.	H&E, IHC、 ultrastaging
P. J. Paley	2016	85	Prospective	All	ICG	Cervical	Robotic	Complete pelvic and paraaortic lymphadenectomy if high risk or in the absence of SLN mapping or unilateral mapping	H&E
A. Papadia	2016	42	Retrospective	All	ICG	Cervical	Laparoscopic	PLND and/or PALND	H&E, IHC、 ultrastaging
G. Baiocchi	2017	75	Prospective	All	Patent blue dye	Cervical	NR	Pelvic ± para-aortic lymphadenectomy	H&E, IHC、 ultrastaging
I. Biliatis	2017	54	Prospective	All	Methylene blue or patent blue	Uterine	NR	Bilateral pelvic lymphadenectomy	H&E
F. Farzaneh	2017	30	Prospective	Endometrioid、 Papillary serous	Tc-99m or(TC-99m and Blue dye)	Cervical	NR	Pelvic lymphadenectomy in all cases and para-aortic lymphadenectomy in selected cases (clear cell, papillary serous, grade 2 or 3 endometrioid adenocarcinomas, stage II).	NR
R. W. Holloway	2017	200	Prospective	All	ISB + ICG or ISB	Cervical	Robotic	Pelvic lymphadenectomy was performed in all cases. Para-aortic lymphadenectomy procedures were performed for patients with endometrioid G1 or G2 tumors and 50% or more myometrial invasion on frozen section or any G3 and type 2 histologies, and for patients with suspicious pelvic lymph nodes confirmed with metastases on frozen section.	H&E, IHC、 ultrastaging
E. C. Rossi	2017	340	Prospective	All	ICG	Cervical	Robotic	Pelvic lymphadenectomy with or without para-aortic lymphadenectomy.	H&E, IHC、 ultrastaging
P. T. Soliman	2017	101	Prospective	All	ICG or Blue dye or (TC-99m and Blue dye)	Cervical	Robotic or Laparoscopic	Pelvic and para-aortic lymphadenectomy	H&E, IHC、 ultrastaging

(Continued)

TABLE 2 Continued

Author	Year	Study Size	Study Method	Cancer Histology	Tracer Used	Injection Site	Route of Surgery	Reference Standard	Pathology Assessment
E. J. Tanner	2017	52	Prospective	All	ISB or ICG	Cervical	Robotic	Pelvic and para-aortic lymph nodes	H&E, IHC、ultrastaging
S. Taskin	2017	71	Prospective	All	ICG	Cervical	Laparoscopic	Complete pelvic lymphadenectomy,paraaortic lymphadenectomy if high risk	H&E, IHC、ultrastaging
O. Touhami	2017	128	Retrospective	All	Blue dye、Technetium-99、Indocyanine green、Blue dye + technetium-99、Indocyanine green + technetium-99	Cervical	Laparoscopic or Robotic or Open	Pelvic lymphadenectomy,the indication and extent of the para-aortic lymphadenectomy (PAL) was left at the discretion of the surgeon.	H&E, IHC、ultrastaging
N. Body	2018	119	Retrospective	All	ICG	Cervical	Laparoscopic or Robotic or Open	All patients underwent total hysterectomy and bilateral salpingo-oophorectomy and a complete pelvic lymph node dissection following SLN mapping. Paraaortic node dissection was performed at the surgeon's discretion.	H&E, IHC、ultrastaging
K. J. Eoh	2018	50	NR	All	ICG	Uterine or Cervical	Laparoscopic	Systematic bilateral pelvic lymph node	H&E
A. Rajanbabu	2018	69	Prospective	All	ICG	Cervical	Robotic	Pelvic and paraaortic LND was done based on pre-operative risk factors (endometrial biopsy result and MRI staging).	H&E
C. Shimada	2018	57	Retrospective	All	TC-99m or/and ICG	Cervical	Laparoscopic or Open	Lymphadenectomy, the extent of lymphadenectomy was at the discretion of the attending surgeon.	H&E, IHC、ultrastaging
Tanaka T	2018	211	NR	All	TC-99m or IDG or ICG	Cervical	Laparoscopic or Open	All of the patients underwent laparoscopic or abdominal hysterectomy, bilateral salpingo-oophorectomy and an SLN biopsy with or without PLND and paraaortic lymph node dissection (PAND).	H&E
S. Togami	2018	113	Prospective	All	ICG	Cervical or Uterine	Laparoscopic or Robotic or Open	Complete pelvic lymphadenectomy,paraaortic lymphadenectomy if high risk	H&E
F. J. Backes	2019	184	Prospective	All	ISB and ICG	Cervical	Robotic	SLN biopsy was followed by complete pelvic lymphadenectomy (aortic lymphadenectomy at the discretion of the surgeon).	H&E, IHC、ultrastaging
J. A. Kennard	2019	414	Retrospective	All	ISB and ICG	Cervical	Robotic	Completion pelvic lymphadenectomy was performed in all patients during this time of this study for quality assurance to determine false negative rates (FNR) for surgeons in the group.	H&E, IHC、ultrastaging

