Sentinel lymph node assessment in endometrial cancer: a systematic review and meta-analysis

Anna Jo Bodurtha Smith, MD, MPH, MSc; Amanda Nickles Fader, MD; Edward J. Tanner, MD

BACKGROUND: In the staging of endometrial cancer, controversy remains regarding the role of sentinel lymph node mapping compared with other nodal assessment strategies.
OBJECTIVE: We conducted a systematic review to evaluate the diagnostic accuracy and clinical impact of sentinel lymph node mapping in the management of endometrial cancer.
DATA SOURCES: We searched Medline, Embase, and the Cochrane Central Registry of Controlled trials for studies published in English before March 25, 2016 (PROSPERO CRD42016036503).
STUDY ELIGIBILITY CRITERIA: Studies were included if they contained 10 or more women with endometrial cancer and reported on the detection rate, sensitivity, and/or impact on treatment or survival of sentinel lymph node mapping.
STUDY APPRAISAL AND SYNTHESIS METHODS: Two authors independently reviewed abstracts and full-text articles for inclusion and assessed study quality. The detection rate, sensitivity, and factors associated with successful mapping (study size, body mass index, tumor histology and grade, injection site, dye type) were synthesized through random-effects meta-analyses and meta-regression.
RESULTS: We identified 55 eligible studies, which included 4915 women. The overall detection rate of sentinel lymph node mapping was 81% (95% confidence interval, 77—84) with a 50% (95% confidence interval, 44—56) bilateral pelvic node detection rate and 17% (95% confidence interval, 11—23) paraaortic detection rate. There was no difference in detection rates by patient body mass index or tumor histology and grade. Use of indocyanine green increased the bilateral detection rate compared with blue dye. Additionally, cervical injection increased the bilateral sentinel lymph node detection rate but decreased the paraaortic detection rate compared with alternative injection techniques. Intraoperative sentinel lymph node frozen section increased the overall and bilateral detection rates. The sensitivity of sentinel node mapping to detect metastases was 96% (95% confidence interval, 91—98); ultrastaging did not improve sensitivity. Compared with women staged with complete lymphadenectomy, women staged with sentinel lymph node mapping were more likely to receive adjuvant treatment.
CONCLUSION: Sentinel lymph node mapping is feasible and accurately predicts nodal status in women with endometrial cancer. The current data favors the use of cervical injection techniques with indocyanine green. Sentinel lymph mapping may be considered an alternative standard of care in the staging of women with endometrial cancer.

Key words: endometrial cancer, robotic surgery, sentinel lymph node

Endometrial cancer is the most common gynecological malignancy in the United States, with its incidence increasing because of rising obesity rates.[1] Lymph node status is the most important predictor of survival and also guides postoperative treatment planning.[2] Whereas evaluation of lymph nodes has been included in surgical staging criteria for endometrial cancer since 1988, the optimal procedure for lymph node assessment is controversial. Performance of pelvic and paraaortic lymphadenectomy (LND) has been associated with improved survival in cohort studies, but 2 randomized controlled trials demonstrated no impact on survival.[3,4] For high-grade histologies of endometrial cancer, LND remains relevant, given the greater risk of nodal involvement and recurrence associated with these histologies.[4] However, because there are risks of lymphedema and intraoperative complications associated with LND, many gynecological oncologists omit LND in select patients with endometrial cancer.[5]

Sentinel lymph node (SLN) mapping has been proposed as a technique to identify lymph node metastases while reducing the surgical morbidity associated with complete LND.[6] An SLN is defined as the first node to receive drainage from a primary tumor and is the most likely to harbor metastases in cancers with lymphatic spread. SLN mapping may also detect aberrant lymphatic drainage that would be missed on routine LND. SLN mapping is established as the standard of care for the staging of breast cancer and melanoma among other cancers.[7,8] However, adapting its use in endometrial cancer has been more challenging, given the complexity and bilaterality of the nodal basins that drain the uterus.

Whereas early results for SLN mapping in endometrial cancer were promising, other research has raised concerns about the adequacy of nodal detection, especially for paraaortic nodes.[9,10] Moreover, body mass index (BMI) may limit the lymphatic spread of tracers used in SLN mapping, which could limit its efficacy in endometrial cancer.[11,12]

For these reasons, current guidelines do not yet recommend SLN mapping as the standard of care in the staging of this malignancy, although national societies and organizations that define treatment

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standards are increasingly recognizing the utility of this staging approach. For instance, the National Comprehensive Cancer Network states that "selected patients with apparent uterine-confined endometrial carcinoma may be candidates for sentinel lymph node mapping … the expertise of the surgeon and attention to technical detail is critical."[13]

Nonetheless, the last meta-analysis of SLN mapping outcomes in endometrial cancer was conducted in 2012.[14] Since that time, numerous studies have been published, demonstrating major advances in SLN technology and techniques.[15] A contemporary understanding of SLN detection rates and technique limitations is critical to advancing surgical staging standards and optimizing mapping in this setting. Thus, the objectives of this systematic review and meta-analysis are as follows: (1) to evaluate the diagnostic accuracy of SLN mapping for the staging of endometrial cancer, (2) to analyze factors associated with the diagnostic accuracy of SLN mapping, and (3) to assess the clinical impact of SLN detection in the management of endometrial cancer.

Materials and Methods

Search strategy

We searched Medline, Embase, and the Cochrane Library from database inception to March 25, 2016. Electronic searches were supplemented by reviewing reference lists of included studies and prior systematic reviews, hand-searching the journal *Gynecologic Oncology*, and contacting the authors of included studies for any additional published or unpublished studies meeting review inclusion criteria. When the search strategy identified a meeting abstract, we searched Medline for an associated full-text article by the same author group. We developed search terms based on prior systematic reviews and input from a reference librarian (Table 1). We limited articles to English language only.

Details of the review protocol were registered on PROSPERO, an international database of prospectively registered systematic reviews, and can be accessed at http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42016036503.

Inclusion/exclusion criteria

Studies were included if they had the following criteria: (1) included 10 or more women diagnosed with International Federation of Gynecology and Obstetrics stage 1 or higher endometrial cancer; (2) examined the diagnostic accuracy and/or clinical impact of sentinel lymph node mapping; and (3) reported outcomes measures including, but not limited to detection rate, sensitivity, negative predictive value, adverse events, treatment impact, overall survival, and/or progression-free survival.

We included all ages, tumor history, grade and stage, and all techniques and settings of sentinel node detection and dissection. We excluded studies with fewer than 10 women with endometrial cancer and meeting abstracts, reviews, case reports, or editorials. To avoid overlapping patient data in publications on the same cohort, we included the articles with the largest sample size.

After removal of duplicates using Mendeley, 2 reviewers screened titles and abstracts for initial eligibility assessment. After abstract screening, 2 reviewers reviewed full-text articles for inclusion/exclusion. Review agreement was assessed with the kappa statistic, and disagreements were resolved by consensus.

Data extraction and quality assessment

Data were extracted by 2 independent reviewers using a standardized form. These data consisted of author, year of publication, study setting, study design, patient population, SLN technique, available outcome data, adverse events, and items for quality assessment. For the SLN technique, we extracted data on surgical approach (robotic, laparoscopic, laparotomy), use of preoperative lymphoscintigraphy, injection site (cervical vs intrauterine), use of a radioactive tracer, use of indocyanine green or blue dye, and histological assessment of SLN with intraoperative frozen section or ultrastaging.

Ultrastaging was defined as any additional processing of sentinel lymph nodes beyond routine lymph node evaluation and often included additional sectioning and staining of SLNs with hematoxylin and eosin (H&E) dye; all cases using immunohistochemistry were considered to use ultrastaging. Two reviewers independently assessed the risk of bias in included studies using the QUADAS-2 tool. Differences were resolved through review of the original articles.

Because the uterus is a central organ and drains to bilateral nodal basins in the pelvis, we examined SLN detection rates by patient and by hemipelvis (defined as side-specific detection) as previously

TABLE 1
Search terms

Search engines

PubMed	Embase	Cochrane Library
([Sentinel lymph node biopsy) [mesh] or (sentinel and node*) or (sentinel and lymph*) or (lymphatic mapping) or (sentinel and biops*]) and ([endometri* or uterus or uterine or corpus uteri) and (neoplasm* or cancer or cancers or carcinoma* or malignanc* or tumor or tumors) or endometrial neoplasms [mesh] or uterine neoplasms [mesh] or "endometrial stromal tumors [mesh]])	Endometrium cancer/exp or uterus cancer/exp or endometri* or uterus or uterine or corpus uteri and (neoplasm* or cancer* or carcinoma* or malignanc* or tumor*) and (sentinel and lymph* or (sentinel and node*) or (sentinel and biops*) or (sentinel and (dissection* or excision* or removal)) or (lymphatic and mapping) or sentinel lymph node biopsy/exp or sentinel lymph node/exp)	1. Sentinel and ([lymph or node* or biops*]) or lymphatic mapping 2. (endometri* or uterus or uterine or corpus uteri) and (neoplasm* or cancer or cancers or carcinoma* or malignanc* or tumor or tumors) 3. 1 and 2

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described in the literature.[6,9] We defined the overall detection rate as the percentage of patients undergoing SLN procedures in which at least 1 sentinel node was identified on either side of an individual patient's hemipelvis and the bilateral detection rate as the percentage of patients with at least 1 sentinel node identified in each hemipelvis of an individual patient.

We defined the paraaortic detection rate as the percentage of patients undergoing SLN procedures in which at least 1 paraaortic node was identified on either side of an individual patient's hemipelvis. Occasionally nonlymphatic tissue is harvested during SLN mapping, and we excluded these nonnodal samples from SLN detection rates when reported.

We defined sensitivity as the percentage of patients with at least 1 positive SLN divided by all patients with successful lymph node detection and lymph node metastases. Given the impossibility of false-positive results (eg, any SLN with metastases is a positive node), specificity was defined as 100%.

Analysis

We used Stata 11.0 (StataCorp, College Station, TX) to conduct aggregate data random-effects meta-analyses and evaluate heterogeneity of the included studies. We calculated overall, bilateral, side-specific, and paraaortic detection rates, sensitivity, and negative predictive value estimates from data provided in the source papers. We conducted meta-analyses of detection rates using a random-effects model.

For sensitivity, we used a bivariate mixed-effects binomial regression model for the meta-analysis.[16] We used stratified bivariate meta-analyses and meta-regression to explore heterogeneity in effect estimates, according to study size, patient average BMI, tumor (histology, grade), and SLN technique (surgical approach, use of preoperative lymphoscintigraphy, injection site, radioactive tracer, use of dye and radioactive tracer, indocyanine green dye usage, intraoperative frozen section) characteristics. When studies reported results for multiple subgroups (eg, comparing dyes), we included the total rate in the main meta-analysis and the subgroup rates in the stratified meta-analyses and meta-regressions.

We assessed heterogeneity among the studies using the I^2 statistic and visual inspection of funnel plots.

Results

Of the 1230 abstracts screened, 55 articles including 4915 women with endometrial cancer were eligible for inclusion (Figure 1).[11,12,17-65] The kappa statistic for interrater reliability was 96%. Twenty-one studies were conducted in North America, 23 in Europe, 6 in the Middle East, 3 in Asia, and 2 in South America (Table 2). Most studies included SLN mapping followed by completion pelvic LND with or without paraaortic LND for high-grade or non-endometrioid histology endometrial cancer as the comparison. The majority of studies were prospective (87%) with consecutive patient enrollment (87%) (Appendix Table 1).

