American Journal of Obstetrics and Gynecology

Patient-centered outcomes following sentinel lymph node dissection in endometrial cancer: A systematic review

--Manuscript Draft--

Manuscript Number:	
Article Type:	Systematic Review
Section/Category:	Oncology
Keywords:	endometrial cancer; endometrial carcinoma; lymph node biopsy; minimally invasive surgery; patient-reported outcomes, sentinel lymph node
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Manuscript Region of Origin:	AUSTRALIA
Abstract:	Objective: Sentinel lymph node dissection (SLND) is presently used by the majority of gynecologic oncologists for surgical staging of endometrial cancer. SLND assimilated into routine surgical practice because it increases precision of surgical staging and may reduce morbidity compared to a full, systematic LND. Previous research focused on the accuracy of SLND. Patient-centered outcomes have never been conclusively demonstrated. The objective of this systematic review was to evaluate patient-centered outcomes of SLND for endometrial cancer patients. Data sources: Literature published in the last five years (January 2015 to April 2020) was retrieved from PubMed, EMBASE, and Cochrane library, across five domains: (1) perioperative outcomes; (2) adjuvant treatment; (3) patient-reported outcomes (PROMS); (4) lymphedema, and (5) cost. Study eligibility criteria: Studies were required to report on adult women (18 years and above) who had undergone SLND for the treatment of endometrial cancer. Only original works, published in English language in peer-reviewed journals were included. Study appraisal and synthesis methods: The checklist of the Preferred Reporting Items for Systematic Review and Meta-Analyses guided our systematic review. Covidence software ascertained a standardized and monitored review process. Results: We identified 21 eligible studies. Included studies were highly heterogeneous, with widely varying outcome measures and reporting. SLND was associated with shorter operating times and lower estimated blood loss compared to systematic LND, but intra-operative and post-operative complications were not conclusively different. There was either no impact, or a trend towards less adjuvant treatment used in patients with SLND compared to systematic LND. SLND had lower prevalence rates of lymphedema compared to systematic LND, although this was shown only in three retrospective studies. Costs of surgical staging were lowest for no-node sampling, followed by SLND, then LND. PROMS were unable to be compared because of a lack of studies. Conclusions: The quality of evidence on patient-centered outcomes associated with SLND for surgical staging of endometrial cancer is poor, particularly in PROMs, lymphedema and cost. The available studies were vulnerable to bias and confounding.

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THE UNIVERSITY OF QUEENSLAND
AUSTRALIA

02 October 2020

Editor-in-chief,

Dr Catherine Bradley

American Journal of Obstetrics and Gynecology

Dear Dr Bradley,

Please accept the enclosed research paper “Patient-centered outcomes following sentinel lymph node dissection in endometrial cancer: A systematic review”.

Current standard treatment of endometrial cancer is surgical removal of the uterus, bilateral fallopian tubes and ovaries (THBSO) to remove the primary tumor. In addition, practice management guidelines mandate removal and histopathological assessment of lymph nodes to determine the extent of the disease; a process referred to as “surgical staging”. Surgical staging is now increasingly done using sentinel lymph node dissection (SLND). While SLND’s accuracy to detect the relevant nodes has been studied prospectively, this research paper aimed to evaluate the evidence-base on patient-centered outcomes following SLND for the treatment of endometrial cancer. Previous research has focused on the accuracy of SLND, however the effect of SLND on key patient outcomes has not been conclusively shown.

We reviewed literature published across multiple domains including perioperative outcomes, adjuvant treatments received, patient reported outcomes and lymphedema. Our review found potentially favorable patient intra- and postoperative outcomes of SLND compared to systematic lymph node dissection, however also highlights the substantial lack of high-quality studies comparing SLND with other methods of staging.

As the value of systematic lymph node dissection is further called into question, it may become increasingly necessary to compare SLND, as the new standard of care, to no node dissection, or molecular-based staging.

We acknowledge all authors have contributed to this paper. The manuscript is not under review at any other journal.

Sincerely,

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Patient-centered outcomes following sentinel lymph node dissection in endometrial cancer: A systematic review

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Conflict of Interest: The authors have no conflict of interest to declare.

Word Count: 4603

Condensation: Sentinel lymph node dissection (SLND) has potentially favorable patient-centered outcomes over systematic LND, however high-quality evidence comparing SLND with other methods of staging is lacking.

Short title: Patient-centered outcomes following sentinel lymph node dissection in endometrial cancer

AJOG at a Glance:

A. The purpose of this study was to evaluate patient-centered outcomes of SLND for endometrial cancer patients including perioperative outcomes, adjuvant treatments received, patient-reported outcomes (PROs), and lymphedema.

B. SLND was associated with shorter operating times and lower estimated blood loss compared to systematic LND, but intra-operative and post-operative complications were not conclusively different.

C. This systematic review found potentially favorable patient intra- and postoperative outcomes of SLND compared to systematic LND, however also highlights the substantial lack of high-quality studies comparing SLND with other methods of staging.

Keywords: endometrial cancer; endometrial carcinoma; lymph node biopsy; minimally invasive surgery; patient-reported outcomes, sentinel lymph node

Abstract

Objective: Sentinel lymph node dissection (SLND) is presently used by the majority of gynecologic oncologists for surgical staging of endometrial cancer. SLND assimilated into routine surgical practice because it increases precision of surgical staging and may reduce morbidity compared to a full, systematic LND. Previous research focused on the accuracy of SLND. Patient-centered outcomes have never been conclusively demonstrated. The objective of this systematic review was to evaluate patient-centered outcomes of SLND for endometrial cancer patients.

Data sources: Literature published in the last five years (January 2015 to April 2020) was retrieved from PubMed, EMBASE, and Cochrane library, across five domains: (1) perioperative outcomes; (2) adjuvant treatment; (3) patient-reported outcomes (PROs); (4) lymphedema, and (5) cost.

Study eligibility criteria: Studies were required to report on adult women (18 years and above) who had undergone SLND for the treatment of endometrial cancer. Only original works, published in English language in peer-reviewed journals were included.

Study appraisal and synthesis methods: The checklist of the Preferred Reporting Items for Systematic Review and Meta-Analyses guided our systematic review. Covidence software ascertained a standardized and monitored review process.

Results: We identified 21 eligible studies. Included studies were highly heterogeneous, with widely varying outcome measures and reporting. SLND was associated with shorter operating times and lower estimated blood loss compared to systematic LND, but intra-operative and post-operative complications were not conclusively different. There was

either no impact, or a trend towards less adjuvant treatment used in patients with SLND compared to systematic LND. SLND had lower prevalence rates of lymphedema compared to systematic LND, although this was shown only in three retrospective studies. Costs of surgical staging were lowest for no-node sampling, followed by SLND, then LND. PROs were unable to be compared because of a lack of studies.

Conclusions: The quality of evidence on patient-centered outcomes associated with SLND for surgical staging of endometrial cancer is poor, particularly in PROs, lymphedema and cost. The available studies were vulnerable to bias and confounding.

Introduction

Endometrial cancer is the fifth most common cancer diagnosed in women in developed countries. Globally, it has an incidence of 382,069 new cases per year[1] and in the United States endometrial cancer is the most commonly diagnosed gynecological cancer, with 65,620 new cases estimated to be diagnosed in 2020.[2]

Practice management guidelines for endometrial cancer recommend removal of the primary tumor (total hysterectomy, bilateral salpingo-oophorectomy)[3-5] and also prescribe surgical staging to determine the extent of the disease, which is achieved through removal and histopathological assessment of lymph nodes.[6,7] Surgical staging was introduced to gynecological oncology practices based on the results of observational, clinicopathologic studies[8,9] but not prospective, randomized trials comparing systematic lymph node dissection (LND) versus no LND. Consequently, the International Federation of Gynaecologists and Obstetricians (FIGO) adopted a surgical staging system in 1988.[10]

Sentinel lymph node dissection (SLND) evolved from systematic LND using advanced intraoperative imaging technology and has assimilated into routine surgical practice.[11-13] Presumed benefits of SLND are that it increases the precision of surgical staging because technology highlights fewer positive nodes for surgical removal thus sparing removal of normal, negative nodes.[13,14] Therefore, it may reduce the morbidity associated with a full LND because fewer nodes are removed[15] while still obtaining accurate information on lymph node status, which generates information on the patients' risk of relapse. High-level evidence suggests SLND is accurate to replace systematic LND in endometrial cancer, identifying at least one sentinel node in 86% of patients.[16] Its sensitivity to detect node-positive disease is 97.2% and its negative predictive value is 99.6%. Previous research[17,18]

has focused on the surgical technique[19] (FILMS), the selection of tracer used and accuracy of SLND.

Objective

The effect of SLND on key patient outcomes has not been conclusively shown. Therefore, the objective of this systematic review was to evaluate patient-centered outcomes of SLND for endometrial cancer patients including perioperative outcomes, adjuvant treatments received, patient reported outcomes (PROs), and lymphedema.

Methods

Search strategy

The checklist of the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guided our systematic review. The review was registered in the International Prospective Register of Systematic Reviews (CRD42020180339). Literature published in the last five years (January 2015 to April 2020) was retrieved searching the electronic databases PubMed, EMBASE, and the Cochrane library.