(Continued)

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TABLE 2 Continued

Author	Year	Study Size	Study Method	Cancer Histology	Tracer Used	Injection Site	Route of Surgery	Reference Standard	Pathology Assessment
J. Persson	2019	257	Prospective	All	ICG	Cervical	Robotic	Pelvic and infrarenal para-aortic lymphadenectomy	H&E, IHC、 ultrastaging
S. Taşkin	2019	286	Retrospective	All	ICG or blue dye	Cervical	Laparoscopic or Robotic or Open	Pelvic ± para-aortic lymphadenectomy	H&E, IHC、 ultrastaging
T. Wang	2019	98	Retrospective	All	ICG	Cervical	Laparoscopic	Pelvic ± para-aortic lymphadenectomy	H&E, IHC、 ultrastaging
L. Ye	2019	131	Prospective	All	ICG	Cervical	Laparoscopic	Complete bilateral lymphadenectomy was then performed in all patients. Patients with high-risk histologies(grade 3 endometrioid, carcinosarcoma, serous, clear cell, or undifferentiated carcinoma) underwent simultaneous paraaortic lymphadenectomy to the inferior mesenteric artery and lymentectomy.	H&E, IHC、 ultrastaging
J. Zuo	2019	115	Prospective	Endometrioid	Carbon nanoparticle	Cervical or Uterine	Laparoscopic	Para-aortic lymph node sampling procedures were performed for low-risk patient (Based on the MRI result: primary tumor is less than 2 cm in diameter, less than 50% myometrial invasion, and the pathology is non-poorly differentiated carcinoma), while the para-aortic lymphadenectomy was performed for non-low risk patient.	H&E, IHC、 ultrastaging
Ş. Gezer	2020	81	Prospective	All	TC-99m	Cervical or Uterine	Open	Pelvic and paraaortic lymphadenectomy procedures	H&E, IHC、 ultrastaging
F. Martinelli	2020	208	Retrospective	All	ICG or TC-99m	Uterine	Laparoscopic	Lymphadenectomy (pelvic ± aortic)	H&E, IHC、 ultrastaging
M. Renz	2020	90	Retrospective	All	ICG	Cervical	NR	Complete pelvic lymphadenectomy,paraaortic lymphadenectomy if high risk	H&E
V. S	2020	35	Prospective	All	TC-99m	Cervical	Open	Complete pelvic and lower para-aortic lymphadenectomy	H&E
M. A. Angeles	2021	102	Prospective	All	TC-99m	Uterine	Laparoscopic	Systematic pelvic and paraaortic lymphadenectomy	H&E, IHC、 ultrastaging
E. Curcio	2021	44	Retrospective	All	ICG	Cervical	Robotic	Systematic pelvic LND was performed in case of negative bilateral mapping, and for tumors >2 cm in greatest dimension or invading >50% of the myometrium. Pelvic and paraaortic LND up to the level of the renal veins was attempted for all grade 3 tumors, uterine serous cancer, clear cell carcinoma, and carcinosarcoma.	H&E, IHC、 ultrastaging

(Continued)