FIGURE 1
Flow diagram of study selection

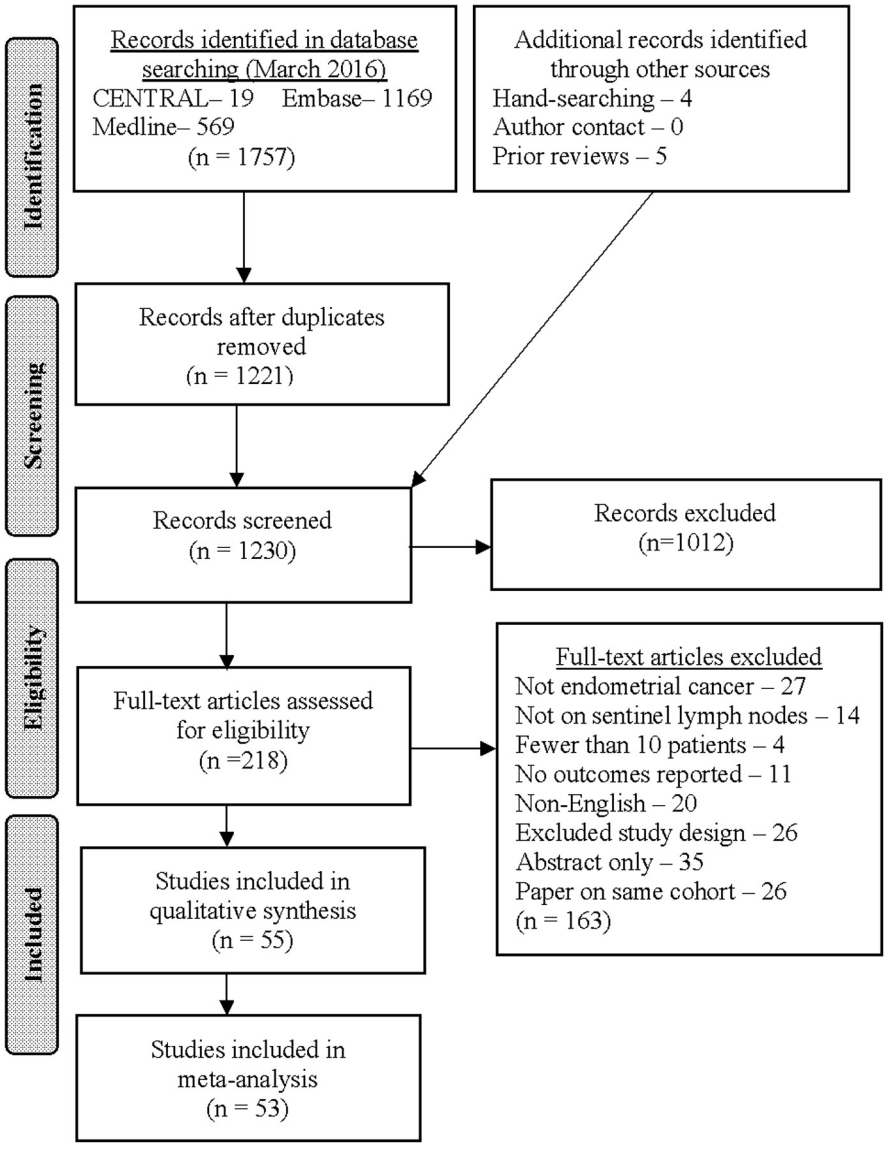

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TABLE 2
Characteristics of included studies

Author, year	Country	Study size	Study method	Time period	Cancer histology	Tracer used	Injection site	Route of surgery	Reference standard	Pathology assessment
Allameh et al, 2015[17]	Iran	15	Prospective	November 2012 through February 2014	All	Tc-99m and patent blue	Uterine	Open	LND	H&E, IHC, ultrastaging
Altgassen et al, 2007[18]	Germany	25	Prospective	4/2004-3/2006	All	Patent blue	Uterine	Open	Pelvic LND if tumor size (>2 cm), grading (>G1), and invasion (>IA), paraaortic LND if intraoperative state sufficient	H&E
Ballester et al, 2013[19]	France	85	Retrospective	July 2002 through March 2009	All	Patent blue	Cervical	Laparoscopic	Complete pelvic LND, paraaortic LND if high-risk endometrial cancer or metastatic pelvic SLN at intraoperative or definitive histology	H&E, IHC, ultrastaging
Basta et al, 2005[20]	Poland	36	NR	NR	NR	Blue dye +/- Tc-99m, ICG	Cervical & Uterine	NR	LND	IHC, ultrastaging
Bats et al, 2008[21]	France	43	Prospective	January 2002 through March 2006	All	Isosulfan blue	Cervical	Laparoscopic	Pelvic and paraaortic LND if stage IC cancer as assessed based on the depth of myometrial invasion on the preoperative MRI scan, pelvic node involvement, adnexal involvement, and serous carcinoma histology	H&E, IHC, ultrastaging
Buda et al, 2016[22]	Italy	118	Retrospective	October 2010 through May 2015	All	Tc-99m sulfur, patent blue	Cervical	Laparoscopic	Complete Pelvic LND, paraaortic LND if positive preoperative PET/CT and in absence of SLN mapping or unilateral mapping	H&E, IHC, ultrastaging
Burke et al, 1996[23]	United States	15	Prospective	NR	All	Tc-99m and patent blue	Uterine	Open	Selective pelvic and para-aortic LND with bilateral biopsies from 3–4 pelvic sites and 1–2 aortic sites	NR
Darai, 2015 (Senti-ENDO)[1]	France	125	Prospective	July 2007 through August 2009	All	Methylene blue	Cervical	Laparoscopic	Complete pelvic LND, paraaortic LND if positive intraoperative histology or after definitive histology	H&E, IHC, ultrastaging

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TABLE 2
Characteristics of included studies *(continued)*

Author, year	Country	Study size	Study method	Time period	Cancer histology	Tracer used	Injection site	Route of surgery	Reference standard	Pathology assessment
Delaloye et al, 2007[25]	Switzerland	60	Prospective	July 2001 through June 2005	All	Methylene blue or patent blue	Uterine	Open	Complete pelvic and paraaortic LND	H&E, IHC
Desai et al, 2014[26]	United States	120	Retrospective	April 2011 through June 2013	All	Blue dye or ICG	Cervical	Robotic	Selective pelvic and paraaortic LND (surgeon discretion)	H&E, IHC, ultrastaging
Eitan et al, 2015[27]	Israel	74	NR	January 2012 through December 2014	All	Methylene blue	Cervical	Robotic	Memorial Sloan Kettering algorithm (LND if failed mapping, surgeon discretion paraaortic LND)	NR
Eriksson et al, 2016[28]	United States	642	Retrospective	2004–2008 (LND), 2006–2013 (SLN)	Endometrioid	Tc-99m	Cervical	NR	Memorial Sloan Kettering algorithm	H&E, IHC, ultrastaging
Farghali et al, 2015[29]	Egypt	93	NR	May 2007 through May 2011	All	Tc99m sulfide and patent blue	Uterine	Open	Selective pelvic and paraaortic LND by tumor grade, invasion depth, size, location, and patient fitness	H&E, IHC, ultrastaging
Favero et al, 2015[30]	Brazil	42	Prospective	January 2008 through December 2012	All	Tc-99m	Uterine	Laparoscopic	Complete pelvic and paraaortic LND	H&E, ultrastaging
Ferraioli et al, 2015[31]	France	30	Retrospective	December 1998 through May 2012	Endometrioid, clear cell, papillary serous	Tc-99m and isosulfan blue	Cervical	Laparoscopic	Pelvic LND and paraaortic by guidelines	H&E, ultrastaging
Fersis et al, 2004[32]	Germany	10	Prospective	NR	All	Isosulfan blue	Uterine	Open	Complete pelvic LND, paraaortic LND when indicated	Ultrastaging
Frumovitz et al, 2007[33]	United States	18	Prospective	2002–2004	All	Isosulfan blue and ICG	Uterine	Open	Complete pelvic and paraaortic LND	H&E, ultrastaging
Gien et al, 2005[34]	Canada	16	Prospective	September 2002 through March 2004	All	Blue dye	Uterine	Open	Complete pelvic LND, paraaortic LND if high-risk histology	NR

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TABLE 2
Characteristics of included studies *(continued)*

Author, year	Country	Study size	Study method	Time period	Cancer histology	Tracer used	Injection site	Route of surgery	Reference standard	Pathology assessment
Holloway et al, 2016[35]	United States	119	Retrospective	July 2006 through June 2013	All	Tc-99m and patent blue	Cervical	Robotic	Pelvic LND if cancer >1 cm, myometrial invasion >one third, or high-grade histology; paraaortic LND if grade 3 tumor/type 2 histology, any depth of invasion, positive lymph nodes on frozen section, low-grade tumor with middle or outer-third myometrial invasion	H&E, IHC, ultrastaging
Holub et al, 2004[36]	Czech Republic	25	Prospective	February 2000 through September 2003	All	Tc-99m and patent blue or Tc-99m and ICG	Cervical and uterine	Laparoscopic	Complete pelvic LND, paraaortic LND if suspicious pelvic lymph nodes	NR
How et al, 2012[37]	Canada	100	Prospective	December 2010 through April 2012	All	Tc-99m and methylene blue	Cervical	Robotic	Complete pelvic LND, para-aortic LND if type II, grade 2 or 3 endometrioid, carcinosarcoma, positive SLN on intraoperative frozen section, or grossly enlarged pelvic LNs	H&E, IHC, ultrastaging
How et al, 2015[38]	Canada	100	Prospective	April 2013 through August 2014	All	Tc-99m and ICG	Cervical	Robotic	Complete pelvic LND, paraaortic LND if preoperative type II, grade 3 endometrioid, positive SLN on intraoperative frozen section, or grossly enlarged paraaortic LNs	H&E, IHC, ultrastaging
Kadkhodayan et al, 2014[39]	Iran	24	NR	October 2010 through December 2012	All	Blue and radiotracer	Cervical	NR	Complete pelvic LND, para-aortic LND if clear cell, serous, or adenosquamous type or grade 2–3 endometrioid	H&E
Kataoka et al, 2016[67]	Japan	55	Prospective	April 2009 through December 2012	All	Methylene blue	Uterine	Open	Complete pelvic LND, para-aortic LND if metastasis to pelvic lymph node, myometrial invasion >50%, grade 3, serous adenocarcinoma, or clear cell adenocarcinoma	H&E, IHC, ultrastaging
Koskas et al, 2013[40]	France	187	Prospective	2007–2011	All	ICG or methylene blue	NR	Laparoscopic	Complete pelvic LND, paraaortic LND if type II, metastases on intraoperative histology or after definitive histology	H&E, ultrastaging

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(continued)

TABLE 2
Characteristics of included studies *(continued)*

Author, year	Country	Study size	Study method	Time period	Cancer histology	Tracer used	Injection site	Route of surgery	Reference standard	Pathology assessment
Kuru et al, 2011[41]	Turkey	26	Prospective	2010–2011	All	Tc-99m and patient blue	Cervical and Uterine	Open	Complete pelvic LND, paraaortic LND by guidelines	H&E, IHC, ultrastaging
Laios et al, 2015[42]	United Kingdom	28	Prospective	October 2012 through September 2014	All	Methylene blue	Cervical	Laparoscopic	Complete pelvic and paraaortic LND	Ultrastaging
Lelievre et al, 2004[43]	France	12	Prospective	January 2002 through December 2002	All	Methylene blue	Cervical	Laparoscopic	Complete pelvic LND, para-aortic LND if pelvic metastasis on intraoperative frozen SLN	H&E, IHC, ultrastaging
Li et al, 2009[44]	China	31	NR	September 2004 through February 2007	All	Tc-99m and methylene blue	Uterine	Open	Complete pelvic LND, selective paraaortic LND	H&E
Lopes et al, 2007[45]	Brazil	40	Prospective	February 2002 through December 2005	All	Patent blue	Uterine	Open	Selective pelvic and paraaortic LND	H&E, IHC, ultrastaging
Lopez-De la Manzanara et al, 2014[46]	Spain	50	Prospective	September 2011 through December 2013	All	Tc-99m	Cervical	Laparoscopic	Complete pelvic LND, selective paraaortic LND	H&E, ultrastaging
Mais et al, 2010[47]	Italy	34	Prospective	NR	All	Tc-99m and patent blue	Cervical	Laparoscopic	Complete pelvic LND, selective paraaortic LND	H&E, IHC, ultrastaging
Mosgaard et al, 2013[54]	Denmark	32	Prospective	October 2005 through December 2008	Adenocarcinoma	Tc-99m and blue dye	Uterine	Open	Complete pelvic and paraaortic LND	H&E, IHC, ultrastaging
Mucke et al, 2014[48]	Germany	31	Prospective	August 2008 through April 2012	All	Tc99m with or without blue dye	Uterine	Laparoscopic	Complete pelvic and paraaortic LND	H&E, IHC, ultrastaging
Naaman et al, 2016[64]	Israel	53	Retrospective	January 2013 through November 2014	All	ICG	Cervical	Laparoscopic	Complete pelvic LND or Memorial Sloan Kettering algorithm	H&E, IHC, ultrastaging
Niikura et al, 2013[49]	Japan	100	NR	June 2001 through December 2012	All	Tc-99m and blue dye	Cervical and Uterine	Open	Complete pelvic and paraaortic LND	H&E, IHC, ultrastaging