The overarching research topic of patient-centered outcomes of SLND for the treatment of endometrial cancer was divided into five searches. Each of these searches was then summarized in narrative form, resulting in five sub-sections, or 'chapters' within the review. This method was selected as it allowed the authors to capture literature across five important domains including (1) perioperative outcomes (2) adjuvant treatment (3) patient-reported outcomes (4) lymphedema outcomes, and (5) cost. The division of the review into five sections allowed for a comprehensive and clearly categorized delineation of articles that contributed to each areas of interest.

The search terms used for all five searches included: (sentinel-node biopsy OR sentinel lymph node OR sentinel lymph node biopsy) AND (endometrial cancer OR endometrial carcinoma OR endometrial neoplasms OR endometrium carcinoma OR “cancer of the endometrium”). Additional search terms were then added for each of the five searches, for example: AND (Patient Reported Outcome Measures OR Quality of Life). The search strategy was tailored to multiple databases including MedLine and Embase. A complete list of search terms is provided in the Supplementary material.

Study eligibility

Only original works, published in English language in peer-reviewed journals were included. Studies were required to report on adult women (18 years and above) who had undergone SLND for the treatment of endometrial cancer. Studies were included if they reported on at least one of the five topics of interest. We excluded studies with fewer than 10 patients, as well as articles not available in English and studies on animals. Reviews, commentaries, editorials, letters, protocol papers, conference proceedings, guidelines, and clinical trial registrations were also excluded.

Study selection

Two reviewers (MO, HO) used the software program Covidence[20] to screen the titles and abstracts of papers identified through the literature search under the guidance of a third reviewer (MJ). Disagreements were resolved through discussion between the two reviewers, and consultation with other review authors (MJ, AO) to make a final decision. The full-text of all potentially relevant articles was obtained and screened against the pre-

defined selection criteria. The reference lists of these articles were checked for additional relevant papers.

Data extraction

All records were stored in Endnote. Data extracted included author, year, country of study, study design, patient population and sample size, time period, intervention, outcome measure(s), summary of reported findings, and items for quality assessment. Two reviewers (MO, HO) tabulated study characteristics for each of the final studies in Excel and this data was then audited by other members of the review team (MJ, AO).

Quality assessment

Two researchers (MO, HO) assessed the quality of studies included in the final review using the appropriate appraisal tool for each included study's design. The quality assessment was then audited by a member of the review team (MJ) to settle any disagreements detected. The quality of observational studies were assessed using the Newcastle-Ottawa Scale, available for cohort, case-control, and cross-sectional studies. The Newcastle-Ottawa Scale consists of a 9 item checklist to evaluate the quality of non-randomized studies to be used in a systematic review.[21] The quality of cost-effectiveness studies were assessed using the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) Statement. A CHEERS score was calculated for each included study, with one point allocated per item and a maximum of 24 points.[22]

Results

Characteristics of the included studies

A total of 1,807 citations were identified from the original search, with 500 remaining after removal of duplicates. Following title and abstract screening, 46 potentially relevant studies were identified and the full-text copies were obtained for comparison against the full selection criteria. The reference lists of these articles were checked for relevant papers and an additional 9 articles were added for full text review, resulting in a total of 55 papers. Of these, 34 were excluded as they did not meet at least one of the inclusion criteria. Reasons for exclusion included studies with <10 patients (n= 2), unrelated outcome measure (n=10), unrelated intervention (n=14), unrelated patient population (n=1), unrelated study design (n= 1), and articles where participants studied had >50% overlap with another included study (n=6). Therefore, a total of 21 unique studies were included in the final review. A PRISMA flow diagram outlining the process of selecting studies is presented in Figure 1.

Of the 21 studies, five studies were prospective observational,[23-27] one was using a historical control,[28] eleven were retrospective observational studies,[15,29-38] three were retrospective database reviewes,[39-41] and one used a decision analysis model.[42] There were no prospective randomized trials.

Of the 21 studies, five compared SLND to systematic LND,[27,28,30,37,42] and seven studies compared SLND to no node sampling and systematic LND,[15,29,31,38-41] Four studies compared SLND between different surgical techniques; between single site versus multi-port,[24,33] mini-laparoscopy versus standard laparoscopy[32] and different tracers.[25] Five studies had no comparison groups.[23,26,34,35,43]

Quality Assessment

The mean quality score of non-randomized studies was 6.8 (range 4 to 9). Of these, the mean quality score of the cohort studies was 6.9, and only one cross-sectional study[24] was

included with a total quality score of 5. Two studies[39,42] were evaluated using the CHEERS Statement and received scores of 16/24 and 18/24 respectively.

Characteristics of the included patients

Participant demographics and clinical characteristics are detailed in Table 1 and included patient age, body mass index (BMI), American Society of Anesthesiologists Classification (ASA) score, postoperative histological cell type (endometrioid versus other), final FIGO stage (I, II, III, or IV), and FIGO grade (1, 2, or 3). Data on histopathology, stage and grade were assumed to be postoperative data unless reported otherwise.

Of the 21 included publications, 18 reported mean or median patient age. The mean/median age of women ranged from 53 years[33] to 79.5 years.[27] BMI was reported in 16 studies with the mean/median BMI of women ranging from 23 kg per m^2 [23] to 35.2.[29] Four studies reported ASA scores. One study[43] reported a median ASA score of 2, while another[29] reported ASA scores of ≥3 (n= 63). The remaining two studies reported median ASA scores of 2 (range 1-3). Final histology was reported in 12 studies. Histologic types included 3,060 endometrioid cancers and 712 other cancer types (including: non-endometrioid, endometrial atypical hyperplasia, endometrial intraepithelial neoplasia, serous, clear cell, carcinosarcoma and mucinous). Fifteen studies reported FIGO stage, most frequently stage I (n= 4028) and least frequently stage IV (n= 8). Ten studies reported cancer grade (median= 1; range 1-3).

Perioperative Outcomes

Thirteen studies reported operating time, estimated blood loss (EBL), length of stay (LOS), procedure-related morbidity and conversion rates (Table 2). These studies included a total

of 5,922 patients, with 1,164 patients receiving SLND. Of the 13 studies, four were prospective,[23,24,26,27] two included retrospective and prospective cohorts[28,38] and seven were retrospective studies.[15,29,30,32,33,40,43] There was considerable heterogeneity within the group of publications with regards to inclusion and exclusion criteria for histopathology, stage, grade and surgical management, and some studies also included patients with complex atypical hyperplasia (n=3). All 13 studies reported using a SLND protocol, with the most common being the National Comprehensive Cancer Network SLND algorithm (n=3). Seven studies compared SLND to either no node assessment or varying extents of systematic LND, and three studies reported on SLND when they compared other factors e.g. single site vs multiport, differing port size. Three studies reported only on cohorts having SLND, with no comparisons.

Operating time was reported in all 13 included studies. Median or mean operating time ranged from 118.5 mins[26] to 235 mins[27] in the SLND groups. In studies comparing SLND to systematic LND (n=7),[15,27-30,38,40] all reported a lower mean/median operating time in SLND and five[15,29,30,38,40] demonstrated a statistically significant difference. In studies that compared SLND to no node dissection (n=4), two demonstrated longer operating time in the SLND group,[15,40] one demonstrated the same operating time between the groups,[38] and one found a longer operating time in the group with no node dissection.[29]

Estimated blood loss was reported in eleven studies, with some reporting mean or median, and one study reporting the proportion of patients with less than 100mL estimated blood loss.[24] Estimated blood loss (mean or median) ranged from 20mL[15] to 160mL[43] in SLND groups. In studies comparing SLND with systematic LND (n=6),[15,27-30,38] all but one[27] reported a lower mean/median blood loss with SLND compared to systematic LND, and four[15,28,29,38]

245 demonstrated a statistically significant reduction. Of studies (n=3)[15,29,38] comparing
246 estimated blood loss with SLND to no node dissection, one found higher blood loss with
247 SLND,[38] one found no difference between the two groups,[29] and one found higher blood loss
248 with no node dissection.[15]

249 Post-operative length of stay was reported in nine of the 13 studies. Three compared length
250 of stay between SLND and systematic LND,[28,29,40] and two studies compared length of stay
251 between SLND and no node dissection.[29,40] Post-operative length of stay was reported
252 differently in each of these studies; one reported mean hours of length of stay,[28] one
253 reported percentages discharged on the same day as surgery, after one day and after more
254 than one day[40] and one reported the proportion of patients staying for more than 2 days.[29]

255 Seven of the 13 studies reported intra-operative complications and all 13 studies reported
256 on post-operative complications. Of studies comparing intra-operative complications in
257 patients undergoing SLND compared to systematic LND (n=4),[15,29,30,38] three studies
258 reported lower rates of intra-operative complications in SLND groups[15,29,38] (with only one
259 reaching statistical significance),[15] and one study reported a higher rate of intra-operative
260 complications in the SLND group (not statistically significant).[30] Of studies that compared
261 SLND to no node dissection (n=3), two found that the SLND groups had lower intra-
262 operative complications,[29,38] and one found that the SLND group had a higher rate of intra-
263 operative complications compared to no node dissection.[15]