TABLE 2 Continued

Author	Year	Study Size	Study Method	Cancer Histology	Tracer Used	Injection Site	Route of Surgery	Reference Standard	Pathology Assessment
M. C. Cusimano	2021	156	Prospective	All	ICG	Cervical	Laparoscopic or Robotic	Grade 2 endometrioid EC required bilateral PLND,and high-grade EC required bilateral PLND and PALND	H&E, IHC、ultrastaging
S. Liang	2021	90	Prospective	All	ICG or CNPs or ICG + CNPs	Cervical	Laparoscopic or Open	Systemic pelvic lymphadenectomy was performed. Para-aortic lymphadenectomy was performed at the surgeon's discretion	H&E
V. G. Pineda	2021	88	Retrospective	All	ICG+Tc99 or Tc99 +Blue dye or ICG	Cervical	Laparoscopic	Complete pelvic and paraaortic lymphadenectomy	H&E, IHC、ultrastaging
N. Sánchez-Izquierdo	2021	52	Retrospective	All	ICG and TC-99m	Uterine	Laparoscopic	Pelvic and paraaortic lymphadenectomy	H&E, IHC、ultrastaging
S. Somashekhar	2021	100	Prospective	All	ICG	Cervical	Robotic	Complete pelvic and para-aortic node dissection	ultrastaging
Q. Wang	2021	92	Retrospective	All	ICG	(Cervical and Uterine) or Cervial	Laparoscopic	Pelvic lymphadenectomy with or without infrarenal para-aortic lymphadenectomy	H&E, IHC、ultrastaging
D. Altin	2022	128	Retrospective	All	MB or ICG	Cervical	Laparoscopic or Open or Robotic	Pelvic ± paraaortic lymphadenectomy	H&E, IHC、ultrastaging
M. Gedgaudaite	2022	90	Prospective	All	ICG	Cervical	Laparoscopic	LND	NR
A. Torrent	2022	48	Prospective	All	ICG and TC-99m	(Cervical and Uterine) or Cervial	NR	Pelvic ± paraaortic lymphadenectomy	H&E, IHC、ultrastaging
Y. Xue	2022	159	Retrospective	All	ICG	Cervical	Laparoscopic	Systematic lymphadenectomy	H&E, IHC、ultrastaging

H&E, Hematoxylin and eosin; IHC, Immunohistochemistry; LND, Lymphadenectomy; NR, Not reported; SLN, Sentinel lymph node; Tc-99m, Technecium-99; ICG, Indocyanine green; ISB, Isosulfane blue; MB, Methylene blue; CNP, Carbon nanoparticle.

Of the 62 articles, 35 (56.5%) were prospective studies, 22 (35.5%) were retrospective studies, and the remaining 5 (8%) articles did not clearly account for the study methods.

Risk of bias of included studies

The quality assessment of all included studies is presented in the (Figures 2A, B). The risk of bias varied across 4 domains. Most of the studies were at low risk of bias in the patient selection, index test and reference standard domains.However, 55 studies were at high risk of bias in the flow and timing domain, due to the fact that some patients received PALND in addition to PLND as a reference standard and some did not, or not included in the final analysis due to failure of sentinel lymph node visualization in some patients. All 62 studies were highly applicable to our research question across all three domains, except 25 studies containing insufficient data to make a judgement.

Synthesis of results

The median age was reported in thirty-six studies. The study-level median age was 62.5 years (range 52-71), and the median BMI was reported in 32 studies. The study-level median BMI was 27.5 kg/m2 (range 22-38). The majority of the 62 articles 42 (67.7%) used only cervical injections, 12 (19.4%) used only uterine injections, and the remaining 8 (12.9%) used cervical and/or uterine injections. Twenty of the 62 articles (32.2%) referenced use of only ICG, 7 (11.3%) referenced use of only blue dye, 7 (11.3%) referenced use of only Tc-99 m, and the remaining 28 articles (45.2%) referenced use of multiple dyes.