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TABLE 2
Characteristics of included studies *(continued)*

Author, year	Country	Study size	Study method	Time period	Cancer histology	Tracer used	Injection site	Route of surgery	Reference standard	Pathology assessment
Paley et al, 2016[50]	United States	123	Prospective	March 2012 through May 2015	All	ICG	Cervical	Robotic	Pelvic and paraaortic LND if serous, clear cell, or carcinosarcoma histology preoperative, tumor size >2 cm, >50% myometrial invasion, grade 3 histology, suspicious nonsentinel pelvic or paraaortic lymph nodes, positive SLN on frozen	H&E, ultrastaging
Pandit-Taskar et al, 2010[51]	United States	40	Prospective	NR	NR	Tc-99m and patent blue	Cervical	Open	Complete pelvic LND, selective paraaortic LND	NR
Papadia et al, 2016[52]	Switzerland	75	Prospective	December 2012 through September 2015	All	Tc-99m	Cervical	Laparoscopic	Pelvic LND unless type I well differentiated <50% myometrial invasion, paraaortic LND if type 2 or type 1 poorly differentiated, or >50% invasion	H&E, IHC, ultrastaging
Pelosi et al, 2003[53]	Italy	16	NR	February 2001 through April 2002	Adenocarcinoma	Tc-99m	Cervical	Laparoscopic	Complete pelvic LND, selective paraaortic LND	H&E, IHC, ultrastaging
Perrone et al, 2008[68]	Italy	40	Prospective	January 2001 through March 2007	All	Tc-99m and blue dye	Cervical	Laparoscopic	Complete pelvic LND, paraaortic LND in high-grade EC or suspicious SLN	H&E, IHC, ultrastaging
Raimond et al, 2014[69]	France	156	Retrospective	Janu 2000 through December 2012	Endometrioid, adenocarcinoma, adenosquamous	Tc-99m	Cervical	Open	Complete pelvic LND, selective paraaortic LND	H&E, IHC, ultrastaging
Raspagliesi et al, 2004[55]	Italy	18	Prospective	NR	Adenocarcinoma	ICG	Uterine	Open	Pelvic LND if myometrial invasion >50% or grade 3 tumor, paraaortic LND if serous papillary or clear cell	H&E, ultrastaging
Robova et al, 2009[56]	Czech Republic	91	Prospective	January 2004 through December 2007	Endometrioid, adenosquamous	Methylene blue +/- Tc-99m	Uterine	Open	Complete pelvic and para-aortic LND	H&E, ultrastaging
Rossi et al, 2013[76]	United States	29	Prospective	November 2011 through December 2012	All	Blue dye or ICG with or without Tc-99m	Cervical	Robotic	Complete pelvic and paraaortic LND	H&E, ultrastaging

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(continued)

TABLE 2
Characteristics of included studies *(continued)*

Author, year	Country	Study size	Study method	Time period	Cancer histology	Tracer used	Injection site	Route of surgery	Reference standard	Pathology assessment
Sawicki et al, 2015[57]	Poland	188	Prospective	February 2011 through August 2014	All	Tc-99m	Cervical and uterine	Open	Pelvic and paraaortic LND if grade 3, >50% myometrial invasion or cervical involvement; not if morbid obesity, advanced age, or poor general status	H&E
Schiavone et al, 2016[70]	United States	48	Prospective	January 1998 through August 2014	Uterine carcinosarcoma	Blue dye or indocyanine green	Cervical	Laparoscopic	Surgeon-discretion LND or Memorial Sloan Kettering algorithm	H&E, IHC, ultrastaging
Solima et al, 2012[59]	Italy	80	Prospective	January 2005 through December 2010	All	ICG or isosulfan blue	Uterine	Open	Complete pelvic or paraaortic LND if endometrioid stage IB+, clear cell, or serous carcinoma	H&E, IHC, ultrastaging
St Clair et al, 2016[28]	United States	643	Prospective	September 2005 through December 2011	All	Tc-99m	Cervical	Robotic	Memorial Sloan Kettering algorithm	H&E, IHC, ultrastaging
Tanner et al, 2015[12]	United States	111	Prospective	September 2012 through November 2014	All	Tc-99m and patent blue	Cervical	Robotic	Complete pelvic and paraaortic LND if grade 3 endometrioid or type II cancer, positive SLN	H&E
Torné et al, 2013[11]	Spain	74	Prospective	March 2006 through March 2011	All	Tc-99m and patent blue	Uterine	Laparoscopic	Complete pelvic and paraaortic LND	H&E, IHC, ultrastaging
Touhami et al, 2015[60]	Canada	268	NR	November 2010 through November 2013	All	Patent blue	Cervical	Laparoscopic	Complete pelvic LND, paraaortic lymph node sampling	H&E, IHC, ultrastaging
Touhami et al, 2015[61]	Canada	19	Retrospective	April 2005 through March 2014	Uterine serous carcinoma	Patent blue	Cervical	Open	Complete pelvic LND, paraaortic if type 2, positive SLN, or preoperative radiological assessment suspicious	NR
Valha et al, 2015[62]	Czech Republic	18	Prospective	June 2012 through February 2014	NR	Tc-99m, patent blue	Uterine	Open	Complete pelvic and paraaortic LND	H&E, IHC, ultrastaging
Vidal et al, 2013[63]	France	66	Retrospective	May 2003 through June 2009	All	Patent blue	Cervical	Laparoscopic	Complete pelvic LND, paraaortic if positive or paraaortic SLN	H&E, IHC, ultrastaging

CT, computed tomography; *EC*, endometrial cancer; *H&E*, hematoxylin and eosin; *ICG*, indocyanine green; *IHC*, immunohistochemistry; *LND*, lymphadenectomy; *MRI*, magnetic resonance imaging; *NR*, not reported; *PET*, positron emission tomography; *SLN*, sentinel lymph node; *Tc-99m*, technecium-99.

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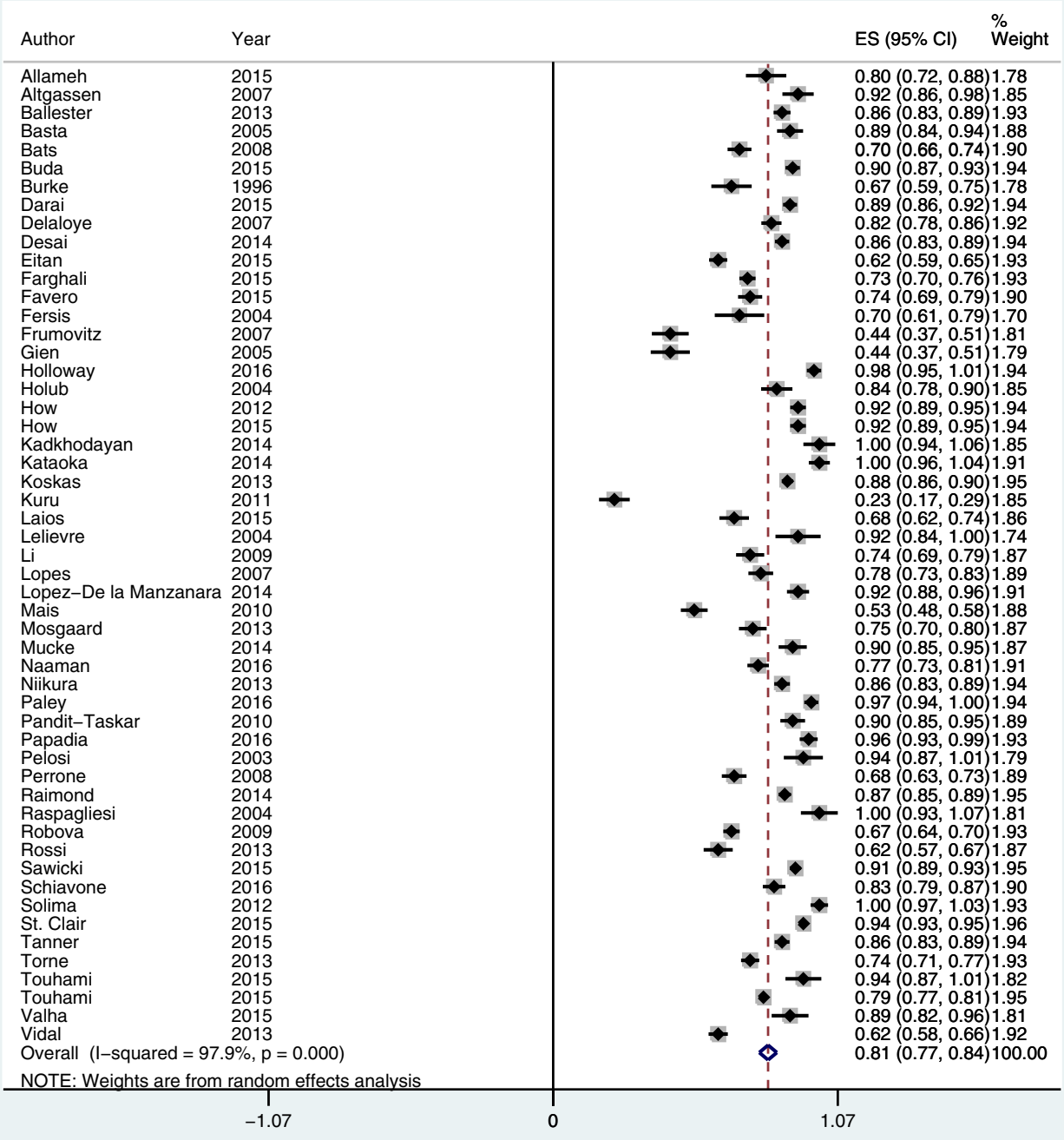
FIGURE 2
Overall SLN detection rate



CI, confidence interval; *SLN*, sentinel lymph node.