264 Of studies (n=7) that compared SLND to systematic LND,[15,27-30,38,40] five[15,28,29,38,40] reported
265 lower rates of post-operative complications with SLND, and three of these reached
266 statistical significance.[15,28,40] One study demonstrated a higher rate of post-operative
267 complications in the SLND group which was not statistically significant.[30] A comparison of

post-operative complications reported in Geppert et al.[27] was unable to be determined due to reporting of multiple risk groups. Of studies (n=4) that compared SLND to no node dissection, two found that post-operative complications were higher in the SLND group,[38,40] while 2 reported higher complications in the group with no node dissection.[15,29]

Five of the 13 studies reported on conversion rates, which ranged between 0.0%[15] and 43%,[27] with no consistent relationship between conversion rate and approach to lymph node sampling reported across the studies.[15,27,29,30] Similarly, of studies comparing conversion rates between SLND compared to no node dissection (n=2), one found higher conversion rates in SLND,[29] and one found higher conversion rates in the group with no node dissection.[15]

Adjuvant Treatment

Overall, eight studies reported the rate of patients who received adjuvant treatment (Table 3). These studies included 56,796 patients, of which 2,478 had a SLND. Four studies were retrospective observational;[34,35,37,38] two reported prospective cohorts (n=2);[26,27] one compared data from a prospective cohort with historical controls;[28] and one was a retrospective database review (n=1).[41] There was significant heterogeneity in patient cohorts, which are described in Table 1. Three of the eight studies compared SLN to systematic LND, two compared SLN to no node sampling and systematic LND, and three reported no comparison group.

Three of five studies comparing SLND to systematic LND (n=5) reported that fewer patients who had a SLND received adjuvant treatment compared to systematic LND,[27,37,38] whereas two studies showed no difference in rates of adjuvant treatment received between the groups.[28,41] Geppert et al.[27] specifically reported that high-risk tumor factors were a larger

291 determinant of receiving adjuvant treatment than the lymph node dissection method.
292 Goebel et al.[35] stated that isolated tumor cells in the sentinel node did not influence
293 adjuvant treatment recommendations in their institution, as other risk factors indicated the
294 need for adjuvant treatment.
295 *PROs*
296 Two of 21 identified studies described PROs.[24,25] Neither of these publications compared
297 SLND to systematic LND or no LND. Buda et al.[25] described PROs as a secondary outcome
298 when comparing two tracer protocols; pre-operative Tc99m nanocolloid (on the day before
299 surgery) plus intra-operative blue dye (from 2010 to 2014), compared to intra-operative ICG
300 or blue dye SLND (from 2014 onwards). In this study, the European Organization for
301 Research and Treatment of Cancer (EORTC) IN-PATSAT32 questionnaire was used to assess
302 patients' satisfaction with the care received by doctors, nurses and the hospital. This study
303 included both patients with clinical stage 1 endometrial (n=106) and stage IA2 to 1B1
304 cervical (n=37) cancer. The authors found higher patient satisfaction and perception of
305 higher quality of care in intra-operative ICG/blue dye compared to the Tc99m radiocolloid
306 group possibly due to the need for hospital admission on the day prior to surgery, patient
307 discomfort due to pre-operative injection of radiocolloid, imaging performed 3 hours after
308 the injection and exposure to radiation through pre-operative imaging.

309 Mereu et al.[24] conducted a prospective multicenter case-control study comparing 51
310 patients who had robotic multiport TLHBSO and SLND versus 25 robotic single site surgery
311 for low risk endometrial cancer or complex atypical hyperplasia from 2017 to 2019. The
312 authors assessed PROs using the EORTC questionnaire QLW-C30 up to 12 months post-
313 surgery. This study reported better physical function in the single site compared to the
314 multiport group (97.1 vs 91.6, $p = 0.007$) at 6 and 12 months post-operatively, but no

315 statistically significant differences in emotional, cognitive or social functioning or fatigue.
316 The authors described less pain in the multiport versus the single port group (98.6 vs 94.4, p
317 = 0.029) at 6 months post-operatively. There were no statistically significant differences in
318 body image and cosmetic results between the two approaches.

319 *Lymphedema*

320 Of 21 included studies, three publications reported lower limb lymphedema (LLL)
321 outcomes.[15,27,31] All three studies compared SLND to systematic LND and found SLND had
322 lower incidence or point prevalence of lymphedema compared to systematic LND.

323 Leitao et al.[31] reported point prevalence of self-reported lymphedema from a retrospective
324 cross sectional study including 599 patients who had surgery for endometrial cancer
325 between 2006 and 2012, comparing patients who had SLND (n=180) versus systematic LND
326 (n=352), versus hysterectomy without a lymph node dissection (n=67). At a minimum of 44
327 months after surgery, patients were asked to complete a validated 13-item lymphedema
328 and quality of life questionnaire. Self-reported LLL prevalence was 49 of 180 (27%) after
329 SLND, 144 of 352 (41%) after systematic LND (OR 1.85, p=0.002), even after adjusting for
330 radiation therapy and BMI. The prevalence of LLL was 27 of 67 (40.3%) after hysterectomy
331 alone.

332 Geppert et al.[27] conducted a prospective, non-randomized single-center cohort study
333 between 2014 and 2016, comparing incidence of lymphedema, lymphocele and chylous
334 ascites formation in 188 patients with endometrial cancer. Patients with high-risk pre-
335 operative features (non-endometrioid cell type, FIGO grade 3, non-diploid flow cytometry,
336 myometrial invasion deeper than 50%, cervical invasion) received a systematic LND whereas
337 patients with low-risk features had a SLND. The incidence of LLL was assessed by a

physiotherapist specialized in LLL assessment using the Common Toxicity Criteria Version 3.0 classification. At a follow up of 12 months, the incidence of grade 1 LLL was significantly lower after SLND compared to systematic LND (1/76 patients, 1.3% vs 15/83 patients, 18.1%, p = 0.0003).

Accorsi et al.[15] performed a retrospective cohort study of endometrial cancer patients treated surgically at a single institution in Brazil. Patients were categorized into one of four groups; hysterectomy only (n=54), hysterectomy with SLND (n=61), hysterectomy with systematic pelvic +/- para-aortic LND (n=89) and hysterectomy with SLND and systematic LND (n=46). Postoperative complications were captured at 90 days post-surgery and included LLL as graded by the Memorial Sloan Kettering Cancer Centre's Surgical Secondary Events Grading System. LLL was found only in patients who had systematic pelvic +/- para-aortic LND (10.1%), compared to 0% in all other groups (p=0.01). There was no difference in rates of LLL when comparing SLND and no node dissection (0% vs 0%).

Cost

Three of 21 studies described cost outcomes for SLND. Two studies[39,42] compared SLND to systematic LND, finding that SLND attracted lower costs than systematic LND. Additionally, Wright et al.[39] also compared SLND to no lymph node assessment, finding that no nodal assessment had lower costs than both SLND and systematic LND.

Suidan et al.[42] used a decision-analysis model to compare the cost-utility (taking into account cost, survival and quality of life) in low-risk endometrial cancer patients between minimally invasive hysterectomy, bilateral salpingo-oophrectomy with systematic LND, selective LND (based on intra-operative frozen section criteria) and SLND. There was no group of no LND. Year 2016 Medicare reimbursement rates were used to calculate

estimates of cost. Of the three strategies, SLND attracted the lowest cost ($16401 compared to $18041 for systematic LND and $17036 for selective LND, respectively). SLND also had the highest quality of life gain (2.87 QALYs vs 2.79 for systematic LND and 2.81 for selective LND, respectively). Systematic LND attracted the highest cost due to the surgeon, pathology and lymphedema treatment costs associated. SLND had slightly higher pathology fees, but less operating time and lymphedema treatment.

Wright et al.[39] performed a retrospective analysis of 23,362 patients who underwent hysterectomy for endometrial cancer in the United States from 2011 to 2015, and whose records were in the Perspective database. They examined billing and charge codes, finding that 9327 patients (32.8%) did not undergo lymph node assessment, 17669 (62.3%) underwent systematic LND and 1366 (4.8%) underwent SLND, with SLND becoming more frequent over time, and more common during robotic hysterectomy. Mean cost for patients with no nodal assessment was $8877, compared to $9550 for SLND and $10259 for systematic LND, respectively.

Stewart et al.[30] analyzed the hospital financial costs (e.g. operative time, use of intraoperative frozen section, hospital charges) for 203 patients (71 in 2012, 130 in 2017) with clinical Stage I endometrial cancer pre- and post-implementation of a SLND algorithm at a single institution in the United States. Compared to pre-implementation, the authors found a decrease in median hospital charges by 2.73% ($p=0.96$). Within these charges, pharmacy charges decreased by 80.36% ($p<0.01$), and laboratory costs by 86.63% (although not statistically significant), whereas post-anesthesia care charges increased by 40.95% ($p<0.01$), as did pathology charges (by 63.38%, $p<0.01$).

Comment

Main findings

This review summarizes relevant and meaningful clinical and patient-centered outcomes from 21 studies of SLND for endometrial cancer. Amongst the available literature sources, there were no publications reporting the outcomes of randomized clinical trials comparing SLND versus other methods of node sampling or no node sampling, and 14 of the 21 studies were retrospective. 12 of 21 studies compared SLND to systematic LND and very limited data was available for comparisons between SLND and no node sampling.