SLN false negative rate

The false negative rate for sentinel lymph node biopsy for endometrial cancer was 4% (95% CL 3-5) (6304 patients) (Figure 3). There was no significant difference in the false negative rate in patients with endometrial cancer with a high-risk tumor risk grade compared with those with low-risk endometrial cancer (2600 patients); and in intraoperative frozen sections were not significantly associated with the false negative rate. The type of dye used intraoperatively (indocyanine green/blue dye) were not significantly associated with the false negative rate, the false negative rate of SLN was significantly lower for indocyanine green than for Tc-99 m (4% vs. 12%, p=0.042) (4015 patients). The false negative rate of SLN was significantly lower for cervical injections than for uterine injections (4% vs. 10%, p=0.024) (6083 patients). The use of postoperative pathologic ultrastaging was associated with a lower rate of false negative SLNs (4% vs. 11%, p=0.036) (6095 patients) (Table 3).
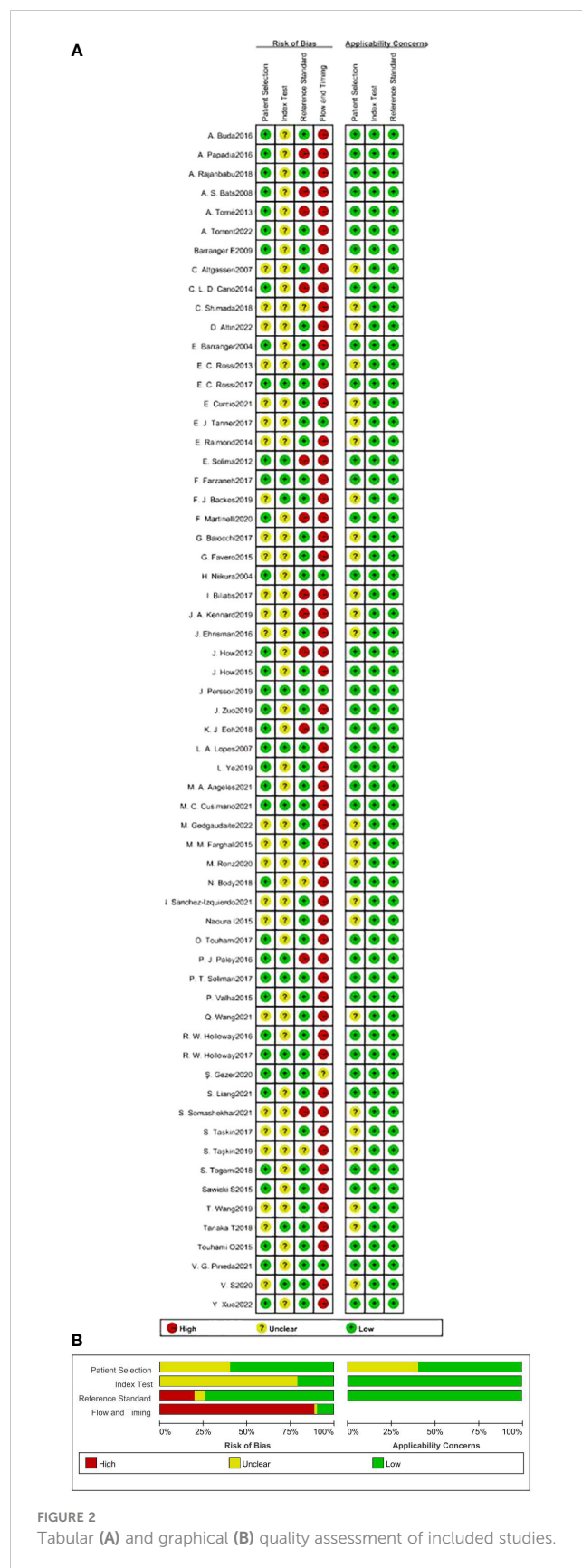