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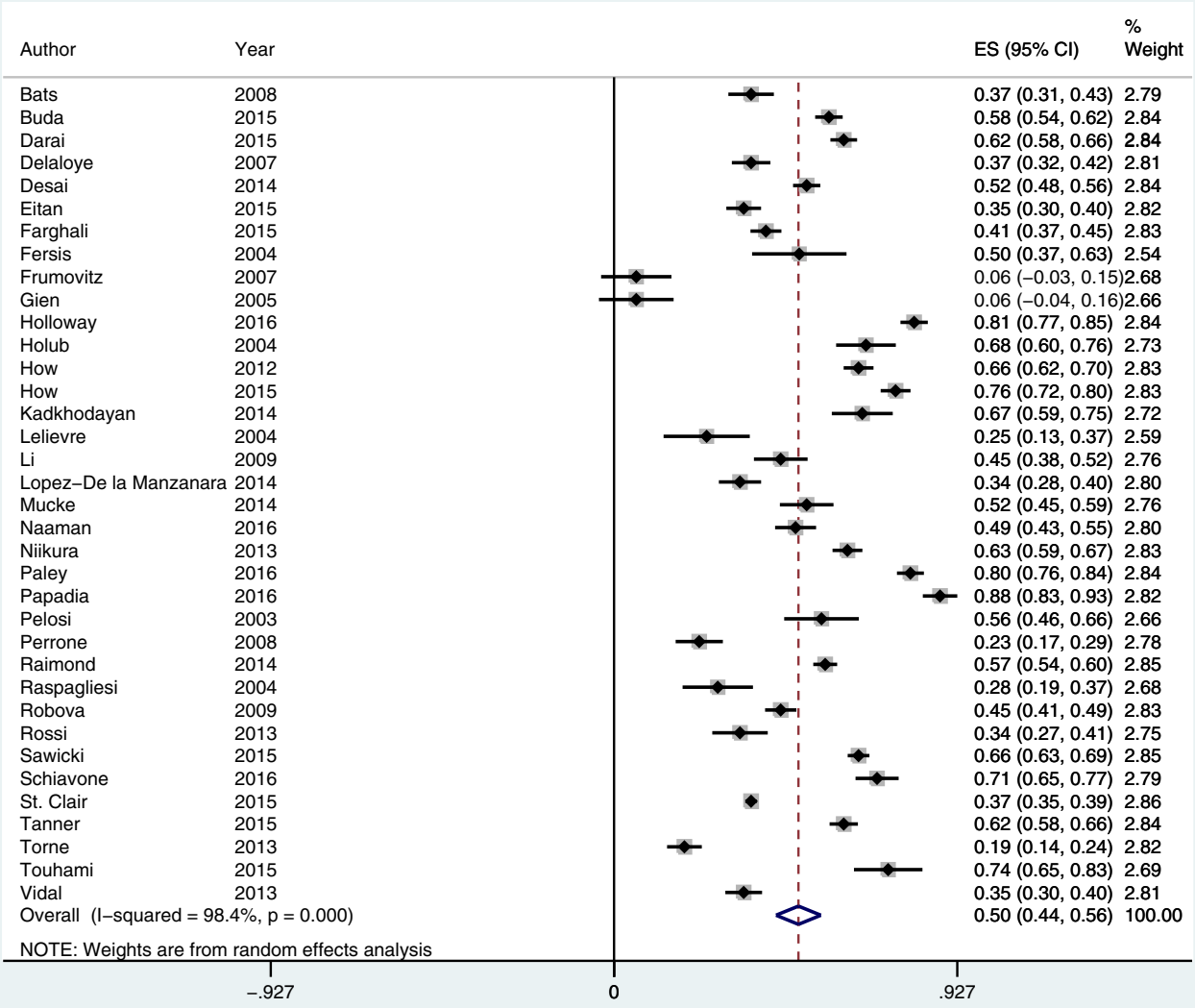
The mean age of the patients was 62 years (95% confidence interval [CI], 61–64) (49 studies), and mean BMI was 30 kg/m^2 (95% CI, 29–31) (35 studies). Forty-two percent of SLN cases were performed by laparotomy (95% CI, 28–56), 41% by laparoscopy (95% CI, 27–54), and 17% with robotic assistance (95% CI, 7–28). Forty-four percent of SLN cases used dye alone to detect SLNs (95% CI, 30–57), 44% used a dye and a radiotracer (95% CI, 30–57), and 12% used a radiotracer alone (95% CI, 4–22). When dye was utilized, a blue dye was used more frequently than indocyanine

FIGURE 3
Bilateral SLN detection rate



CI, confidence interval; *SLN*, sentinel lymph node.

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green (88% vs 12%), and patent blue was the most common blue dye used. Most studies used cervical injection techniques for dye and/or radiotracer distribution (58%, 95% CI, 44−71), 9% used cervical and uterine injection (95% CI, 1−17), and 33% used uterine injection alone (95% CI, 23−51).

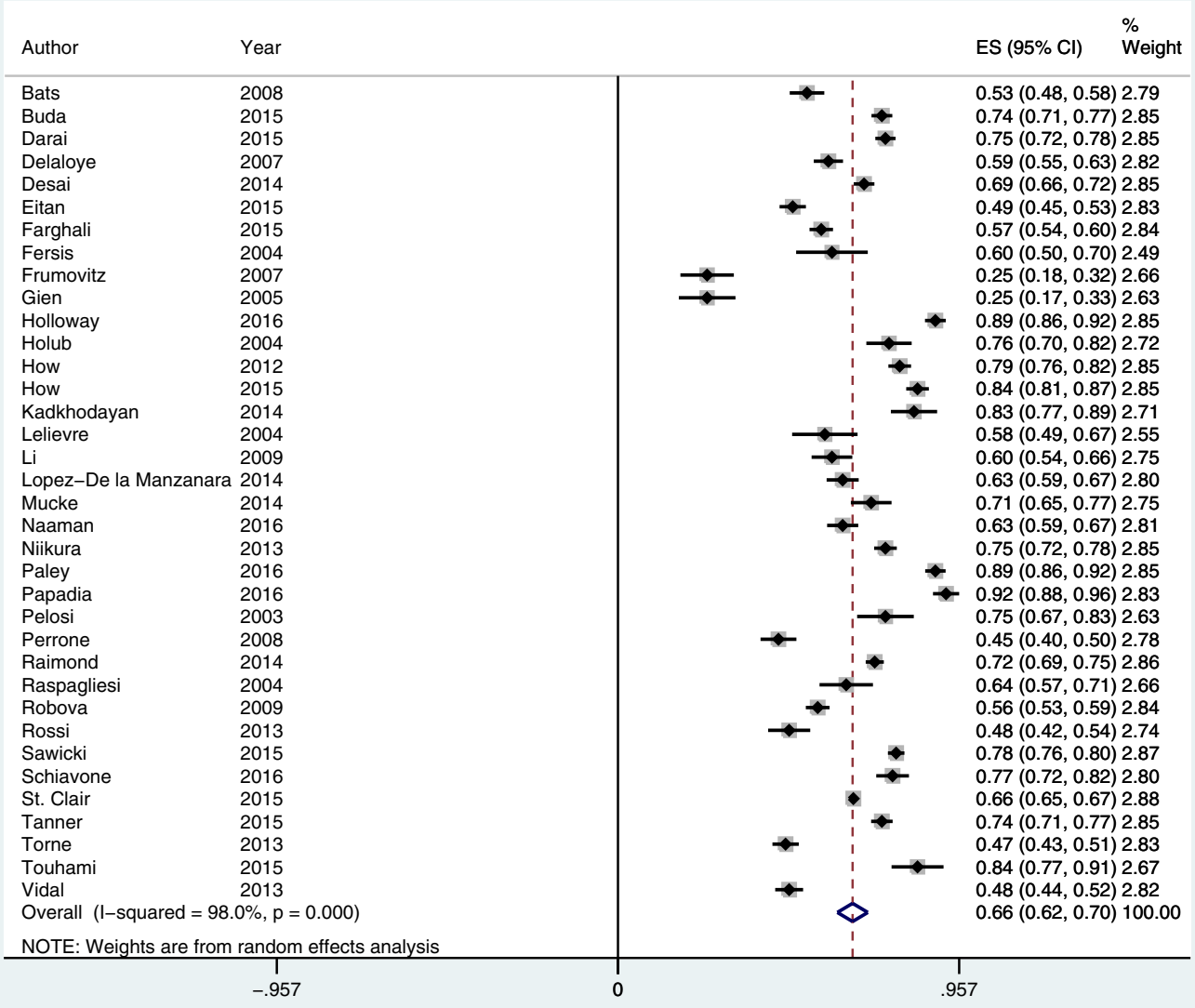
SLN detection rates

The SLN detection rate ranged from 23% to 100%, with a pooled average of 81% (95% CI, 77−84, 53 studies) (Figure 2). The bilateral detection rate ranged from 6% to 88%, with a pooled average of 50% (95% CI, 44−56, 36 studies) (Figure 3). The side-specific detection rate ranged from 25% to 92%, with a pooled average of 66% (95% CI, 62−70, 36 studies). The paraaortic detection rate ranged from 0% to 84%, with a pooled average of 17% (95% CI, 11−23, 41 studies) (Figure 4). The mean number of SLNs detected per mapped patient was 2.9 (95% CI, 2.5−3.3, range, 1−8, 49 studies).

Factors associated with SLN detection rates

Nonendometrioid histology (eg, serous, carcinosarcoma, and clear cell) was not associated with any significant differences in SLN detection compared with endometrioid histology ($P = .515$) (Table 3). Additionally, study size, average patient BMI $\geq$30 kg/m^2, tumor grade, and surgical approach were not significantly associated with detection rates. Cervical injection was associated with significantly higher rates of

FIGURE 4
Paraaortic SLN detection rate



CI, confidence interval; *SLN*, sentinel lymph node.

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bilateral SLN detection (56% vs 33%, $P = .003$) compared with uterine injection. However, cervical injection was associated with a significantly lower rate of paraaortic SLN detection than uterine injection (7% vs 27%, $P = .001$). Use of indocyanine green was associated with higher rates of bilateral SLN detection (75% vs 51%, $P = .008$) than blue dye. Preoperative lymphoscintigraphy and combined use of a radiotracer and dye were associated with higher rates of overall SLN detection (86% vs 76%, $P = .016$, and 87% vs 78%, $P = .008$, respectively) but showed no significant difference in rates of bilateral or paraaortic SLN detection.

SLN diagnostic accuracy

The pooled sensitivity of sentinel lymph node detection of metastatic disease was 96% (95% CI, 93–98, 47 studies) (Figure 5). The pooled negative predictive value was 99.7%. In cases with SLN metastases, SLNs were the only positive nodes identified 66% of the time (22 studies).

In cases with positive SLNs, these were macrometastases in 29%, micrometastases in 39%, and isolated tumor cells in 32% of cases (14 studies). There was no significant difference in the sensitivity of SLN detection of metastases by study size, preoperative lymphoscintigraphy, injection site, radiotracer and/or dye used, intraoperative frozen section, or use of ultrastaging (Appendix Table 2).