A central finding of this review is that literature on patient-centered outcomes of SLND compared to other node sampling techniques in endometrial cancer is sparse in all areas, and particularly limited for PROs, lymphedema and cost outcomes. The reported data is prone to bias and confounding. There was minimal stratification for low-risk/high-risk endometrial cancer, which was a major confounding factor for many of the included studies.[44,45] Furthermore, allocation to certain lymph node sampling strategies was often based on uterine-risk factors (e.g. high-risk patients allocated to systematic LND, low-risk patients to SLND), which was another source of potential bias. There was limited comparison of SLND compared to no node sampling, which made it difficult to draw conclusions. There was a large variety of outcomes reported between studies, and a large variation in reporting measures used; for example, for length of stay post-operatively, some studies reported this in days, some in hours, and some reported proportions of patients staying for longer than a certain period of time. This indicates that future research into patient-centered outcomes in endometrial cancer should standardize outcomes reporting to make high quality outcome reviews and meta-analyses feasible.[46,47]

There was a consistent finding of lower operating time for SLND than systematic LND, and lower estimated blood loss in SLND compared to LND. The length of stay, intra-operative and post-operative complications and conversion rates were unable to be conclusively compared between groups. The widely varying study protocols used made extraction of comparable data and drawing conclusions difficult. These differences in SLND protocol, patient populations, and approach to surgery may all contribute to the lack of consistency, for example, postoperative complications for women with no node dissection ranged from 2.0%[40] to 14.7%;[15] while for SLND these ranged from 2.1%[40] to 30.8%.[27]

Eight studies reported adjuvant therapy in patients following SLND. In five studies comparing SLND to systematic LND, patients who underwent SLND received lower or equal adjuvant therapy compared to patients undergoing systematic LND. There was insufficient data to draw conclusions about SLND versus no node sampling. High-risk tumor factors were a larger determinant of receiving adjuvant treatment than the lymph node dissection method[27]. There were wide differences in SLND protocol, patient populations, and approach to surgery, which contributed to widely ranging outcomes reported, for example, the proportion of patients who received adjuvant treatment ranged widely from 20%[38] to 40%.[28]

There were only two studies that investigated PROs following SLND, and neither of these publications compared SLND to systematic LND or no LND. Therefore, we are unable to form conclusions about the impact of SLND on PROs. Those studies available seemed to indicate a reduction in lymphedema with SLND compared to systematic LND, but findings were less clear comparing SLND with no node dissection, with one study reporting the perhaps unexpected finding of higher lymphedema prevalence in patients with no node dissection

(40%) than those with SLND (27%).[31] However, with only three studies reporting on lymphedema as an outcome, the uncertainties on drawing robust conclusions must be regarded as considerable.

Although there were only three studies devoted to the costs of SLND, these provided support for the notion that SLND may be more cost-effective than a systematic LND, but is likely more expensive than no lymph node dissection. These studies had to rely on modelled or routine service data, due to the absence of data from prospective comparative studies. Any future planned randomized-controlled trials should integrate a cost-effectiveness assessment.

Strengths and Limitations

This review summarizes the literature available for patient-centered outcomes for SLND in endometrial cancer over the past five years since SLND has accelerated in many countries of the world. To the best of our knowledge, this is the first review to highlight these aspects of patient care. Rigorous search criteria and exclusion criteria were applied, and the use of Covidence allowed for a standardized and monitored approach to inclusion and exclusion of studies. However, this review is limited by the low number of studies available, and by the lack of standardized reporting limiting the ability to perform a meta-analysis for any outcomes. Non-English studies, and studies with less than 10 patients were excluded. The analysis of results was not weighted by study quality or study size.

Conclusions and Implications

In this systematic review of 21 studies reporting on patient-centered outcomes of SLND, we describe potentially favorable patient intra- and postoperative outcomes of SLND compared

452 to systematic LND, although limited by the substantial lack of high-quality studies comparing
453 the two methods. Results were even less conclusive when comparing SLND to no node
454 dissection due to the limited literature available, which may be reflective of systematic LND
455 being the standard of care in many countries during the study analysis period. As more
456 research calls into question the value of systematic LND, it may become increasingly
457 necessary to compare SLND, as the new standard of care, to no node dissection given the
458 findings of this review.

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Table 1: Patient demographics

Author	Age	BMI	ASA	Inclusion Criteria	Histology/Cell Type	FIGO Stage (I, II, III, IV)	FIGO Grade
Comparison of SLND vs LND or No-node dissection							
Liu (2017) [28]	SLND group: mean 64.5 (SD 10.7) Systematic LND group: mean 64.4 (SD 10.4) P= 0.93	SLND group: mean 31.7 (SD 8.2) Systematic LND group: mean 30.5 (SD 7.0) P= 0.12	–	Pre-operative diagnosis of endometrial adenocarcinoma	SLND group: Endometrioid: 132 Other: 34 Systematic LND group: Endometrioid: 163 Other: 54 P= 0.24	SLND group: I: 139 II: 6 III: 20 IV: 1 Systematic LND group: I: 174 II: 12 III: 24 IV: 5 P= 0.18	SLND group: G1: 84 G2: 37 G3: 11 Systematic LND group: G1: 116 G2: 30 G3: 17
Buda (2017) [37]	Systematic LND: median 62 (range 29-92) SLND: median 63 (range 29-88) P= 0.041	Systematic LND: median 28 (range 16.3-66) SLND: median 25 (range 15.4-50.8) P= 0.0001	–	Pre-operative histological proven biopsy of endometrial cancer apparent confirmed to the uterine body	Systematic LND: Endometrioid: 572 Other: 64 SLND: Endometrioid: 129 Other: 16 P= 0.413	Systematic LND: I: 635 III: 22 SLND: I: 121 III: 23 P= <0.0001	–
Gomez-Hidalgo (2018) [41]	No LND: <50 n=2165; 50-59	–	–	Malignant uterine cancers Stage I to III diagnosed as their first	No LND: Endometrioid: 10,900 Other: 2757	No LND: I: 12,388 II: 529	–

	n=4201; 60-69 n=4584; 70-79 n=1758; >80 n= 949 SLND: <50 n=187; 50-59 n=565; 60-69 n=741; 70-79 n=342; >80 n= 94 Systematic LND: <50 n=3704; 50-59 n=10,499; 60-69 n=14,968; 70-79 n=7233; >80 n=2049 [a] P= <0.001			or only cancer and confirmed with positive histology.	SLND: Endometrioid: 1519 Other: 410 Systematic LND: Endometrioid: 27,578 Other: 10,875 P= <0.001	III: 740 SLND: I: 1610 II: 71 III: 246 Systematic LND: I: 29,505 II: 2330 III: 6618 P= <0.001	
Geppert (2018) [27]	High-risk systematic infra-renal LND: median 68 (range 39-84) High risk systematic infra-mesenteric LND: 70.5 (60-81) High-risk systematic pelvic LND: 73 (44-80)	High-risk systematic infra-renal LND: median 26.9 (range 18.8-40.6) High risk systematic infra-mesenteric LND: median 27.7 (range 20.9-45.3)	–	Endometrial cancer	High-risk systematic infra-renal LND: Endometrioid: 58 Other: 27 High risk systematic infra-mesenteric LND: Endometrioid: 7 Other: 3 High-risk systematic pelvic LND: Endometrioid: 10 Other: 4	High-risk systematic infra-renal LND: I: 57 II: 4 III: 23 IV: 1 High risk systematic infra-mesenteric LND: I: 5 II: 0 III: 5	–

	High-risk SLND: median 79.5 (range 63-90) Low-risk SLND: median 67.5 (range 39-89)	High-risk systematic pelvic LND: median 33.5 (range 19.7-46.6) High-risk SLND: median 29.7 (range 21.9-57.1) Low-risk SLND: median 28.7 (range 18.1-61.7)			High-risk SLND: Endometrioid: 15 Other: 11 Low-risk SLND: Endometrioid: 52 Other: 1	IV: 0 High-risk systematic pelvic LND: I: 7 II: 2 III: 5 IV: 0 High-risk SLND: I: 21 II: 0 III: 4 IV: 1 Low-risk SLND: I: 52 II: 0 III: 1 IV: 0	
Imboden (2019) [38]	No LND: median 62.8 (range 37-92) SLND: median 62.9 (range 32-92) Systematic LND: median 64.8 (range 38-86) P= 0.481	No LND: median 31.0 (range 18-60) SLND: median 28.0 (range 18-52) Systematic LND: median 29.9 (range 17-48) P= 0.026	–	FIGO Stage 1, endometrioid histology, Grade 1 or 2 endometrial cancer at final diagnosis after surgical staging	–	No LND: I: 103 SLND: I: 118 Systematic LND: I: 58 P= 0.000	No LND: G1: 71, G2: 32 SLND: G1: 53, G2: 65 Systematic LND: G1: 22, G2: 36 P= 0.000