FIGURE 2
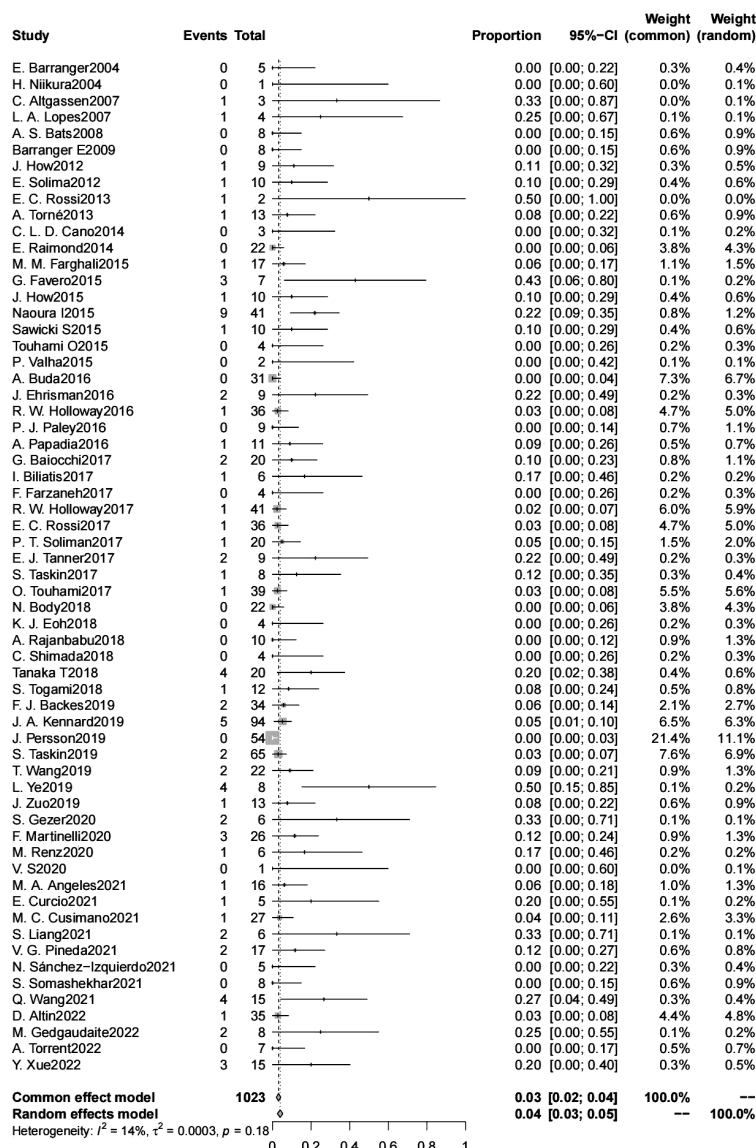Tabular (A) and graphical (B) quality assessment of included studies.

FIGURE 3
SLN false negative rate.

Comment

Principal findings

We performed a meta-analysis of 62 articles containing 6304 patients studying sentinel lymph nodes in endometrial cancer. We came to 3 main conclusions: 1. The overall false negative rate of sentinel lymph node biopsy for endometrial cancer was 4% (95% CL 3-5). 2. Cervical injection, indocyanine green dye tracer, and postoperative pathological ultrastaging reduced the false negative rate of SLNB. 3. There was no significant difference in the false negative rate between high-grade and low-grade patients (9% vs. 6%, p=0.519).

Comparison with existing literature

Sentinel lymph node biopsy (SLNB) has been widely accepted as the standard of care for surgical staging of low-grade endometrial

cancer (EC), but its value in high-grade EC remains controversial. Various international guidelines suggest SLNB as a reasonable alternative option for high-grade EC subtypes (84, 85). However, although the value of SLNB in high-grade EC remains, there are questions about the accuracy of this technique in patients with high-grade histologic subtypes due to the greater risk of lymph node metastasis in high-risk endometrial cancer and concerns about isolated para-aortic lymph node involvement due to alternative lymphatic drainage (16). In a previous study, the results of a prospective single-center clinical study indicated that SLNB had a false negative rate of up to 80% in high-risk tissue types of endometrial cancer, while the false negative rate in low-risk types of endometrial cancer was only 0 (67). In another stud, it was concluded that SLN mapping was more effective in patients with LIR than in patients with HIR, with sensitivities of 100.00% and 75.00%, respectively (p > 0.05), and a higher rate of missed

TABLE 3 Univariate Meta-Regression of SLN false negative rate and study variables.