TABLE 3
Univariate meta-regression of SLN detection rate and study characteristics

Variables	Studies, n	Overall detection, % (95% CI)	*P* value	Bilateral detection, % (95% CI)	*P* value	Para-aortic detection, % (95% CI)	*P* value
Study characteristics							
Study size							
≥ 30 patients	53	83.2 (79.8–86.6)	.101	41.5 (25.7–57.2)	.148	16.0 (9.2–22.7)	.710
<30 patients		75.4 (66.1–84.7)		52.8 (45.9–59.6)		18.7 (4.90–32.6)	
Patient and tumor characteristics							
Patient BMI							
Average BMI ≥30 kg/m^2	35	82.2 (75.6–88.9)	.728	49.2 (38.7–59.7)	.437	16.5 (7.1–26.0)	.863
Average BMI <30 kg/m^2		84.3 (80.2–88.5)		55.8 (45.1–66.5)		17.8 (9.5–26.1)	
Tumor grade							
Grade 1	5[a]	78.4 (61.7–95.0)	.941	N/A	NR	N/A	NR
Grade II–III		77.6 (64.7–90.4)		N/A		N/A	
Tumor histology							
Endometrioid	7[a]	81.6 (72.9–90.2)	.598	N/A	NR	N/A	NR
Nonendometrioid		75.8 (59.3–92.4)		N/A		N/A	
SLN technique characteristics							
Surgical approach							
Robotic	50	85.6 (79.0–92.2)	.266	46.2 (39.2–53.1)	.133	12.8 (4.0–21.6)	.616
Laparotomy, laparoscopy		79.0 (75.2–82.9)		58.2 (44.6–71.7)		17.9 (10.8–25.0)	
Preoperative lymphoscintigraphy							
Yes	53	86.6 (83.1–90.2)	0.016	51.4 (42.6–60.1)	0.603	14.1 (8.1–20.2)	0.408
No		76.2 (71.0–81.3)		47.7 (39.4–56.0)		19.7 (9.2–30.3)	
Injection site							
Cervical	52[a]	80.2 (75.7–84.8)	.622	55.5 (48.7–62.3)	.003	6.7 (3.4–10.1)	.001
Uterine		77.6 (71.2–84.1)		33.0 (24.2–41.9)		26.8 (15.3–38.2)	
Radiotracer used							
Yes	53[a]	84.9 (81.5–88.4)	.101	48.0 (40.4–55.6)	.165	14.9 (8.3–21.4)	.458
No		78.3 (73.4–83.1)		57.2 (48.6–65.8)		10.5 (4.1–16.9)	
Dye and radiotracer used							
Yes	53[a]	87.7 (84.4–90.9)	.015	51.2 (43.9–58.5)	.748	11.6 (4.7–18.5)	.674
No		77.7 (73.3–82.1)		53.2 (44.8–61.6)		14.0 (7.5–20.5)	
Dye tracer							
Indocyanine green	53[a]	90.3 (84.8–95.0)	.125	74.6 (65.9–83.3)	.008	13.5 (0–29.5)	.771
Blue dye		81.0 (77.8–84.3)		50.5 (45.5–55.5)		10.7 (5.7–15.7)	
Intraoperative frozen section	42						
Yes		90.4 (86.8–94.0)	.029	63.6 (52.9–74.4)	.030	9.4 (2.2–16.6)	.292
No		78.3 (73.8–82.8)		45.4 (37.9–53.0)		16.3 (8.4–24.2)	

Average refers to mean or median, whichever was reported in the study.

BMI, body mass index; *CI*, confidence interval; *N/A*, not applicable (eg, only 1 study reporting detection rates comparing subgroup characteristics); *NR*, not reported; *SLN*, sentinel lymph node.

[a] Includes 3 studies comparing ICG and blue dye,[12,22,28] 2 comparing radiotracer with/without dye,[57,67] 3 comparing cervical vs uterine injection,[41,49,76] 5 comparing grade 1 vs grades 2–3,[22,27,29,37,64] and 5 comparing endometrioid and non-endometrioid histology.[22,27,29,37,64]

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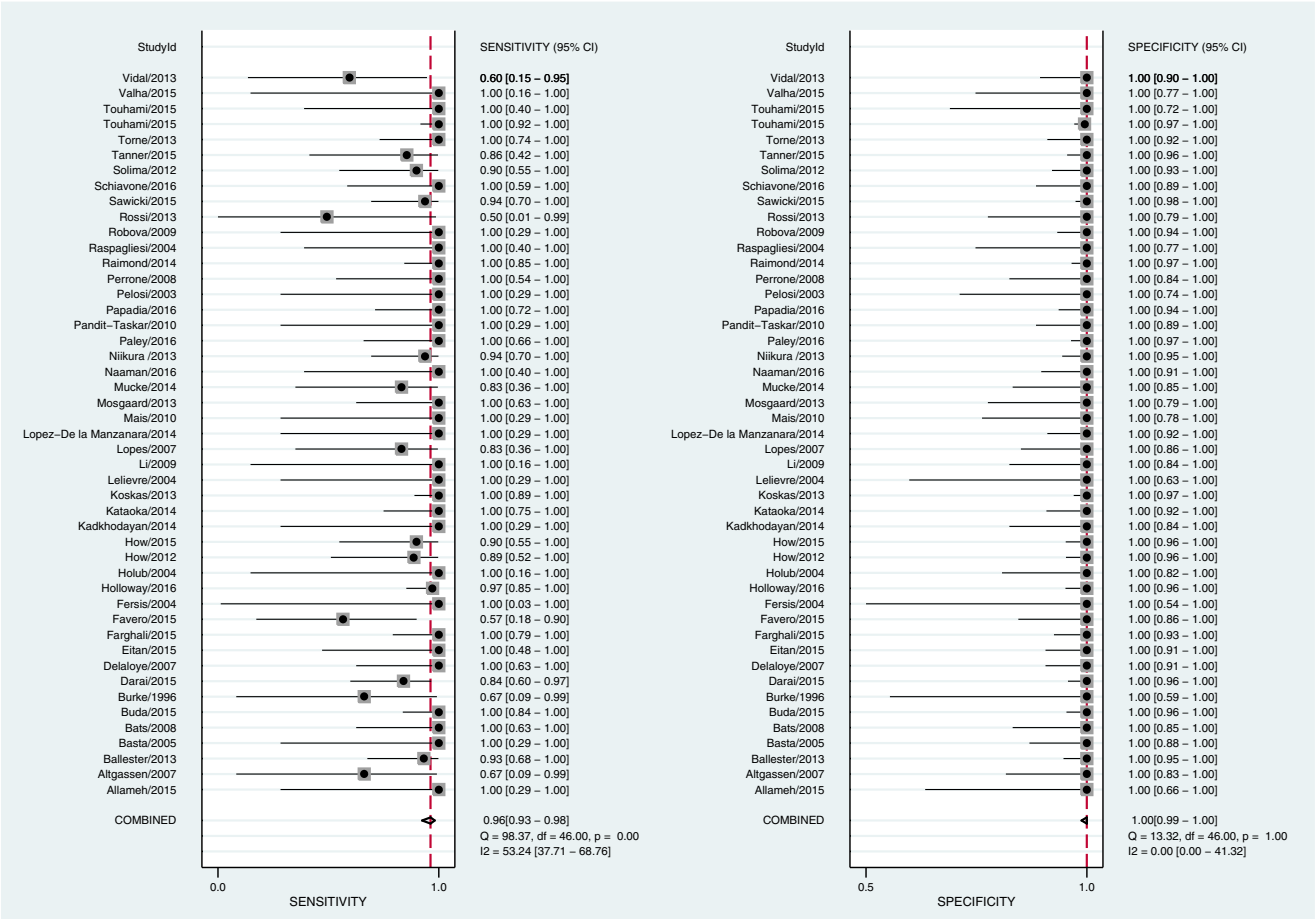
FIGURE 5
Sensitivity of SLN detection



CI, confidence interval; *SLN*, sentinel lymph node.

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Operating time and adverse events

The additional operating time for SLN mapping compared with LND ranged from 3 to 40 minutes (6 studies).[23,28,35,43,44,55] One study reported lower blood loss with SLN mapping compared with LND.[52]

In the 24 studies reporting on adverse events (n = 1390 women), 1 patient had an anaphylactic reaction to the blue dye[34]; no other serious adverse events related to SLN mapping were reported.[11,21,24,26,29,30,33,34,36-38,41,44,46,48,50,52,54,55,59,64,66-68] Seven patients experienced serious complications related to completion LND after SLN mapping (5 lymphoceles, 2 vascular injuries).[30,36,50,55-59] None of the studies reporting adverse events reported long-term outcomes comparing the risk of lymphedema in patients undergoing either SLN mapping alone or in comparison with complete lymphadenectomy.

Association of SLN mapping with treatment and survival

Four of the 5 studies comparing SLN mapping with standard of care (ie, pelvic and aortic lymphadenectomy by regional endometrial cancer guidelines) found that SLN mapping increased the use of adjuvant therapy (Table 4).[24,35,65,69,70] The sole study in which adjuvant therapy use did not increase with the performance of SLN mapping was in patients with uterine carcinosarcoma.

Three of 3 studies with a median follow-up of 17−50 months found no difference in the progression-free survival between patients with successful and failed SLN mapping.[65,69,70] Three of 3 studies with a median follow-up of 16−32 months found no difference in the progression-free survival for patients who underwent SLN mapping compared with patients who underwent primary LND.[24,33,53,71]

Comment

In this systematic review and meta-analysis of 55 studies including 4915 women investigating the utility of SLN mapping for endometrial cancer, the following 3 primary findings emerged: (1) the pooled overall SLN detection rates were relatively high at 81% (95% CI, 77−84) with 51% (95% CI, 45−54) bilateral nodal detection; (2) the pooled sensitivity of SLN mapping for the

TABLE 4
Associations between SLN mapping, endometrial cancer treatment, and survival

Study	Study size	SLN reference standard	Comparison group	Follow-up time (range)	Treatment	Recurrence-free survival
Darai, 2015[1]	125	Complete pelvic LND, paraaortic LND if positive intraoperative histology or after definitive histology	None	50 (5–77 mo)	Chemotherapy more frequent with positive SLN (50% vs 12.5%, $P = .009$)	84.7% No difference with or without SLN detection
Eriksson et al, 2016[65]	642 (SLN), 493 (LND)	Memorial Sloan Kettering algorithm (LND if failed mapping, surgeon discretion paraaortic LND)	Complete pelvic and paraaortic LND	36 mo	Adjuvant therapy more frequent in SLN cohort (27.1% vs 10.8%, $P < .001$)	94.9% (SLN), 96.8% (LND) No difference
Ferraioli et al, 2014[71]	10 (relapse), 20 (controls)	Pelvic LND and paraaortic by guidelines	Endometrial cancer after SLN mapping and LND without recurrence matched on age, FIGO stage, and histopathology	21.9 (8–45 mo)	—	No difference in recurrence with or without SLN detection
Frumovitz et al, 2007[33]	18	Complete pelvic and paraaortic LND	None	32.4 (1–45 months)	—	Failed SLN detection in 3/3 patients with recurrence
Holloway et al, 2016[35]	119 (SLN), 661 (LND)	Pelvic LND if cancer >1 cm, myometrial invasion >one third, or high-grade histology; paraaortic LND if grade 3 tumor/type 2 histology, any depth of invasion, positive lymph nodes on frozen section, low-grade tumor with middle or outer-third myometrial invasion	Non–SLN-mapped patients with same criteria for pelvic and/or paraaortic LND	—	Adjuvant chemotherapy and radiation more frequent in SLN cohort (28.6% vs 16.3%, $P < .003$)	—
Pelosi et al, 2003[53]	16	Complete pelvic LND, selective paraaortic LND	—	16.7 (4–22 mo)	—	No recurrence
Raimond et al, 2014[69]	156 (SLN), 115 (LND)	Complete pelvic LND, selective paraaortic LND	Complete pelvic LND, selective paraaortic LND	60 mo	Adjuvant therapy more frequent in SLN cohort (22% vs 13%, $P < .001$)	88.4% (SLN), 84.2% (LND) No difference in mean time to recurrence (16.6 vs 17 mo)
Schiavone et al, 2016[70]	48 (SLN), 88 (LND)	Memorial Sloan Kettering algorithm (LND if failed mapping, surgeon discretion paraaortic LND)	Complete pelvic and paraaortic LND	16.2 (1–77 mo, SLN), 62 (3–176, LND)	No difference in adjuvant therapy (92% vs 90%, $P = .15$)	3 year progression-free survival: 23 mo (SLN), 23.2 (LND)

FIGO, International Federation of Gynecology and Obstetrics; *LND*, lymphadenectomy; *SLN*, sentinel lymph node.

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detection of lymphatic metastases was high at 96% (95% CI, 92–98); (3) and the use of cervical injection with combination blue dye and radiotracer or indocyanine green dye alone increased the overall SLN detection rate.

Notably, we identified a higher pooled detection rate and a higher pooled sensitivity for the detection of lymphatic metastases than in prior meta-analyses.[9,14,72] Our analysis suggests that the SLN detection rate and sensitivity in endometrial cancer approaches those observed in breast cancer and melanoma, malignancies in which SLN mapping is the standard of care.[7] These improvements may reflect gynecological surgeons' growing experience with SLN mapping and increased utilization of more innovative dye and detection techniques.