Polan (2019) [40]	No nodes: mean 61.7 (SE 0.25) Systematic LND group: mean 64.4 (SE 0.31) SLND group: mean: 63 (SE 0.90) P= <0.001	No nodes: median 35.8 (IQR 29.5-43.4) Systematic LND group: median 32.7 (IQR 27.4-39.0) SLND group: median: 36.5 (IQR 30.3-40.8) P= <0.001	No nodes: 1: 29 2: 862 3: 1083 4: 75 Systematic LND group: 1: 15 2: 498 3: 553 4: 23 SLND group: 1: 0 2: 64 3: 80 4: 0 P= 0.02	Endometrial cancer, Stage I-III	–	No nodes: I: 1750 II: 152 III: 147 Systematic LND group: I: 798 II: 142 III: 149 SLND group: I: 123 II: 11 III: 10 P= <0.001	–
Accorsi (2019) [15]	No nodes: median 61 (range 35–89) SLND group: median: 60 (range 44-87) Systematic LND group: median 62 (range 31–80)	No nodes: median 31.8 (range 21.9–51) SLND group: median 33 (range 21.4-48.3) Systematic LND group: median	No nodes: 1: 6 2: 36 3: 8 4: 2 SLND group: 1: 7 2: 42 3: 12 4: 0	Endometrial cancer	No nodes: Endometrioid: 43 Other: 11 SLND group: Endometrioid: 49 Other: 12 Systematic LND group: Endometrioid: 43 Other: 44	–	No nodes: G1: 23 G2: 19 G3: 10 SLND group: G1: 21 G2: 29 G3: 9 Systematic LND group: G1: 5

	SLND + systematic LND group: median 63 (range 46−77) P = 0.152	30.4 (range 18.0−46.3) SLND + systematic LND group: median 29.3 (range 22.2−41.3) P = 0.019	Systematic LND group: 1: 12 2: 67 3: 8 4: 1 SLND + systematic LND group: 1: 7 2: 26 3: 3 4: 0 P = 0.410		SLND + Systematic LND group: Endometrioid: 28 Other: 18 P= <0.001		G2: 29 G3: 49 SLND + Systematic LND group: G1: 5 G2: 26 G3: 14 P= <0.001
Casarin (2020) [29]	Systematic LND: mean 63.9 (SD 9.9) SLND group: mean 64.1 (SD 10.9)	Systematic LND: mean 38.1 (SD 9.6) SLND group: mean 35.2 (SD 8.7)	Systematic LND: ASA ≥3: 79 SLND group: ASA ≥3: 63	Apparent Stage I-III endometrial cancer	–	–	–
Stewart (2020) [30]	SLND group: median 64.1 (range 27.6-87.1) Systematic LND group: 61.4 (30.7-84.5)	SLND group: median 33.9 (range 18.4-58.1) Systematic LND group: 33.9 (19.2-58.0)	–	Biopsy-proven, newly diagnosed clinical Stage I endometrial cancer	SLND group: Endometrioid: 91 Other: 39 Systematic LND group: Endometrioid: 61 Other: 10 P= 0.016	SLND group: I: 109 II: 2 III: 17 IV: 2 Systematic LND group: I: 60	–

	P= 0.19	P= 0.60				II: 4 III: 7 IV: 0 P= 0.32	
Leitao (2020)[31 b]	<u>SLN group:</u> median 61 (range 34-85) <u>LND group:</u> median 61 (range 27-83) <u>Hyst group:</u> median 61 (range 31-85) P= 0.37	<u>SLN group:</u> median 29.1 (range 17.9–67.6) <u>LND group:</u> median 29 (range 18.2–59.1) <u>Hyst group:</u> median 33 (range 19.5–68.6) P= 0.99	–	Endometrial cancer	<u>SLN group:</u> Endometrioid: 162 Other: 18 <u>LND group:</u> Endometrioid: 256 Other: 96 <u>Hyst group:</u> Endometrioid: 54 Other: 13 P= <0.001	<u>SLN group:</u> I: 159 II: 2 III: 18 IV: 1 <u>LND group:</u> I: 271 II: 12 III: 59 IV: 10 <u>Hyst group:</u> I: 62 II: 1 III: 1 IV: 2 P= 0.01	<u>SLN group:</u> G1: 122 G2: 34 G3: 24 <u>LND group:</u> G1: 135 G2: 88 G3: 129 <u>Hyst group:</u> G1: 48 G2: 10 G3: 8 P= <0.001
Comparison of other surgical techniques							
Uccella (2017) [32]	<u>3mm group:</u> median 59 (range 38-74)	<u>3mm group:</u> median 25.6 (range 19.2-39.8)	–	Clinical stage I endometrial cancer	<u>3mm group:</u> Endometrioid: 13 Other: 2 <u>5mm group:</u>	<u>3mm group:</u> I: 15 II: 0 III: 0	<u>3mm group:</u> G1: 6 G2: 5 G3: 4

	5mm group: median: 62 (range 44-84) P = 0.39	5mm group: median 25.3 (range 18.1-50.7) P = 0.87			Endometrioid: 19 Other: 4 P= >0.99	5mm group: I: 20 II: 2 III: 1 P= 0.54	5mm group: G1: 9 G2: 7 G3: 7 P= 0.97
Moukarzel (2017) [33]	Single-site cohort: median 53 (range 45-77) Multiport cohort: median 62 (range 41-82) P= 0.14	Single-site cohort: median 24.6 (range 20.2-29.6) Multiport cohort: median 27.2 (range 21-29.7) P= 0.38	–	Definitive histological diagnosis of CAH or low-grade (1 or 2) endometrial adenocarcinoma on pre-operative endometrial biopsy	–	Single-site cohort: CAH: 5 I: 9 Multiport cohort: CAH: 2 I: 11 P= 0.84	-
Mereu (2020) [24]	Single site group: mean 61.4 (SD: 10.4) Multiport group: mean 61.9 (SD: 11.4) P= 0.85	Single site group: mean 24.8 (SD 3.8) Multiport group: mean 29.0 (SD 6.1) P= <0.001	–	Clinical diagnosis of low-risk endometrial cancer (FIGO stage IA, Grade 1-2) or atypical endometrial hyperplasia	Single site group: Endometrioid: 18 Other: 7 Multiport group: Endometrioid: 45 Other: 6 P= 0.077	Single site group: I: 17 III: 1 Multiport group: I: 44 III: 1 P= 0.060	Single site group: G1: 4 G2: 14 G3: 0 Multiport group: G1: 22 G2: 22 G3: 1 P= 0.080
Publications without comparison groups							
Hagen (2016) [26]	Median: 65.5 (range 35-91)	Median: 27.5 (range 17.9-49.6)	–	Apparent early stage endometrial cancer	Endometrioid: 89 Other: 19	I: 87 II: 2 III: 19	-
St Clair (2016) [34]	Median: 61 (range 30-90)	Median: 30 (range 16-69)	–	Endometrial cancer Stage I-III	Endometrioid: 724 Other: 120	I: 723 II: 20	G1: 479 G2: 177

						III: 99 IV: 2	G3: 188
Goebel (2020) [35]	Median: 59 (range 44-87)	–	–	Endometrial cancer	Endometrioid: 20 Other: 1	I: 15 II: 1 III: 4 IV: 1	G1: 13 G2: 5 G3: 2
Peiretti (2019) [43]	Median: 67 (range 33-86)	Median: 31 (range 19-58)	Median: 2 (range 2-3)	Biopsy proven endometrial cancer with apparent clinical stage I	–	I: 11 II: 1 III: 2	G1 or G2: 10 G3: 4
Mereu (2018) [23]	Median: 60 (range 55-69)	Median: 23 (range 21-33)	–	Clinical diagnosis of low-risk endometrial cancer (FIGO Stage IA, Grade 1-2) or atypical endometrial hyperplasia	–	–	G1: 8 G2: 4 G3: 2
Publications with insufficient demographic information							
Buda (2016) [25]							
Wright (2017) [39]							
Suidan (2018) [42]							

[a] Age reported categorically

[b] P values for SLN vs LND only

SLND, sentinel lymph node dissection; *SLN*, sentinel lymph node; *LND*, lymph node dissection; *CAH*, complex atypical hyperplasia.