Study Variables	Number of Patients	Overall Detection% (95% CI)	p-value
Tumor Risk Grade	2600		
Low Risk		0.06 (-0.007,0.14)	
High Risk		0.09 (0.05,0.14)	0.519
Injection Site	6083		
Cervical		0.04 (0.02,0.05)	
Uterine		0.10 (0.04,0.15)	0.024
Dye Tracer	4015		
Indocyanine green (ICG)		0.04 (0.02,0.06)	
Blue dye		0.05 (0.006,0.09)	0.792
Tc-99m		0.12 (0.05,0.19)	0.042
Intraoperative Frozen Section	6145		
Yes		0.04 (0.02,0.06)	
No		0.04 (0.02,0.06)	0.984
Intraoperative Pathologic Ultrastaging	6095		
Yes		0.04 (0.02, 0.05)	
No		0.11 (0.04, 0.17)	0.036

diagnoses in patients with HIR (82). In contrast, a prospective trial showed that SLN biopsy plus side-specific LND is a reasonable alternative to full LND when SLN is not detected in high-risk endometrial cancer (53). The results of a retrospective study support the same idea (86). The largest meta-analysis to date of false negative rates for sentinel lymph node biopsies for low- and high-risk endometrial cancer supported the conclusion that SLNB accurately detected lymph node metastases in high-grade EC with a false negative rate of 8% (95% CI 4-16), comparable to false negative rates for low-grade EC, melanoma, vulvar cancer, and breast cancer. This suggests that SLNB can replace complete lymph node dissection as the standard of care for surgical staging of patients with high-grade EC (17). The latest, a prospective cohort study (FIRES) included all risk groups, all histologic subtypes, and all stages of endometrial cancer, the accuracy of the sentinel lymph node in predicting lymph node metastasis is very high (87). In our meta-analysis, we also concluded that there was no significant difference in the false negative rate in patients with high-risk endometrial cancer compared with those with low-risk endometrial cancer. Unlike previous studies, our study involved an increased number of included articles as well as sample size, and we used meta-regression to explore the effect of tumor risk class on the combined false negative rate, which makes our findings more comprehensive and specific. This provides a close confirmation that sentinel lymph node biopsy is a feasible technical option in patients with high-risk endometrial cancer.

Currently, there is still controversy about the injection site and other modalities of SLN localization tracers. The injection modalities can be roughly divided into two main categories: cervical injection and uterine body injection; uterine body injection can be subclassified as subserosal tissue, deeper myometrial and hysteroscopically guided peritumoral injections. Considerable prospective data suggest that myometrial and endometrial injections appear to be more compatible with lymphatic drainage of endometrial tumors (88), but the complexity of their manipulation makes them not easily achievable. Cervical injections are technically more straightforward; however, their distance from the tumor raises concerns about their effectiveness (34). In contrast, proponents of cervical injection sites for endometrial cancer argue that the anatomical distribution of the SLNs corresponds to injections into the uterine corpus and coincides with the most common sites of lymphatic metastasis (internal iliac, external iliac, and obturator lymph nodes) for endometrial cancer (89). A prospective study showed that two lymphatic pathways consistent with pelvic SLNs were identified regardless of whether the injection site was the cervix or uterine fundus (90). This suggests that the location of the pelvic channel and SLNs is independent of the tracer injection site. Even with these controversies, due to the simplicity and time-saving nature of cervical injections compared to other injection modalities, the cervix is easily accessible even in minimally invasive procedures, and reliable injections can be performed with minimal additional equipment (91, 92). Therefore, cervical injections are used in most patients and currently represent the most reported modality in the literature. Most of the 62 articles in our study 42 (67.7%) involved use of only cervical injections, 12 (19.4%) involved use of only uterine injections, and the remaining 8 (12.9%) involved use of cervical and/or uterine injections. Some prospective and retrospective studies have demonstrated that pelvic sentinel lymph node localization by cervical tracer injection is a feasible and accurate technique for lymph node evaluation in endometrial cancer (52, 65, 90, 93). Especially for high-risk cancers, the cervix has been shown to be a viable and accurate site for tracer injection (92). However, it has been shown that cervical injections have a significantly lower para-aortic SLN detection rate than uterine injections (7% vs. 27%, p=0.001) (17). Uterine injections of para-abdominal aortic SNs test much higher (94). However, most studies have shown that cervical injections are associated with a significantly higher bilateral SLN detection rate than uterine injections, especially for the pelvic region. A large review of the literature on current techniques and outcomes of lymphatic localization of endometrial cancer summarized the detection rates of injection in the uterine corpus (7 studies), cervical injection (7 studies), and hysteroscopic injection (6 studies) and concluded that despite the controversy, cervical injection is associated with high detection rates (95). From another study, it was noted that although the detection rate of SLNs in the para-aortic region was slightly higher in patients receiving uterine injections, the difference relative to cervical injections was not statistically significant; instead, cervical injections allowed for better identification of lymph nodes in the pelvic region (96). It is now well established that cervical injections increase detection rates, and while high lymph node detection rates may allow for lower leakage of metastatic lymph nodes, there are few studies on the correlation between cervical injections and false negative rates. In this study, we were the first to compare the false negative rates of