Additionally, these data provide the rationale to consider SLN mapping as an alternative standard of care in select

women with apparent early-stage endometrial cancer, especially when SLN mapping is performed by experienced, high-volume endometrial cancer surgeons.

SLN mapping with indocyanine green demonstrated high rates of bilateral mapping.[73,74] Given that other dye types and the combination of dye and radiotracer demonstrated high overall SLN detection rates but did not significantly improve bilateral mapping rates, indocyanine green could be considered as the preferred mapping agent for SLN mapping of endometrial cancer.

Additionally, the use of indocyanine green has several advantages compared with radiocolloids, including less pain with injection, lower cost, fewer adverse effects, and quick transcutaneous real-time visualization.[15,73] Preoperative lymphoscintigraphy did not significantly increase bilateral or paraaortic detection rates, but there were a variety of methods (eg, different radiotracers and imaging modalities) and time delays used. Further research is needed to explore the possible benefits of preoperative lymphoscintigraphy in surgical planning for endometrial cancer, especially given the potential costs of this technique.

Cervical injection increased bilateral SLN detection rates, but we did not observe that cervical injection increases paraaortic detection as suggested in a prior review.[10] This, however, may not have a substantial impact on patient outcomes. Whereas paraaortic metastases are a poor prognostic indicator, the incidence of paraaortic metastases in the absence of pelvic metastases is exceedingly low (1−5%), especially in women with low-grade endometrial cancer. If paraaortic SLN mapping fails, pelvic SLN mapping is likely sufficient in most patients, given the low likelihood of isolated paraaortic metastases in this setting.

Interestingly, we did not identify a significant difference in sensitivity of SLN mapping with ultrastaging, despite the large number of studies (n = 44) utilizing this nodal evaluation technique. This may reflect the limited experience and lack of uniform ultrastaging guidelines in endometrial cancer. Alternatively, the studies included in our meta-analysis may not be powered to ascertain the impact of ultrastaging of SLNs. Because ultrastaging is a costly and time-consuming lymphatic assessment strategy, further research is needed regarding the value of this approach and the impact of the micrometastases and isolated tumor cells identified through ultrastaging on endometrial cancer prognosis.[75]

The controversy surrounding the value of ultrastaging in endometrial cancer reflects the broader uncertainty regarding the value of lymphatic assessment in endometrial cancer. Although prospective randomized trial data demonstrate the limited impact of lymphadenectomy on survival, retrospective data suggest a therapeutic benefit of lymphadenectomy in high-risk patients.[3,4] As such, the true value of SLN mapping may be to allow the tailoring of adjuvant therapy for high-risk patients while also minimizing the risk of harm that occurs with full lymphadenectomy.

Given remaining uncertainties, the assessment of lymph nodes continues to be an important aspect of surgical staging in select women with endometrial cancer and is recognized by the National Comprehensive Cancer Network as a procedure that provides important prognostic information that may alter adjuvant treatment decisions.[13] Our data showed that SLN mapping led to upstaging of a number of women and helped tailor the subsequent receipt of additional therapy, such as chemotherapy and/or radiation, known to improve survival.[4] We were underpowered to detect any differences in survival associated with SLN vs other strategies of lymph node assessment.

Strengths and limitations

Our systematic review and meta-analysis has limitations. We excluded non-English studies. We did not have individual patient data with which to analyze the impact of BMI, which may have biased BMI results toward the null. We found evidence of a significant small-study effect within our meta-analyses and in publication bias (data available on request). Nonetheless, although there was substantial variation between studies, this heterogeneity was largely explained by the SLN mapping variables that were included and controlled for in our meta-regressions.

Finally, an area of great interest that is notably absent from the reviewed literature is the lymphedema risk in women with endometrial cancer who undergo SLN mapping. Lymphedema rates after complete pelvic and aortic LND may be as high as 20% in this setting.

One of the potential advantages of SLN mapping is the reduced disruption of lymphatic channels compared with more comprehensive lymphadenectomy. In the breast cancer literature, replacing axillary lymphadenectomy with SLN mapping resulted in a two thirds reduction in the risk of lymphedema in the affected extremity.[7] Future studies on SLN mapping in endometrial cancer should consider assessment of lymphedema in the postoperative and surveillance periods. We await the results of a prospective trial evaluating the baseline lymphedema risk with lymphadenectomy in endometrial cancer (https://clinicaltrials.gov/ct2/show/NCT00956670).

Conclusions and implications

In this contemporary systematic review and meta-analysis of 55 studies, sentinel lymph node mapping successfully identified nodal metastases in the vast majority of the women with endometrial cancer, with high sensitivity for the detection of lymphatic metastases. Cervical injection techniques and the use of indocyanine green dye likely increase bilateral sentinel node detection rates. Sentinel lymph node mapping is emerging as an alternative standard of care in the staging and management of select women with endometrial cancer. ■

REFERENCES

1. Morice P, Leary A, Creutzberg C, Abu-Rustum N, Darai E. Endometrial cancer. Lancet (London, England) 2016;387:1094-108.
2. Sharma C, Deutsch I, Lewin SN, et al. Lymphadenectomy influences the utilization of adjuvant radiation treatment for endometrial cancer. Am J Obstet Gynecol 2011;205:562.e1-9.
3. Frost JA, Webster KE, Bryant A, Morrison J. Lymphadenectomy for the management of

endometrial cancer. Cochrane Database Syst Rev 2015;9:CD007585.
4. Todo Y, Kato H, Kaneuchi M, Watari H, Takeda M, Sakuragi N. Survival effect of para-aortic lymphadenectomy in endometrial cancer (SEPAL study): a retrospective cohort analysis. Lancet (London, England) 2010;375:1165-72.
5. Fotopoulou C, Kraetschell R, Dowdy S, et al. Surgical and systemic management of endometrial cancer: an international survey. Arch Gynecol Obstet 2015;291:897-905.
6. Abu-Rustum NR. Sentinel lymph node mapping for endometrial cancer: a modern approach to surgical staging. J Natl Compr Canc Netw 2014;12:288-97.
7. Mansel RE, Fallowfield L, Kissin M, et al. Randomized multicenter trial of sentinel node biopsy versus standard axillary treatment in operable breast cancer: the ALMANAC Trial. J Natl Cancer Inst 2006;98:599-609.
8. Niebling MG, Pleijhuis RG, Bastiaannet E, Brouwers AH, van Dam GM, Hoekstra HJ. A systematic review and meta-analyses of sentinel lymph node identification in breast cancer and melanoma, a plea for tracer mapping. Eur J Surg Oncol 2016;42:466-73.
9. Kang S, Yoo HJ, Hwang JH, Lim M-C, Seo S-S, Park S-Y. Sentinel lymph node biopsy in endometrial cancer: meta-analysis of 26 studies. Gynecol Oncol 2011;123:522-7.
10. Cormier B, Rozenholc AT, Gotlieb W, Plante M, Giede C. Sentinel lymph node procedure in endometrial cancer: a systematic review and proposal for standardization of future research. Gynecol Oncol 2015;138:478-85.
11. Torné A, Pahisa J, Vidal-Sicart S, et al. Transvaginal ultrasound-guided myometrial injection of radiotracer (TUMIR): a new method for sentinel lymph node detection in endometrial cancer. Gynecol Oncol 2013;128:88-94.
12. Tanner EJ, Sinno AK, Stone RL, Levinson KL, Long KC, Fader AN. Factors associated with successful bilateral sentinel lymph node mapping in endometrial cancer. Gynecol Oncol 2015;138:542-7.
13. Fayna Ferkle N, Nicole McMillian P, Jillian Scavone M, et al. NCCN guidelines index uterine neoplasms TOC discussion NCCN guidelines, version 2. 2016 panel members uterine neoplasms MD/liaison, Dana-Farber/Brigham and Women's Cancer Center. Available at: https://www.nccn.org/professionals/physician_gls/pdf/uterine.pdf. Accessed May 30, 2016.
14. Ansari M, Rad MAG, Hassanzadeh M, et al. Sentinel node biopsy in endometrial cancer: systematic review and meta-analysis of the literature. Eur J Gynaecol Oncol 2013;34:387-401.
15. Zhang X, Li Y, Zhou Y, et al. Diagnostic performance of indocyanine green-guided sentinel lymph node biopsy in breast cancer: a meta-analysis. PLoS One 2016;11:e0155597.
16. Dwamena BA. Midas: a program for meta-analytical integration of diagnostic accuracy studies in Stata. Ann Arbor (MI): StatCorp; 2007.
17. Allameh T, Hashemi V, Mohammadizadeh F, Behnamfar F. Sentinel lymph node mapping in early stage of endometrial and cervical cancers. J Res Med Sci 2015;20:169-73.
18. Altgassen C, Pagenstecher J, Hornung D, Diedrich K, Hornemann A. A new approach to label sentinel nodes in endometrial cancer. Gynecol Oncol 2007;105:457-61.
19. Ballester M, Naoura I, Chereau E, et al. Sentinel node biopsy upstages patients with presumed low- and intermediate-risk endometrial cancer: results of a multicenter study. Ann Surg Oncol 2013;20:407-12.
20. Basta A, Pityński K, Basta P, Hubaiewska-Hoła A, Opławski M, Przeszlakowski D. Sentinel node in gynaecological oncology. Reports Pract Oncol Radiother 2005;10:91-4.
21. Bats A-S, Clement D, Larousserie F, et al. Does sentinel node biopsy improve the management of endometrial cancer? Data from 43 patients. J Surg Oncol 2008;97:141-5.
22. Buda A, Crivellaro C, Elisei F, et al. Impact of indocyanine green for sentinel lymph node mapping in early stage endometrial and cervical cancer: comparison with conventional radiotracer Tc and/or blue dye. Ann Surg Oncol 2016;23:2183-91.
23. Burke TW, Levenback C, Tornos C, Morris M, Wharton JT, Gershenson DM. Intraabdominal lymphatic mapping to direct selective pelvic and paraaortic lymphadenectomy in women with high- risk endometrial cancer: results of a pilot study. Gynecol Oncol 1996;62:169-73.
24. Daraï E, Dubernard G, Bats A-S, et al. Sentinel node biopsy for the management of early stage endometrial cancer: long-term results of the SENTI-ENDO study. Gynecol Oncol 2015;136:54-9.
25. Delaloye J-F, Pampallona S, Chardonnens E, et al. Intraoperative lymphatic mapping and sentinel node biopsy using hysteroscopy in patients with endometrial cancer. Gynecol Oncol 2007;106:89-93.
26. Desai PH, Hughes P, Tobias DH, et al. Accuracy of robotic sentinel lymph node detection (RSLND) for patients with endometrial cancer (EC). Gynecol Oncol 2014;135:196-200.
27. Eitan R, Sabah G, Krissi H, et al. Robotic blue-dye sentinel lymph node detection for endometrial cancer—factors predicting successful mapping. Eur J Surg Oncol 2015;41:1659-63.
28. St Clair CM, Eriksson AGZ, Ducie JA, et al. Low-volume lymph node metastasis discovered during sentinel lymph node mapping for endometrial carcinoma. Ann Surg Oncol 2016;23:1653-9.
29. Farghali MM, Allam IS, Abdelazim IA, et al. Accuracy of sentinel node in detecting lymph node metastasis in primary endometrial carcinoma. Asian Pac J Cancer Prev 2015;16:6691-6.
30. Favero G, Pfiffer T, Ribeiro A, et al. Laparoscopic sentinel lymph node detection after hysteroscopic injection of technetium-99 in patients with endometrial cancer. Int J Gynecol Cancer 2015;25:423-30.
31. Ferraioli D, Chopin N, Beurrier F, Carrabin N, Buenerd A, Mathevet P. The incidence and clinical significance of the micrometastases in the sentinel lymph nodes during surgical staging for early endometrial cancer. Int J Gynecol Cancer 2015;25:673-80.
32. Fersis N, Gruber I, Relakis K, et al. Sentinel node identification and intraoperative lymphatic mapping. First results of a pilot study in patients with endometrial cancer. Eur J Gynaecol Oncol 2004;25:339-42.
33. Frumovitz M, Bodurka DC, Broaddus RR, et al. Lymphatic mapping and sentinel node biopsy in women with high-risk endometrial cancer. Gynecol Oncol 2007;104:100-3.
34. Gien LT, Kwon JS, Carey MS. Sentinel node mapping with isosulfan blue dye in endometrial cancer. J Obstet Gynaecol Can 2005;27:1107-12.
35. Holloway RW, Gupta S, Stavitzski NM, et al. Sentinel lymph node mapping with staging lymphadenectomy for patients with endometrial cancer increases the detection of metastasis. Gynecol Oncol 2016;141:206-10.
36. Holub Z, Jabor A, Lukac J, Kliment L. Laparoscopic detection of sentinel lymph nodes using blue dye in women with cervical and endometrial cancer. Med Sci Monit 2004;10:CR587-91.
37. How J, Lau S, Press J, et al. Accuracy of sentinel lymph node detection following intraoperative cervical injection for endometrial cancer: a prospective study. Gynecol Oncol 2012;127:332-7.
38. How J, Gotlieb WH, Press JZ, et al. Comparing indocyanine green, technetium, and blue dye for sentinel lymph node mapping in endometrial cancer. Gynecol Oncol 2015;137:436-42.
39. Kadkhodayan S, Shiravani Z, Hasanzadeh M, et al. Lymphatic mapping and sentinel node biopsy in endometrial cancer—a feasibility study using cervical injection of radiotracer and blue dye. Nucl Med Rev 2014;17:55-8.
40. Koskas M, Chereau E, Ballester M, et al. Accuracy of a nomogram for prediction of lymph-node metastasis detected with conventional histopathology and ultrastaging in endometrial cancer. Br J Cancer 2013;108:1267-72.
41. Kuru O, Topuz S, Sen S, Iyibozkurt C, Berkman S. Sentinel lymph node biopsy in endometrial cancer: description of the technique and preliminary results. J Turkish Ger Gynecol Assoc 2011;12:204-8.
42. Laios A, Volpi D, Tullis IDC, et al. A prospective pilot study of detection of sentinel lymph nodes in gynaecological cancers using a novel near infrared fluorescence imaging system. BMC Res Notes 2015;8:608.
43. Lelievre L, Camatte S, Le Frere-belda MA, et al. Sentinel lymph node biopsy in cervix and corpus uteri cancers. Int J Gynecol Cancer 2004;14:271-8.
44. Li B, Wu L, Li X, et al. Sentinel lymph node identification in endometrial cancer. Clin Oncol Cancer Res 2009;6:124-8.