Table 2: Sentinel lymph node and perioperative patient outcomes

Author (year)	**Study size: total number of patients (number in SLND group)**	**Study design**	**SLN protocol**	**Comparison**	**Operative time (mins)**	**Estimated intraoperative blood loss (mL)**	**Length of stay**	**Perioperative Complications and Conversion Rates**
Comparison of SLND vs Systematic LND or No node dissection								
Liu (2017) [28]	381 (166)	Single center retrospective + prospective cohort	National Comprehensive Cancer Network SLN mapping algorithm (SLN mapping, frozen section if failed mapping + systematic pelvic LND on side where SLN not identified)	Complete systematic pelvic with selective peri-aortic LND if high risk on frozen section	Systematic LND group: mean 144.6 (SD 48.0) SLND group: mean 135.8 (SD 37.2) P = 0.053	Systematic LND group: mean 79.0cm^3 (SD 70.0) SLND group: mean 57.3cm^3 (SD 58.0) P = 0.0014	Mean hours of stay Systematic LND group: 9.9 (SD 13.5) SLND group: 9.94 (SD 8.4) P = 0.97	Post-operative: Systematic LND: 10/77 (13%) SLND: 8/153 (5.2%) P = 0.04
Geppert (2018) [27]	278 (79)	Single center prospective cohort	SLN mapping, followed by systematic LND if failure to map and high risk	Different extent of LND + uterine risk	High-risk systematic infra-renal LND: median 226 (154-440) High-risk systematic infra-mesenteric LND:	High-risk systematic infra-renal LND: median 100 (10-700) High-risk systematic infra-mesenteric LND:	–	Post-operative complications High-risk systematic infra-renal LND: 16/85 (18.8%) High-risk systematic infra-mesenteric LND: 4/10 (40%) High-risk systematic pelvic LND: 6/14 (43%) High risk SLND: 8/26 (30.8%)

					median 212 (145-277) High-risk systematic pelvic LND: median 186 (129-347) High-risk SLND: median 157.5 (range 89-272) Low-risk SLND: median 135 (range 97-212)	median 100 (10-300) High-risk systematic pelvic LND: median 50 (0-200) High risk SLND: median 100 (range-10-500 Low risk SLND: median 50 (range 0-500)		Low risk SLND: 7/53 (13.2%) Conversion Rate: High-risk systematic infra-renal LND: 2/85 (2.4%) High risk systematic infra-mesenteric LND: 1/10 (10%) High-risk systematic pelvic LND: 0/14 (0%) High risk SLND: 2/26 (7.7%) Low risk SLND: 0/53 (0%)
Imboden (2019) [38]	729 (118)	Multicenter prospective + retrospective cohort	SLN detection followed by uterine frozen section and systematic pelvic/para-aortic LND based on uterine risk factors and clinical judgement	No LND, SLN, systematic LND	No LND: median 140 (range 50-540) SLND: median 140 (range 80-480) Systematic LND: median 244 (range 110-510) P = 0.000	No LND: mean 75 (range 10-700) SLND: mean 84 (range 10-400) Systematic LND: mean 240 (range 50-1000) P = 0.000	–	Intra-operative: No LND: 4/103 (3.9%) SLND: 0/118 (0.0%) Systematic LND: 3/58 (5.2%) P = 0.063 Post-operative: No LND: 8/103 (7.8%) SLND: 10/118 (8.5%) Systematic LND: 11/58 (19.0%) P = 0.134
Polan (2019) [40]	3282 (144)	Retrospective database review	SLN by code in Surgeons National Surgical Quality Improvement Program	Systematic LND, no node dissection	No LND: Median 141 (IQR 110-183)	–	Same day discharge % No nodes: 8.3% SLND group: 5.6%	Post-operative: Major complication composite No nodes: 41/2049 (2.0%) SLND: 3/144 (2.1%) Systematic LND: 39/1089 (3.6%)

					SLND group: Median 166 (IQR 138-209) Systematic LND group: Median 171 (IQR 133-211) P = <0.001		Systematic LND group: 11.9%	P = 0.03
Accorsi (2019) [15]	250 (61)	Single center retrospective cohort	Hysteroscopy + SLN mapping	No LND; SLN; systematic pelvic LND +/- para-aortic LND; SLN + systematic LND	No nodes: median 135 (50-270) SLND group: median 152 (60-300) Systematic LND group: median 370 (80-600) SLND + systematic LND group: median 240 (125-400) P = <0.001	No nodes: median 35mL (0-500) SLND group: median 20mL (0-500) Systematic LND group: median 100mL (0-2300) SLND + systematic LND group: median 45mL (0-500) P = <0.001	–	Intra-operative: No nodes: 0/54 (0.0%) SLND group: 1/61 (1.6%) Systematic LND group: 9/89 (10.1%) SLND + systematic LND group: 6/46 (13.0%) P = 0.005 Post-operative: No nodes: 8/54 (14.8%) SLND group: 7/61 (11.5%) Systematic LND group: 34/89 (38.2%) SLND + systematic LND group: 9/46 (19.6%) P = <0.001 Conversion rate: No nodes: 1/54 (1.9%) SLND group: 0/61 (0.0%) Systematic LND group: 2/89 (2.2%)

								SLND + systematic LND group: 0/46 (0.0%)
Casarin (2020) [29]	621 (188)	Single center retrospective observational	National Comprehensive Cancer Network SLN mapping algorithm (SLN mapping, frozen section if failed mapping + systematic pelvic LND on side where SLN not identified)	Systematic pelvic LND; no node dissection	No nodes: mean 155.1 (SD 55.5) SLND group: mean 136.6 (SD 42) Systematic LND group: mean 225.3 (SD 71.4) P LND vs SLND = <0.01 P SLND vs no nodes = 0.002	No nodes: median 50 (IQR 50-100) SLND group: median 50 (IQR 50-100) Systematic LND group: median 100 (IQR 60-200) P LND vs SLND = <0.001 P SLND vs no nodes = 0.26	Length of stay >= 2 days No nodes: 18.3% SLND group: 8.0% Systematic LND group: 23.2% P LND vs SLND = <0.001 P SLND vs no nodes 0.006	Intra-operative: No nodes: 4/235 (1.7%) SLND group: 1/188 (0.5%) Systematic LND group: 4/198 (2.0%) P SLND vs no nodes = 0.30 P LND vs SLND = 0.23 Post-operative (ASC Grade >=2) No nodes: 13/235 (5.5%) SLND group: 9/188 (4.8%) Systematic LND group: 15/198 (7.6%) P LND vs SLND = 0.26 P SLND vs no nodes = 0.73 Conversion rate: No nodes: 0/235 (0.0%) SLND group: 1/188 (0.5%) Systematic LND group: 2/198 (1.0%) P SLND vs no nodes = 0.42 P LND vs SLND = 0.60
Stewart (2020) [30]	203 (130)	Single center retrospective observational	MD Anderson Cancer Centre SLN mapping algorithm (SLN mapping, frozen section if mapping fails to determine	Systematic LND based on high-risk uterine factors	SLND group: Median 171 (range 96-416) Systematic LND group: Median	SLND group: Median 75 (range 10-1500) Systematic LND group: Median	–	Intra-operative: SLND group: 3/130 (2.3% Systematic LND group: 1/71 (1.4%) P = 1.00 Post-operative: SLND group: 4/130 (3.1%)

			need to complete systematic LND)		210 (range 92-366) P = 0.007	100 (range 20-2630) P = 0.081		Systematic LND group: 1/71 (1.4%) P = 0.30 <u>Conversion Rate</u>: SLND group: 9/130 (7.4%) Systematic LND group: 4/71 (6.3%) P = 1.00
Comparison of other surgical techniques								
Uccella (2017) [32]	38 (38)	Multicenter retrospective observational	National Comprehensive Cancer Network SLN mapping algorithm (SLN mapping, frozen section if failed mapping + systematic pelvic LND on side where SLN not identified)	3mm vs 5mm laparoscopic ports	<u>3mm group:</u> median 120 (range 90-180) <u>5mm group:</u> median 135 (range 100-220)	<u>3mm group</u>: median 50 (range 0-150) <u>5mm group</u>: median 50 (range 0-200)	<u>3mm group</u>: 2 days (range 1-3) <u>5mm group</u>: 2 days, range 1-5)	<u>Intra-operative:</u> 3mm group = 0/15 (0.0%) 5mm group = 1/23 (4.3%) <u>Post-operative:</u> 3mm group = 0/15 (0.0%) 5mm group = 3/23 (13%)
Moukarzel (2017) [33]	27 (27)	Single center retrospective cohort	SLN mapping, frozen section to determine need for systematic pelvic/para-aortic LND	Single site vs multiport	<u>Single site group</u>: median 175 (range 150-230) <u>Multiport group:</u> median 184 (range 118-262)	<u>Single-site group</u>: median 50 (range 10-100) <u>Multiport group</u>: median 50 (range 10-500)	<u>Single site group</u>: 100% discharged within 23 hours <u>Multiport cohort:</u> 100% discharged within 23 hours	<u>Intra-operative:</u> Single site group = 0/14 (0.0%) Multiport group = 0/13 (0.0%) <u>Post-operative:</u> Single site group = 0/14 (0.0%) Multiport group = 0/13 (0.0%) <u>Conversion rate:</u> Single site group = 0/14 (0.0%) Multiport group = 0/13 (0.0%)

Mereu (2020) [24]	76 (76)	Multicenter prospective case-control	Robotic TLH + SLN mapping	Robotic single site vs multiport	Single site group: mean 148.7 (SD 18.7) Multiport group: mean 158.2 (SD 47.6) P = 0.247	Single site group: 96% <100mL Multiport group: 84.3% <100mL P = 0.112	Single site group: mean 2.1 days (SD 0.6) Multiport group: mean 3.1 days (SD 1.6) P = <0.0001	Intra-operative: 3/76 (3.9%) of all cases Post-operative: Grade 2 complications = 4/76 (5.2%) of all cases
Publications without comparison groups								
Hagen (2016) [26]	108 (108)	Prospective observational	Memorial Sloan Kettering Cancer Centre algorithm (systematic LND if failed mapping, surgeon discretion para-aortic LND)	No comparison	Median 118.5 (range 50-223)	Median 50mL (Range 10-300)	Two thirds of patients had post-operative length of stay of 1 day	Post-operative: 5/108 (4.6%)
Mereu (2018) [23]	15 (15)	Single center prospective cohort	SLN detection followed by ultrastaging as per Memorial Sloan Kettering Cancer Centre	No comparison	Mean 155 (range 112-175)	–	All patients discharged within 48 hours of surgery	Intra-operative: 1/15 (6.67%)
Peiretti (2019) [43]	14 (14)	Multicenter retrospective observational	Open SLN mapping	No comparison	Median 157.5 (range 70-240)	Median 160mL (range 50-600)	Median 3 days (range 1-6)	Post-operative: 0/14 (0.0%)

SLND, sentinel lymph node dissection; *LND*, lymph node dissection; *CAH*, complex atypical hyperplasia.