cervical injections and uterine injections using meta-analysis, with the conclusion that the false negative rate of SLNs was significantly lower for cervical injections than for uterine injections (4% vs. 10%, p=0.024) (6803 patients). This is consistent with previous studies supporting cervical injections and demonstrates that cervical injections not only increase the detection rate but also reduce the incidence of false negative rates.

Currently a commonly used tracer for SLNB of endometrial cancer included technetium colloid (Tc), blue dye, and indocyanine green (ICG). ICG is currently the most widely used NIR fluorescent dye, and many studies have shown its high sensitivity, specificity, and lymph node detection rate (65, 97). Most guidelines insist on surgeon experience for ICG technique, and it has been demonstrated that the diagnostic accuracy of SLN increases with surgical team experience (98). Blue dye is easy to use and cost-effectiveness. However, the blue dye can diffuse to parametrial area thus interfering with the discovery of regional SLN (99). Since radionuclide needs to be injected 1 day before surgery, it is not conducive to timely observation of sentinel lymph nodes, and the detected lymph nodes may not be the first stop for regional drainage, this condition also occurs frequently among doctors who are initially learning about SLNB, it may be more difficult to detect SLNs close to the cervix as the gamma-probe picks up high activity from the injection site (24). Our study concluded the false negative rate of SLN was significantly lower for indocyanine green than for Tc-99 m (4% vs. 12%, p=0.042) (4015 patients), this is in line with the previous conclusions.

The sentinel lymph node technique is now commonly accepted, but low-volume lymph node metastases occurring as micrometastases (MMs) and isolated tumor cells (ITCs) may be overlooked in routine evaluation when only routine pathology is performed intraoperatively (23). Even though IFS is used intraoperatively, its frequent diagnostic inaccuracy leads to an increased rate of missed diagnoses, which affects the prognosis of patients. Ultrastaging localization of sentinel lymph nodes has been shown to increase the detection of lymph node metastases, including occult low-volume metastases (23, 84). This reduces morbidity compared to systemic pelvic and para-aortic lymph node dissection and provides important prognostic information needed for adjuvant therapy (100). Ultrastaging techniques are essential for proper staging and reducing false negative rates (101). Ultrastaging can also be used as a complement to the deficiencies of frozen sections in endometrial cancer surgery, as an offset to diagnostic errors in IFS and to minimize their negative impact on patient care (102). Many studies have been designed to investigate the use of sentinel lymph node biopsy and ultrastaging techniques compared to lymph node dissection, especially for low-risk disease (46, 52, 103). Most scholars have concluded that low-volume metastases are not meaningful for adjuvant therapy and prognosis in low-risk endometrial cancer, whereas in high-risk endometrial cancer based on the objective effectiveness of adjuvant chemotherapy, it is speculated that adjuvant therapy guided by low-volume metastases may improve prognosis (104, 105). In a systematic review involving 15 studies and including 2259 patients, sentinel lymph nodes were examined using conventional hematoxylin and eosin staining. Subsequently, multiple ultrastaging methods were used, and 14% of patients were found to have positive sentinel lymph nodes. In 37% of these patients, these lymph nodes could be detected only by the ultrastaging method (106). It can also be argued that without pathologic ultrastaging, there is a high risk of missing micrometastases in lymph nodes or isolated tumor cells. In a large prospective FIRES study, the "ultrastaging" approach detected 54% of low-volume metastatic lesions in the sentinel lymph nodes, and it can be assumed that the false negative rate would be significantly higher if only conventional pathological examination was performed on the detected sentinel lymph nodes (52). Although the ultrastaging technique has many merits, serial sectioning is very time consuming for both technicians and pathologists (100). Additionally, its high price has led some hospitals to perform pathological ultrastaging on only some patients, and it is not universally available to every patient. Coupled with the fact that there are different types of ultrastaging techniques available, it is difficult to establish which one to use as a standard. At the same time, a prospective study noted that the OSNA method had high specificity and high accuracy in detecting SLN metastasis in apparent early-stage endometrial cancer (107). This requires us to explore the need for performing pathological ultrastaging. In our study, it was concluded that the use of postoperative pathological ultrastaging was associated with a lower rate of false negative SLNs (4% versus 11%, p=0.036) (6095 patients). This is in line with previous studies. It also demonstrates, once again, the need for the use of ultrastaging techniques in the biopsy of sentinel lymph nodes.