45. Lopes LAF, Nicolau SM, Baracat FF, et al. Sentinel lymph node in endometrial cancer. Int J Gynecol Cancer 2007;17:1113-7.
46. Lopez-De la Manzanara Cano C, Cordero Garcia JM, et al. Sentinel lymph node detection using 99mTc combined with methylene blue cervical injection for endometrial cancer surgical management: a prospective study. Int J Gynecol Cancer 2014;24:1048-53.
47. Mais V, Peiretti M, Gargiulo T, Parodo G, Cirronis MG, Melis GB. Intraoperative sentinel lymph node detection by vital dye through laparoscopy or laparotomy in early endometrial cancer. J Surg Oncol 2010;101:408-12.
48. Mucke J, Klapdor R, Schneider M, et al. Isthmocervical labelling and SPECT/CT for optimized sentinel detection in endometrial cancer: technique, experience and results. Gynecol Oncol 2014;134:287-92.
49. Niikura H, Kaiho-Sakuma M, Tokunaga H, et al. Tracer injection sites and combinations for sentinel lymph node detection in patients with endometrial cancer. Gynecol Oncol 2013;131:299-303.
50. Paley PJ, Veljovich DS, Press JZ, Isacson C, Pizer E, Shah C. A prospective investigation of fluorescence imaging to detect sentinel lymph nodes at robotic-assisted endometrial cancer staging. Am J Obstet Gynecol December 2016;215:117.e1-7.
51. Pandit-Taskar N, Gemignani ML, Lyall A, Larson SM, Barakat RR, Abu Rustum NR. Single photon emission computed tomography SPECT-CT improves sentinel node detection and localization in cervical and uterine malignancy. Gynecol Oncol 2010;117:59-64.
52. Papadia A, Imboden S, Siegenthaler F, et al. Laparoscopic indocyanine green sentinel lymph node mapping in endometrial cancer. Ann Surg Oncol 2016;23:2206-11.
53. Pelosi E, Arena V, Baudino B, et al. Preoperative lymphatic mapping and intraoperative sentinel lymph node detection in early stage endometrial cancer. Nucl Med Commun 2003;24:971-5.
54. Mosgaard BJ, Skovlund VR, Hendel HW. Promising results using sentinel node biopsy as a substitute for radical lymphadenectomy in endometrial cancer staging. Dan Med J 2013;60:A4665.
55. Raspagliesi F, Ditto A, Kusamura S, et al. Hysteroscopic injection of tracers in sentinel node detection of endometrial cancer: a feasibility study. Am J Obstet Gynecol 2004;191:435-9.
56. Robova H, Charvat M, Strnad P, et al. Lymphatic mapping in endometrial cancer: comparison of hysteroscopic and subserosal injection and the distribution of sentinel lymph nodes. Int J Gynecol Cancer 2009;19:391-4.
57. Sawicki S, Lass P, Wydra D. Sentinel Lymph Node Biopsy in Endometrial Cancer—Comparison of 2 Detection Methods. Int J Gynecol Cancer 2015;25:1044-50.
58. Schiavone MB, Zivanovic O, Zhou Q, et al. Survival in patients with uterine carcinosarcoma undergoing sentinel lymph node mapping. Gynecol Oncol 2015;137:99.
59. Solima E, Martinelli F, Ditto A, et al. Diagnostic accuracy of sentinel node in endometrial cancer by using hysteroscopic injection of radiolabeled tracer. Gynecol Oncol 2012;126:419-23.
60. Touhami O, Trinh X-B, Gregoire J, et al. Is a more comprehensive surgery necessary in patients with uterine serous carcinoma? Int J Gynecol Cancer 2015;25:1266-70.
61. Touhami O, Trinh X-BB, Grégoire J, et al. Predictors of non-sentinel lymph node metastasis in patients with positive sentinel lymph node (SLN) in endometrial cancer. Gynecol Oncol 2015;137:22.
62. Valha P, Kucera E, Sak P, Stepanek O, Michal M. Intraoperative subserosal approach to label sentinel nodes in intermediate and high-risk endometrial cancer. Eur J Gynaecol Oncol 2015;36:643-6.
63. Vidal F, Leguevaque P, Motton S, et al. Evaluation of the sentinel lymph node algorithm with blue dye labeling for early-stage endometrial cancer in a multicentric setting. Int J Gynecol Cancer 2013;23:1237-43.
64. Naaman Y, Pinkas L, Roitman S, et al. The added value of SPECT/CT in sentinel lymph nodes mapping for endometrial carcinoma. Ann Surg Oncol 2016;23:450-5.
65. Eriksson AGZ, Ducie J, Ali N, et al. Comparison of a sentinel lymph node and a selective lymphadenectomy algorithm in patients with endometrioid endometrial carcinoma and limited myometrial invasion. Gynecol Oncol 2016;140:394-9.
66. Li B, Li X, Wu L, et al. A pilot study of sentinel lymph nodes identification in patients with endometrial cancer. Bull Cancer 2007;94:E1-4.
67. Kataoka F, Susumu N, Yamagami W, et al. The importance of para-aortic lymph nodes in sentinel lymph node mapping for endometrial cancer by using hysteroscopic radio-isotope tracer injection combined with subserosal dye injection: prospective study. Gynecol Oncol 2016;140:400-4.
68. Perrone AM, Casadio P, Formelli G, et al. Cervical and hysteroscopic injection for identification of sentinel lymph node in endometrial cancer. Gynecol Oncol 2008;111:62-7.
69. Raimond E, Ballester M, Hudry D, et al. Impact of sentinel lymph node biopsy on the therapeutic management of early-stage endometrial cancer: results of a retrospective multicenter study. Gynecol Oncol 2014;133:506-11.
70. Schiavone MB, Zivanovic O, Zhou Q, et al. Survival of patients with uterine carcinosarcoma undergoing sentinel lymph node mapping. Ann Surg Oncol 2016;23:196-202.
71. Ferraioli D, Chopin N, Beurrier F, Carrabin N, Mathevet P. The incidence and clinical significance of the micro-metastases in the sentinel lymph nodes during surgical staging for early endometrial cancer. Int J Gynecol Cancer 2015;25:673-80.
72. Selman TJ, Mann CH, Zamora J, Khan KS. A systematic review of tests for lymph node status in primary endometrial cancer. BMC Womens Health 2008;8:8.
73. Ruscito I, Gasparri ML, Braicu EI, et al. Sentinel node mapping in cervical and endometrial cancer: indocyanine green versus other conventional dyes—a meta-analysis. Ann Surg Oncol 2016;23:3749-56.
74. Xiong L, Gazyakan E, Yang W, et al. Indocyanine green fluorescence-guided sentinel node biopsy: a meta-analysis on detection rate and diagnostic performance. Eur J Surg Oncol 2014;40:843-9.
75. Maaskant-Braat AJ, van de Poll-Franse LV, Voogd AC, et al. Sentinel node micrometastases in breast cancer do not affect prognosis: a population-based study. Breast Cancer Res Treat 2011;127:195-203.
76. Rossi EC, Jackson A, Ivanova A, Boggess JF. Detection of sentinel nodes for endometrial cancer with robotic assisted fluorescence imaging: cervical versus hysteroscopic injection. Int J Gynecol Cancer 2013;23:1704-11.

APPENDIX TABLE 1

Quality assessment of included studies

	Patient selection		Index test		Reference standard			Flow and timing		
Author, year	Was a consecutive or random sample of patients enrolled	Was a case–control design avoided? Did the study avoid inappropriate exclusions?	Were the index test results interpreted without knowledge of the results of the reference standard?	If a threshold was used, was it prespecified?	Reference standard	Is the reference standard likely to correctly classify the target condition?	Were the reference standard results interpreted without knowledge of the results of the index test?	Was there an appropriate interval between the index test and reference standard?	Did all patients receive the same reference standard?	Were all patients included in the analysis?
Allameh et al, 2015[17]	Y	Y	N	NR	Complete pelvic and paraaortic lymphadenectomy	Y	N	NR	Y	Y
Altgassen et al, 2007[18]	Y	Y	N	NR	Complete pelvic lymphadenectomy	Y	N	NR	Y	Y
Ballester 2013[19]	NR	Y	N	NR	Complete pelvic lymphadenectomy, paraaortic lymphadenectomy if high risk	Y	N	NR	Y	Y
Basta et al, 2005[20]	NR	Y	N	NR	Complete pelvic and paraaortic lymphadenectomy	Y	N	NR	Y	Y
Bats et al, 2008[21]	Y	Y	N	NR	Complete pelvic lymphadenectomy, paraaortic lymphadenectomy if high risk	Y	N	NR	Y	Y
Buda et al, 2016[22]	Y	Y	N	NR	Complete pelvic lymphadenectomy, paraaortic lymphadenectomy if high risk	Y	N	NR	Y	Y
Burke et al, 1996[23]	Y	Y	N	NR	Complete pelvic lymphadenectomy, paraaortic lymphadenectomy if high risk	Y	N	NR	Y	Y

Bodurtha Smith. Sentinel lymph nodes and endometrial cancer, a meta-analysis. Am J Obstet Gynecol 2017.