Table 3: Sentinel lymph node and adjuvant treatment

Study	Study size: total number of patients (number in SLN group)	SLN protocol	Comparison group	Adjuvant Treatment
Comparison of SLND vs Systematic LND				
Liu (2017) [28]	381 (166)	National Comprehensive Cancer Network SLND algorithm (SLND, frozen section if failed mapping + systematic pelvic LND on side where SLN not identified)	Systematic pelvic with selective para-aortic LND if high risk on frozen section	Adjuvant treatment (SLND): 67/166 (40.3%) Adjuvant treatment (systematic LND): 85/215 (39.5%)
Buda (2017) [37]	802 (145)	Memorial Sloan Kettering Cancer Centre algorithm (systematic LND if failed mapping, surgeon discretion para-aortic LND)	Frozen section + systematic pelvic LND if high grade features +/- para-aortic LND if positive pelvic nodes at frozen section	Adjuvant treatment (SLND): 35/145 (24.1%) Adjuvant treatment (systematic LND): 272/657 (41.4%) P = <0.0001 Types of treatments similar between the two groups
Gomez-Hidalgo (2018) [41]	54039 (863)	SLND identified on National Cancer Database	Systematic LND; no nodal assessment	Radiation treatment (no node dissection): 1694/13657 (12.4%) Radiation treatment (SLND): 524/1929 (27.2%) Radiation treatment (systematic LND): 9733/38453 (25.3%) P = <0.001 For stage I tumors, no difference in radiation treatment between SLND and systematic LND (aRR = 0.92, 95% CI 0.82-1.05)
Geppert (2018) [27]	188 (79)	SLND. Systematic LND if failed mapping and high risk	Systematic pelvic + para-aortic LND if high-risk endometrial cancer	Adjuvant treatment in low risk with SLND: 2/53 (3.8%) Adjuvant treatment in high-risk with SLND: 9/26 (34.6%) Adjuvant treatment in high-risk with systematic pelvic + infra-renal para-aortic LND: 49/85 (57.6%)

				Adjuvant treatment in high-risk with systematic infra-mesenteric para-aortic and pelvic LND: 5/10 (50%) Adjuvant treatment in high-risk with systematic pelvic LND: 10/14 (71.4%)
Imboden (2019) [38]	279 (118)	SLND, systematic pelvic/para-aortic lymph node dissection based on risk factors at frozen section	No lymph node dissection; Systematic pelvic +/-para-aortic lymph node dissection	Overall, adjuvant treatment given in 16.7% of patients[a] Adjuvant treatment more frequent in systematic LND group than SLND. No difference in adjuvant treatment between SLND group to no node dissection group.
Publications without comparison groups				
St Clair (2016) [34]	844 (844)	Memorial Sloan Kettering Cancer Centre algorithm (systematic LND if failed mapping, surgeon discretion para-aortic LND)	No comparison	Adjuvant treatment including chemotherapy in 87% of patients with positive nodes by isolated tumor cells and 81% of patients with positive nodes by micrometastasis
Hagen (2016) [26]	108 (108)	Memorial Sloan Kettering Cancer Centre algorithm (systematic LND if failed mapping, surgeon discretion para-aortic LND)	No comparison	37/108 (34%) received post-operative chemotherapy
Goebel (2020) [35]	155 (155)	National Comprehensive Cancer Network SLND algorithm (SLND, frozen section if failed mapping + systematic pelvic LND on side where SLN not identified)	No comparison	Isolated tumor cells = 20/23 (87.0%) received chemotherapy postoperatively Micrometastasis = 17/21 (81.0%) received chemotherapy Adjuvant treatment initiated due to high risk uterine factors or advanced stage disease; ITCs did not change adjuvant treatment management.

[a] Raw numbers unavailable

SLND, sentinel lymph node dissection; *LND*, lymph node dissection; *ITC*, isolated tumor cells.

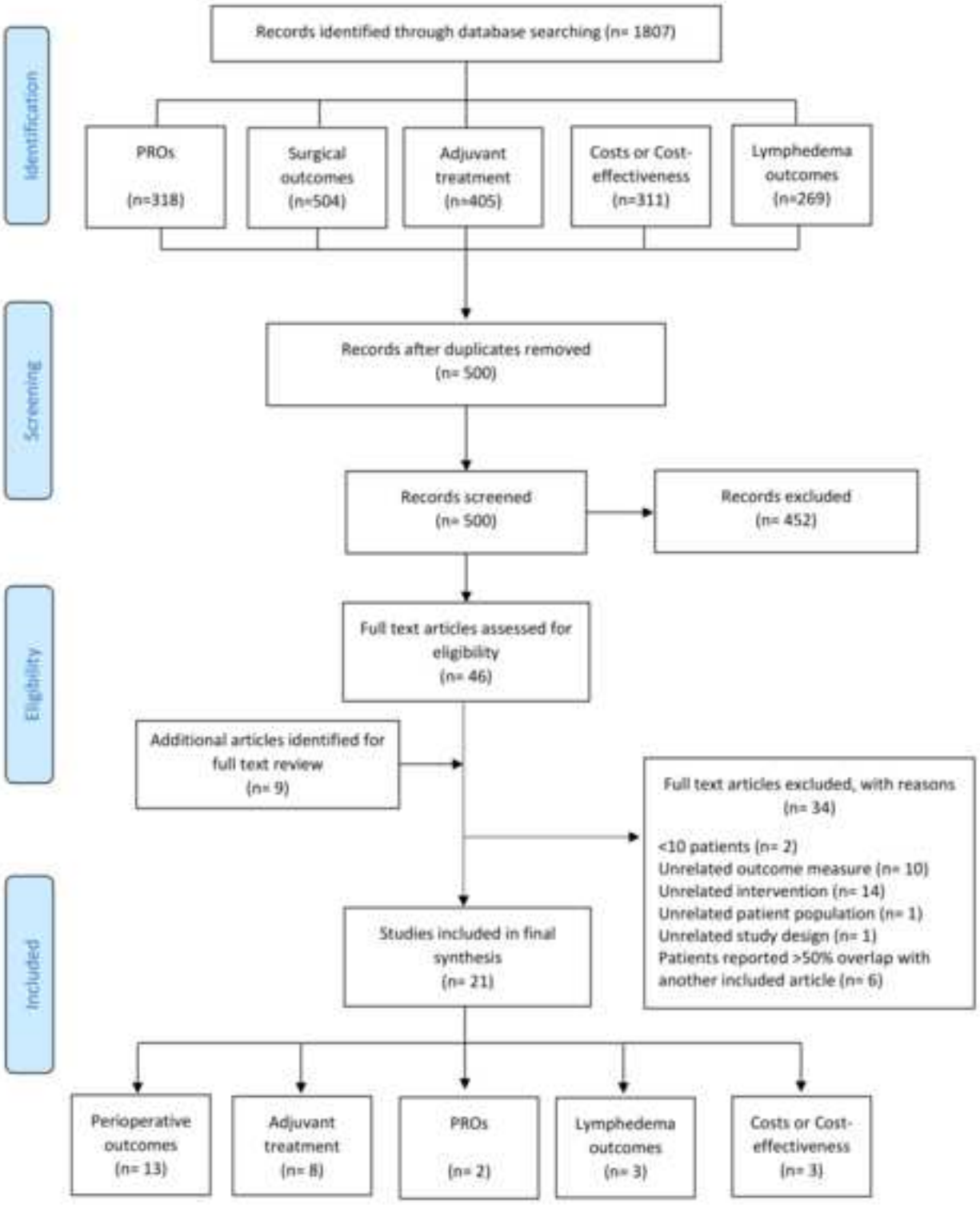
Figures

Figure 1. PRISMA flow diagram of included studies

Preferred Reporting Item for Systematic Reviews and Meta-analyses template.