The current gold standard for the treatment of endometrial cancer is hysterectomy with bilateral salpingooophorectomy (BSO) with lymphadenectomy (108, 109). Nevertheless, in selected cases of patients desiring pregnancy, fertility-sparing treatment (FST) can be proposed, however, the status of lymph nodes during FST cannot be well investigated and evaluated (110). At present, imaging methods such as B-ultrasound, CT and MRI can also be used for the diagnosis of myometrial infiltration and lymph node metastasis (111–113). However, MRI examination is not popular due to its high cost and contraindications, B-ultrasound examination is low in accuracy, and CT examination is limited to endometrial lesions and has no diagnostic value. This makes FST a potential risk factor for false negative lymph node results.

Strengths and limitations

Our study is the largest meta-analysis to date on sentinel lymph node biopsy for endometrial cancer and is the first to involve comprehensively performing stratified and meta-regression analyses of the effect of patient (tracer, injection site, tumor risk grade, intraoperative frozen section, and pathology ultrastaging) characteristics on combined false negative rates. Before us, the largest meta-analysis examining false negative rates for high-risk endometrial cancer included only nine articles (17). Our study has a huge advantage in terms of the number of articles compared to those in previous studies, from 9 previously to 23 in our study, which allows us to have a more comprehensive summary of high-risk endometrial cancers on the basis of our predecessors and a

better response to the false negative rate. However, due to the relatively low incidence of lymph node metastasis in early-stage endometrial cancers, especially for low-risk endometrial cancers, false negative rates could not be obtained for many low-risk endometrial cancers because the statistical analyses were based on the number of lymph node-positive patients. This consideration led to the fact that only 7 of the 23 studies that we included provided reference to the false negative rates of low-risk endometrial cancers, whereas the majority of the articles reported false negative rates of high-risk endometrial cancers. The discrepancy in the number of the low-risk endometrial cancers in the comparison of false negative rates of two groups of low- and high-risk patients may have biased the results to some extent.

Conclusions and implications

The current overall false negative rate for sentinel lymph node biopsy for endometrial cancer is 4% (95% CL 3-5). Sentinel lymph node biopsy for tracer injection in other parts of the uterus (other than the cervix), Tc-99m dye tracer, and failure to perform postoperative pathologic ultrastaging are risk factors for a high false negative rate of SLNB in patients with endometrial cancer; therefore, great attention should be given to the occurrence of leakage of lymph node metastasis after SLNB in this population. There is no difference in the false negative rate of sentinel lymph node biopsy in high-risk versus low-risk endometrial cancer patients, and performing sentinel lymph node biopsy in high-risk endometrial cancer patients is a viable technical option.

Recommendations

In summary, the author provides recommendations for conducting future Sentinel lymph node biopsy of endometrial cancer. The research design should conform to the internationally recognized SPIRIT declaration, strictly follow the PICO principle, and register the research plan before the trial, and the final report should be standardized according to the CONSORT declaration.

Author contributions

M-SF: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Writing – original draft, Writing – review & editing. K-XQ: Writing – review & editing. D-YW: Writing – review & editing. HW: Writing – review & editing. W-WZ: Writing – review & editing. LY: Conceptualization, Funding acquisition, Supervision, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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