(continued)

APPENDIX TABLE 1

Quality assessment of included studies *(continued)*

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Darai, 2015[1]	Y	Y	N	NR	Complete pelvic lymphadenectomy, paraaortic lymphadenectomy if high risk	Y	N	NR	Y	Y
Delaloye et al, 2007[25]	Y	Y	N	NR	Complete pelvic and paraaortic lymphadenectomy	Y	N	NR	Y	Y
Desai et al, 2014[26]	Y	Y	N	NR	Selective pelvic and paraaortic lymphadenectomy (surgeon discretion)	N	N	NR	N	Y
Eitan et al, 2015[27]	Y	Y	N	NR	Pelvic lymphadenectomy if failed SLN mapping, surgeon discretion paraaortic LND (Memorial Sloan Kettering algorithm)	N	N	NR	Y	Y
Eriksson et al, 2016[28]	NR	Y	N	NR	Memorial Sloan Kettering algorithm	N	N	NR	Y	Y
Farghali et al, 2015[29]	NR	Y	Y	NR	Selective pelvic and paraaortic lymphadenectomy by tumor grade, invasion depth, size, location, and patient fitness	N	Y	NR	N	Y

Bodurtha Smith. Sentinel lymph nodes and endometrial cancer, a meta-analysis. Am J Obstet Gynecol 2017. *(continued)*

APPENDIX TABLE 1

Quality assessment of included studies *(continued)*

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Favero et al, 2015[30]	Y	Y	N	NR	Complete pelvic and paraaortic lymphadenectomy	Y	N	NR	Y	N
Ferraioli et al, 2015[31]	NR	N	N	NR	Pelvic and paraaortic lymphadenectomy if high risk	Y	N	NR	Y	Y
Fersis et al, 2004[32]	Y	Y	N	NR	Complete pelvic lymphadenectomy, paraaortic lymphadenectomy if high risk	Y	N	NR	Y	Y
Frumovitz et al, 2007[33]	Y	Y	N	NR	Complete pelvic and paraaortic lymphadenectomy	Y	N	NR	Y	N
Gien et al, 2005[34]	Y	Y	N	NR	Complete pelvic lymphadenectomy, paraaortic lymphadenectomy if high risk	Y	N	NR	Y	Y
Holloway et al, 2016[35]	Y	N	N	NR	Complete pelvic lymphadenectomy, paraaortic lymphadenectomy if high risk	Y	N	NR	Y	N
Holub et al, 2004[36]	Y	Y	N	NR	Complete pelvic lymphadenectomy, paraaortic lymphadenectomy if high risk	Y	N	NR	Y	Y

Bodurtha Smith. Sentinel lymph nodes and endometrial cancer, a meta-analysis. Am J Obstet Gynecol 2017.

(continued)

APPENDIX TABLE 1

Quality assessment of included studies *(continued)*

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Author, year	Was a consecutive or random sample of patients enrolled	Was a case–control design avoided? Did the study avoid inappropriate exclusions?	Were the index test results interpreted without knowledge of the results of the reference standard?	If a threshold was used, was it prespecified?	Reference standard	Is the reference standard likely to correctly classify the target condition?	Were the reference standard results interpreted without knowledge of the results of the index test?	Was there an appropriate interval between the index test and reference standard?	Did all patients receive the same reference standard?	Were all patients included in the analysis?
How et al, 2012[37]	Y	N	N	NR	Complete pelvic lymphadenectomy, paraaortic lymphadenectomy if high risk	Y	N	NR	Y	Y
How et al, 2015[38]	Y	N	N	NR	Complete pelvic lymphadenectomy, paraaortic lymphadenectomy if high risk	Y	N	NR	Y	Y
Kadkhodayan et al, 2014[39]	Y	N	N	NR	Complete pelvic lymphadenectomy, paraaortic lymphadenectomy if high risk	Y	N	NR	Y	Y
Kataoka et al, 2016[67]	Y	Y	N	NR	Complete pelvic lymphadenectomy, paraaortic lymphadenectomy if high risk	Y	N	NR	Y	N
Koskas et al, 2013[40]	Y	Y	N	NR	Complete pelvic lymphadenectomy, paraaortic lymphadenectomy if high risk	N	N	NR	Y	Y
Kuru et al, 2011[41]	Y	Y	N	NR	Complete pelvic lymphadenectomy, paraaortic lymphadenectomy if high risk	Y	N	NR	Y	Y

Bodurtha Smith. Sentinel lymph nodes and endometrial cancer, a meta-analysis. Am J Obstet Gynecol 2017.

(continued)

APPENDIX TABLE 1

Quality assessment of included studies *(continued)*

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Laios et al, 2015[42]	Y	Y	N	NR	Complete pelvic lymphadenectomy	Y	N	NR	Y	Y
Lelievre et al, 2004[43]	Y	Y	N	NR	Complete pelvic lymphadenectomy, paraaortic lymphadenectomy if high risk	Y	N	NR	Y	Y
Li et al, 2009[44]	NR	Y	N	NR	Complete pelvic lymphadenectomy, paraaortic lymphadenectomy if high risk	Y	N	NR	Y	Y
Lopes et al, 2007[45]	Y	Y	N	NR	Pelvic and paraaortic lymphadenectomy if high risk	N	N	NR	Y	Y
Lopez-De la Manzanara et al, 2014[46]	Y	Y	N	NR	Complete pelvic lymphadenectomy, paraaortic lymphadenectomy if high risk	Y	N	NR	Y	Y
Mais et al, 2010[47]	Y	Y	N	NR	Complete pelvic lymphadenectomy, paraaortic lymphadenectomy if high risk	Y	N	NR	Y	Y
Mosgaard et al, 2013[54]	Y	Y	N	NR	Complete pelvic and paraaortic lymphadenectomy	Y	N	NR	Y	Y

Bodurtha Smith. Sentinel lymph nodes and endometrial cancer, a meta-analysis. Am J Obstet Gynecol 2017.

(continued)

APPENDIX TABLE 1

Quality assessment of included studies *(continued)*

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Mucke et al, 2014[48]	Y	Y	N	NR	Complete pelvic and paraaortic lymphadenectomy	Y	N	NR	Y	Y
Naaman et al, 2016[64]	Y	Y	N	NR	Complete pelvic lymphadenectomy or Memorial Sloan Kettering algorithm, paraaortic lymphadenectomy if high risk	N	N	NR	N	Y
Niikura et al, 2013[49]	Y	Y	N	NR	Complete pelvic and paraaortic lymphadenectomy	Y	N	NR	Y	Y
Paley et al, 2016[50]	Y	Y	N	NR	Pelvic and paraaortic lymphadenectomy if high risk	N	N	NR	Y	Y
Pandit-Taskar et al, 2010[51]	Y	Y	N	NR	Complete pelvic lymphadenectomy, paraaortic lymphadenectomy if high risk	Y	N	NR	Y	Y
Papadia et al, 2016[52]	Y	Y	N	NR	Pelvic lymphadenectomy unless type I well differentiated <50% myometrial invasion, paraaortic lymphadenectomy if high risk	N	N	NR	Y	Y

Bodurtha Smith. Sentinel lymph nodes and endometrial cancer, a meta-analysis. Am J Obstet Gynecol 2017. *(continued)*

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Quality assessment of included studies *(continued)*

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Pelosi et al, 2003[53]	Y	Y	N	NR	Complete pelvic lymphadenectomy, paraaortic lymphadenectomy if high risk	Y	N	NR	Y	Y
Perrone et al, 2008[68]	Y	Y	N	NR	Complete pelvic lymphadenectomy, paraaortic lymphadenectomy if high risk	Y	N	NR	Y	Y
Raimond et al, 2014[70]	NR	Y	N	NR	Complete pelvic lymphadenectomy, paraaortic lymphadenectomy if high risk	Y	N	NR	Y	N
Raspagliesi et al, 2004[55]	Y	Y	N	NR	Pelvic lymphadenectomy if high risk	N	N	NR	Y	Y
Robova et al, 2009[56]	Y	Y	N	NR	Complete pelvic and paraaortic lymphadenectomy	Y	N	NR	Y	N
Rossi et al, 2013[76]	Y	Y	N	NR	Complete pelvic and paraaortic lymphadenectomy	Y	N	NR	N	Y

Bodurtha Smith. Sentinel lymph nodes and endometrial cancer, a meta-analysis. Am J Obstet Gynecol 2017. *(continued)*

APPENDIX TABLE 1

Quality assessment of included studies *(continued)*

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Sawicki et al, 2015[57]	Y	Y	N	NR	Pelvic and paraaortic lymphadenectomy if grade 3, >50% myometrial invasion, or cervical involvement; not if morbid obesity, advanced age, or poor general status	N	N	NR	Y	Y
Schiavone et al, 2016[71]	Y	N	N	NR	Surgeon-discretion lymphadenectomy or Memorial Sloan Kettering algorithm	N	N	NR	N	Y
Solima et al, 2012[59]	Y	N	N	NR	Complete pelvic or paraaortic lymphadenectomy if high risk	Y	N	NR	Y	N
St Clair et al, 2016[28]	Y	Y	N	NR	Memorial Sloan Kettering algorithm	Y	N	NR	Y	Y
Tanner et al, 2015[12]	Y	Y	N	NR	Complete pelvic and paraaortic lymphadenectomy if high risk	Y	N	NR	Y	Y
Torné et al, 2013[11]	Y	Y	N	NR	Complete pelvic and paraaortic lymphadenectomy	Y	N	NR	Y	Y
Touhami et al, 2015[60]	Y	Y	N	NR	Complete pelvic lymphadenectomy, paraaortic lymph node sampling	Y	N	NR	Y	Y

Bodurtha Smith. Sentinel lymph nodes and endometrial cancer, a meta-analysis. Am J Obstet Gynecol 2017. *(continued)*

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Touhami et al, 2015[61]	Y	Y	N	NR	Complete pelvic lymphadenectomy, paraaortic lymphadenectomy if high risk	Y	N	NR	Y	Y
Valha et al, 2015[62]	Y	Y	N	NR	Complete pelvic and paraaortic lymphadenectomy	Y	N	NR	Y	Y
Vidal et al, 2013[63]	Y	Y	N	NR	Complete pelvic lymphadenectomy, paraaortic lymphadenectomy if high risk	Y	N	NR	Y	Y

Memorial Sloan Kettering algorithm indicates a pelvic lymphadenectomy if failed mapping, surgeon discretion paraaortic lymphadenectomy.

LND, lymphadenectomy; *N*, no; *NR*, not reported; *SLN*, sentinel lymph node; *Y*, yes.

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APPENDIX TABLE 2
Univariate meta-regression of SLN sensitivity and study characteristics

Characteristics	Sensitivity % (95% CI)	*P* value
Study size		
≥30 patients	0.97 (0.94–0.99)	.78
<30 patients	0.94 (0.85–1.00)	
Preoperative lymphoscintigraphy		
Yes	0.98 (0.95–1.00)	.77
No	0.95 (0.91–0.99)	
Injection site		
Cervical	0.97 (0.94–0.99)	.46
Uterine	0.94 (0.89–1.00)	
Radiotracer used		
Yes	0.97 (0.95–1.00)	.71
No	0.94 (0.89–1.00)	
Dye and radiotracer used		
Yes	0.97 (0.94–0.99)	.84
No	0.95 (0.86–1.00)	
Intraoperative frozen section		
Yes	0.97 (0.92–1.00)	.55
No	0.97 (0.93–1.00)	
Ultrastaging		
Yes	0.97 (0.94–0.99)	.90
No	0.94 (0.86–1.00)	

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