Figure 1

Click here to access/download;Figure(s);Figure 1 - PRISMA Flow Diagram.tiff



Supplementary Table 1. Search strategy

Search number	Search terms
1. Perioperative outcomes	sentinel-node biopsy OR sentinel lymph node OR sentinel lymph node biopsy[Mesh] OR sentinel lymph node[Mesh] AND endometrial cancer OR endometrial carcinoma OR endometrial neoplasms[Mesh] OR endometrium carcinoma OR “cancer of the endometrium” AND treatment outcome[Mesh] OR postoperative complications[Mesh] OR postoperative outcomes OR surgical outcomes OR adverse events OR perioperative outcomes OR postoperative complication OR postoperative complications OR combination of: surgery/surgical AND complication/ complications/ effective/ effectiveness/ outcome/ outcomes
2. Adjuvant treatment	sentinel-node biopsy OR sentinel lymph node OR sentinel lymph node biopsy[Mesh] OR sentinel lymph node[Mesh] AND

	endometrial cancer OR endometrial carcinoma OR endometrial neoplasms[Mesh] OR endometrium carcinoma OR “cancer of the endometrium” AND adjuvant OR Chemotherapy, Adjuvant[Mesh] OR Radiotherapy, Adjuvant[Mesh]
3. Patient-reported outcomes	sentinel-node biopsy OR sentinel lymph node OR sentinel lymph node biopsy[Mesh] OR sentinel lymph node[Mesh] AND endometrial cancer OR endometrial carcinoma OR endometrial neoplasms[Mesh] OR endometrium carcinoma OR “cancer of the endometrium” AND Patient Reported Outcome Measures[Mesh] OR quality of life OR patient reported outcome OR patient reported outcomes OR Quality of Life[Mesh] OR Patient Outcome Assessment[Mesh] OR patient outcome assessment
4. Lymphedema outcomes	sentinel-node biopsy OR sentinel lymph node OR sentinel lymph node biopsy[Mesh] OR sentinel lymph node[Mesh] AND

	endometrial cancer OR endometrial carcinoma OR endometrial neoplasms[Mesh] OR endometrium carcinoma OR “cancer of the endometrium” AND Lymphedema OR Lymphoedema OR Lymphedema[Mesh]
5. Cost	sentinel-node biopsy OR sentinel lymph node OR sentinel lymph node biopsy[Mesh] OR sentinel lymph node[Mesh] AND endometrial cancer OR endometrial carcinoma OR endometrial neoplasms[Mesh] OR endometrium carcinoma OR “cancer of the endometrium” AND cost-benefit analysis[Mesh] OR cost-effectiveness OR cost OR costs

Supplementary Table 2. Newcastle-Ottawa scale for assessment of quality of included studies

Study	Selection				Comparability		Outcome			Quality Score
Cohort Studies	**1**	**2**	**3**	**4**	**1a**	**1b**	**1**	**2**	**3**	
Moukarzel (2017)	*	*	*	*	*	*	*	*	*	9
Mereu (2018)	*	NA	*	*	NA	NA	- [f]	*	*	5
Liu (2017)	*	*	*	*	*	*	*	- [g]	*	8
Geppert (2018)	*	*	*	*	- [d]	- [d]	- [f]	*	*	6
Accorsi (2019)	*	*	*	*	*	*	*	*	*	9
Peiretti (2019)	*	NA	*	*	NA	NA	*	*	*	6
Imboden (2019)	*	*	*	*	*	*	*	*	*	9
Stewart (2020)	*	*	*	*	*	*	- [f]	*	*	8
Uccella (2017)	*	*	*	*	*	*	- [f]	*	*	8
St Clair (2016)	*	NA	*	- [c]	NA	NA	*	*	*	5
Gomez-Hidalgo (2018)	*	*	*	*	*	- [e]	*	- [g]	*	7
Goebel (2020)	*	NA	*	- [c]	NA	NA	*	*	*	5
Hagen (2016)	*	NA	*	*	NA	NA	- [f]	- [g]	*	4
Polan (2019)	*	*	*	*	*	*	*	*	*	9
Casarin (2019)	*	*	*	*	*	*	*	*	*	9
Buda (2016)	- [a]	NA	*	*	*	*	- [f]	*	*	6
Buda (2017)	*	*	*	- [c]	*	*	*	*	*	8
Leitao (2020)	*	*	*	*	*	*	*	*	*	6
	Selection				**Comparability**		**Exposure**			**Quality Score**
Case-Control Studies	**1**	**2**	**3**	**4**	**1a**	**1b**	**1**	**2**	**3**	
Mereu (2020)	*	*	- [b]	*	*	*	- [f]	*	*	7

*Each star represents if individual criterion within the subsection was fulfilled. NA – Not applicable.

Comparability 1a: Study controls for age; 1b: Study controls for BMI and/or previous abdominal surgeries.

[a] Unable to differentiate between endometrial cancer and cervical cancer group.

[b] Controls (robotic multiport group) derived from hospitalised population across three different cities.

[c] Star applied for all studies, except those which included adjuvant treatment outcomes where it was not clearly stated if the study excluded women who had undergone neoadjuvant treatment prior to surgery.

[d] Age and BMI were reported in Table 2, however no statistical analysis to establish comparability was included in results section.

[e] BMI and previous abdominal surgeries not reported.

[f] No confirmation of outcome by reference to secure records (e.g. medical records), record linkage, or structured interview where blind to case/control status.

[g] Length of follow-up not reported.

Newcastle - Ottawa Quality Assessment Scale Cohort Studies

Note: A study can be awarded a maximum of one star (*) for each numbered item within the Selection and Outcome categories. A maximum of two stars (*) can be given for Comparability

Selection

1) Representativeness of the exposed cohort
   a) truly representative of the average *case of endometrial cancer* in the community *
   b) somewhat representative of the average *case of endometrial cancer* in the community *
   c) selected group of users eg nurses, volunteers
   d) no description of the derivation of the cohort
2) Selection of the non-exposed cohort
   a) drawn from the same community as the exposed cohort *
   b) drawn from a different source
   c) no description of the derivation of the non-exposed cohort
3) Ascertainment of exposure
   a) secure record (eg surgical records) *
   b) structured interview *
   c) written self-report
   d) no description
4) Demonstration that outcome of interest was not present at start of study
   a) yes *
   b) no

Comparability

1) Comparability of cohorts on the basis of the design or analysis
2) a) study controls for *age* (select the most important factor) *
   b) study controls for any additional factor: *BMI and/or previous abdominal surgeries* *

Outcome

1) Assessment of outcome
   a) independent blind assessment * (or confirmation of the outcome by reference to secure records, e.g. medical records)
   b) record linkage *
   c) self-report
   d) no description
2) Was follow-up long enough for outcomes to occur
   a) yes (select an adequate follow up period for outcome of interest) *
   b) no

   Star applied if yes, with adequate follow-up defined by:
   - Postoperative outcomes: *Follow up ≥4 weeks after surgery*
   - Lymphedema outcomes: *Follow-up ≥12 months after surgery*
   - Adjuvant treatment outcomes: *Follow-up ≥12 months after surgery*
   - *For studies which reported on multiple outcomes, a star was applied if they met at least one of the above criteria.*
3) Adequacy of follow up of cohorts
   a) complete follow up - all subjects accounted for *
   b) subjects lost to follow up unlikely to introduce bias - small number lost - ≥80% (select an adequate %) follow up, or description provided of those lost) *
   c) follow up rate ≤80% (select an adequate %) and no description of those lost
   d) no statement

   For retrospective studies, follow-up was considered adequate if results/outcomes were reported for at least 80% of women who were initially identified for inclusion in the study (e.g. retrospectively enrolled).

Newcastle - Ottawa Quality Assessment Scale Case-Control Studies

Note: A study can be awarded a maximum of one star (*) for each numbered item within the Selection and Outcome categories. A maximum of two stars (*) can be given for Comparability

Selection

1) Is the case definition adequate?
   a) yes, with independent validation *
   b) yes, eg record linkage or based on self-reports
   c) no description
2) Representativeness of the cases
   a) consecutive or obviously representative series of cases *
   b) potential for selection biases or not stated
3) Selection of Controls
   a) community controls *
   b) hospital controls
   c) no description

Comparability

1) Definition of Controls
   a) no history of disease (endpoint) *
   b) no description of source
2) Comparability
   1) Comparability of cases and controls on the basis of the design or analysis
   a) study controls for *age* (Select the most important factor.) *
   b) study controls for any additional factor: *BMI and/or previous abdominal surgeries* *

Exposure

1) Ascertainment of exposure
   a) secure record (eg surgical records) *
   b) structured interview where blind to case/control status *
   c) interview not blinded to case/control status
   d) written self-report or medical record only
   e) no description
2) Same method of ascertainment for cases and controls
   a) yes *
   b) no
3) Non-Response rate
   a) same rate for both groups *
   b) non respondents described
   c) rate different and no designation

American Journal of Obstetrics & Gynecology

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Date: 02/10/2020 **Manuscript # (if available):**

Manuscript title: *Patient-centered outcomes following sentinel lymph node dissection in endometrial cancer: A systematic review*

Corresponding author: Professor Monika Janda

Authors may either sign the same form or submit individually

I am an author on this submission, have adhered to all editorial policies for submission as described in the Information for Authors, attest to having met all authorship criteria, and all potential conflicts of interest / financial disclosures appears on the title page of the submission.

Signatures are required - typed signatures are unacceptable.

Typed or CLEARLY Printed Name: **Dr Helena Obermair**

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Typed or CLEARLY Printed Name: **Miss Montana O'Hara**

Signature:

Typed or CLEARLY Printed Name: **Prof Andreas Obermair**

Signature:

Typed or CLEARLY Printed Name: **Prof Monika Janda**

Signature:

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	7
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	7
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	8
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	8-9
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	9
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	9
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	9

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	9
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	10
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	10
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	10-11
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	11-18
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	N/A
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	10-11
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	19-21
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	21
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	21-22
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	N/A

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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